# Chapter 10
# Articular Cartilage Regeneration

**Georg N. Duda, Michael Sittinger, Joshua O. Eniwumide, and Evi Lippens**

**Abstract** The glassy translucent material found at the ends of bones, within synovial joints, is termed articular cartilage. While healthy, it provides a low-friction bearing surface, preventing bone-to-bone contact, and to an extent, absorb shock during vigorous activities. However, when damaged could lead to pain, deformity and reduced mobility; the social impact of which, entails high costs in terms of therapeutic treatments and loss of income. The present chapter reviews the common knowledge of the constraints to articular cartilage regeneration; namely cartilage structure, composition and major diseases. The first of the three sections detail the major constituents of the tissue and their structural organization; the tissues mechanical properties, and ends with a brief description of how these features change in an unhealthy cartilage; be it mechanical or disease. In the second section, both clinical and academic approaches are pooled together, to review the current strategies in restoring health to joints with diseased or damaged cartilage. The final section highlights the fact that progression of cartilage disease affects not only the cartilage, but its underlying bone. The implications of the subchondral bone in the propagation of cartilage degeneration are discussed, and finally, their considerations in cartilage defect healing.

**Keywords** Tissue composition • Structural organisation • Mechanical properties • Repair and regeneration strategies • Subchondral tissue

G.N. Duda (✉) • J.O. Eniwumide • E. Lippens
Julius Wolff Institute and Centre for Musculoskeletal Surgery, Berlin-Brandenburg Centre for Regenerative Therapy, Charité-Universitätsmedizin Berlin,
Augustenburger Platz 1, 13353 Berlin, Germany
e-mail: Georg.Duda@charite.de

M. Sittinger
Tissue Engineering Laboratory and Berlin-Brandenburg Center for Regenerative Therapies, Department of Rheumatology and Clinical Immunology, Charité-Universitätsmedizin Berlin,
Tucholskystrasse 2, Berlin 10117, Germany



G. Steinhoff (ed.), *Regenerative Medicine - from Protocol to Patient*,
DOI 10.1007/978-3-319-28386-9_10

## 10.1 In Health and Sickness

### *10.1.1 Structure and Function*

Articular cartilage is found at the end of bones as a thin, white tissue. This tissue consists mainly of extracellular matrix (ECM), and has a relatively low density of cells. The adult tissue is known to be devoid of blood vessels, lymph vessels, and nerves (Poole 1997; Stockwell and Meachim 1979). The thickness of adult human cartilage generally varies between 2 and 7 mm (Meachim and Stockwell 1979). This variation is evident both between joints and also within different regions of the same joint.

The efficient functioning of the synovial joints is made possible by the presence of articular cartilage. Lining the surfaces of diarthrodial joints, articular cartilage provides a low-friction bearing surface and prevents bone-to-bone contact (Guilak and Mow 2000; Mow et al. 1980). Major load bearing joints, such as the hip, knee and ankle are subjected to peak stresses up to three times body weight during normal walking or higher during stumbling (Guilak and Mow 2000; Mow et al. 1992; Weightman and Kempson 1979). Under these high stresses, articular cartilage deforms, effectively reducing both the contact stresses and the pressures transmitted to the underlying bone (Ateshian and Wang 1997; Kim et al. 1994; McCutchen n.d.; Weightman and Kempson 1979). Cartilage also exhibits impact resistance, which permits a degree of shock absorbance during vigorous activities such as running and jumping.

### *10.1.2 Composition*

Articular cartilage consists of Water, Collagen, and non-collagenous proteins, and cells. These are approximated to be 70–80 %, 10–15 %, and 5–10 % of the tissues wet weight, respectively, while the cells are approximately 5 % of the tissues volume. Notably these features vary amongst species, from joint to joint and within different locations of the same joint (Buckwalter and Mankin 1997; Stockwell and Meachim 1979).

#### 10.1.2.1 Collagen

Collagen is a large protein family with at least 27 members (Boot-Handford et al. 2003; Eyre 2004). They can be distinguished by their distinct amino acid composition and hence polypeptide chains (Meisenberg and Simmons 1998). The collagen types present in articular cartilage are types II, VI, IX, X and XI (Eyre et al. 1992). Type II collagen makes up 95 % of the solid composition of the mature human articular cartilage (Eyre et al. 1992). It is derived from procollagen molecules

containing amino ($NH_2$)-and carboxyl (COOH)-terminal extension peptides that are cleaved, extracellular, prior to fibrilcollagens (Ryan and Sandell 1990).

Due to their abundance in articular cartilage, type II and type X collagen are often used as indicators for extracellular matrix (ECM) formation by cultured chondrocytes and to ascertain a chondrogenic phenotype of differentiating stem cells.

Type XI collagen contributes less than 5 % to the total collagen content of the articular cartilage. In cartilaginous tissues, collagen XI forms heterotypic narrow fibrils with collagens type II and type IX (Grant et al. 1988). Type VI collagen is a short-helical heterotrimer. Its monomers are arranged intracellular into anti-parallel staggered dimers and then into tetramers by lateral aggregation of two dimmers, then secreted into the ECM. In the pericellular environment, collagen VI has been implicated in both the maintenance of chondron integrity and cell-matrix signaling. Type IX collagen accounts for 10 % of human fetal cartilage. This proportion decreases with age, reaching 1–2 % in mature human articular cartilage. This molecule can be considered a protoglycan, due to its possession of a chondroitin sulphate chain (Huber et al. 1988). Type X collagen is a short-chain collagen, which forms a mat-like network in the hypertrophic cartilage matrix and around differentiating chondrocytes (Kwan et al. 1986). It is found in either the cartilaginous tissues undergoing endochondral ossification, such as the hypertrophic zones of the growth plate, or the calcified zone in mature articular cartilage (Ayad et al. 1987).

#### 10.1.2.2 Proteoglycans

Proteoglycans (PGs) are the most abundant non-collagenous macromolecular components in mammalian cartilage, making up approximately 10–15 % of the mature mammalian articular cartilage. These are defined as having a protein core to which one or more glycosaminoglycan (GAG) chains are covalently attached. GAGs present in articular cartilage include chondroitin sulphate, keratan sulphate and hyaluronan. The GAG chains are often crucial to the functional properties of the PG (Hardingham and Fosang 1992). However, for PGs such as decorin and biglycan, which bind to growth factors and modulate their activities, evidence exist, suggesting that it is their protein core and not their GAG chains that mediates the binding function (Cheifetz et al. 1988; Ruoslahti and Yamaguchi 1991). The most abundant PG, accounting for up to 90 % of mature articular cartilage PG is aggrecan. As GAG builds up in the cells ECM, aggrecan molecules bind non-covalently along a hyaluronan chain to form an aggrecan-hyaluronan complex. The aggregate, having molecular weight approximately 50,000 kDa is associated with load distribution in articular cartilage (Hardingham and Fosang 1992). Smaller PG molecules present in cartilage include biglycan, decorin and fibromodulin (Knudson and Knudson 2001). These leucine-rich PGs bind to collagen type II and play important roles in ECM organization (Pulkkinen et al. 1990; Vogel et al. 1984).

PGs have important roles in collagen fibrillogenesis, organization of collagen networks and in providing rigidity to the ECM. Chondrocytes express cell surface PGs (Knudson and Knudson 2001), which interact with growth factors such as,

basic Fibroblastic Growth Factor (bFGF) in order to regulate cell activities. Similar to types II and X collagen, PG provide a reliable indicator of biosynthetic activities of chondrocytes in culture (Knight et al. 1998; Lee et al. 2003). Other common examples of such proteins are Anchorin CII. These bind to the surface of the chondrocytes and anchor it to the collagen fibrils in the ECM and cartilage oligomeric matrix proteins, which also bind to chondrocytes (Mollenhauer et al. 1984). These proteins maintain the chondrocytes phenotype, and are used as markers of cartilage turnover and can control the progression of cartilage degradation in osteoarthritic cartilage (Salter 1993). Other proteins, such as fibronectin and tenascin have roles in matrix organization, cell-matrix interaction and the tissue response to inflammatory conditions such as osteoarthritis (Buckwalter and Mankin 1997; Nishida et al. 1995).

#### 10.1.2.3 Extracellular Matrix Fluid

Water is the largest component of articular cartilage. It makes up to 80 % of cartilage wet weight in the surface zone, and decreases to approximately 65 % within the deep zone. The high affinity of articular cartilage for water is due to the charge density of the hydrophilic PG molecules. The PGs encapsulate the water within their matrices, forming a gel-like substance, with pore size of approximately 6.9 nm (Meachim and Stockwell 1979). These pores contribute to the diffusivity of the small molecules and water through articular cartilage (Lusse et al. 2000; Maroudas 1979). Matrix water contains small gasses, proteins and dissolved electrolytes ($Na^+$, $Cl^-$, $Ca^{2+}$, $SO_3^-$, $COO^-$ etc.). The cations balance the negatively charged PGs, thereby influencing the mechanical properties of the tissue (Guilak et al. 1999). A large proportion of the ECM fluid can move freely in and out of the tissue under applied load (Buckwalter and Mankin 1997). Therefore during normal joint loading, the cartilage is compressed and the water is squeezed out of the loaded region. As the region is unloaded, the water is re-imbibed and the original volume is restored with time. This movement of cartilage fluid is crucial in joint lubrication, transport of macromolecules within articular cartilage and nutrition of the cells therein.

#### 10.1.2.4 Chondrocytes

The cartilage ECM and its associated proteins are synthesized, assembled and organized into a highly ordered framework by its cellular component, the articular chondrocytes (Buckwalter and Mankin 1997; Muir 1995). The chondrocytes attempt to maintain the ECM and their associated protein by their continual replacement in health, disease and following trauma. However, this depends on the cells ability to detect changes in the matrix composition, which may be due to macromolecular degradation, or the mechanical demands placed upon the tissue. Although relatively sparse in density, the chondrocytes are the only living units available to adapt cartilage to changes in its surroundings. The chondrocyte is surrounded by a thin layer of matrix, called the pericellular matrix (PCM) which together with the enclosed cell is called the chondron. The composition, structure and function of the PCM is

different from the surrounding ECM and plays an important role as transducer of both mechanical and biochemical signals to the chondrocytes (Wilusz et al. 2014). Not only the elastic modulus of the PCM is different from its surrounding ECM, also a higher proteoglycan content is found in the PCM compared to the ECM. Therefore, tissue deformation and the associated changes in interstitial water content that occur during loading will result in dynamic changes in the physicochemical and osmotic environment of the cell and may provide critical signals for regulating the cell's response to loading (O'Conor et al. 2014; Wilusz et al. 2014).

Individually, chondrocytes have been found to be metabolically active, with a glycolytic rate per cell similar to that of cells found in vascularized tissues. However, the adult tissue as a whole, has a comparatively low metabolic activity due to its low cell density of approximately one cell per 100 $\mu m^3$ (Buckwalter et al. 2005). Both cell proliferation and ECM synthesis decline following skeletal maturity in normal tissue.

### *10.1.3 Organization*

The structure and composition of articular cartilage changes with depth from the joint surface (Buckwalter et al. 1987; Clarke 1971; Lane and Weiss 1975; Lipshitz et al. 1976; Muir et al. 1970; Ratcliffe and Mow 1976). Although these changes are continuous, articular cartilage has been divided into four distinct zones/layers (Fig. 10.1). These are termed the superficial zone (I), transitional zone (II), the deep or radial zone (III), and the zone of calcified cartilage (IV). PGs occupy the interfibrillar space and their concentrations increase from the surface to a maximum in the transitional zone, and then diminishes toward the deep zone (Comper 1996; Muir 1980; Poole et al. 1982). The volumetric concentration of collagen fibers in human articular cartilage increases from the superficial (16–31 %) to the deep zone (14–42 %), while that of the cell decrease by a factor of about three from the surface to the deep zone. The superficial zone is closest to the articular surface. It is approximately 250 μm thick for human articular cartilage, and is the thinnest of the four zones. Chondrocytes in this zone are flattened and oriented parallel to the articular surface (Meachim and Stockwell 1979). Collagen fibers in this region are very fine and, are arranged tangentially to the surface of the cartilage, thus deriving its alternative name; the tangential zone (Buckwalter et al. 1987). The most superficial part of this region is termed the lamina splendens and is devoid of cells, but consists of fine fibers and polysaccharides.

In the transitional zone, chondrocytes are spherical in form and fairly uniform in distribution. The collagen fibrils in this zone are generally larger and more randomly organized. There is a higher concentration of PGs and lower water content when compared with the superficial zone (Buckwalter and Mankin 1997). The deep zone has a thickness greater than 500 μm, making it the thickest of the four zones. Chondrocytes of the deep zone are spherical, and are arranged in columns of four to nine cells, oriented perpendicularly to the joint surface (Meachim and Stockwell 1979). Collagen fibers within the deep zone are arranged perpendicularly to the articular surface. The zone of calcified cartilage separates the radial zone and

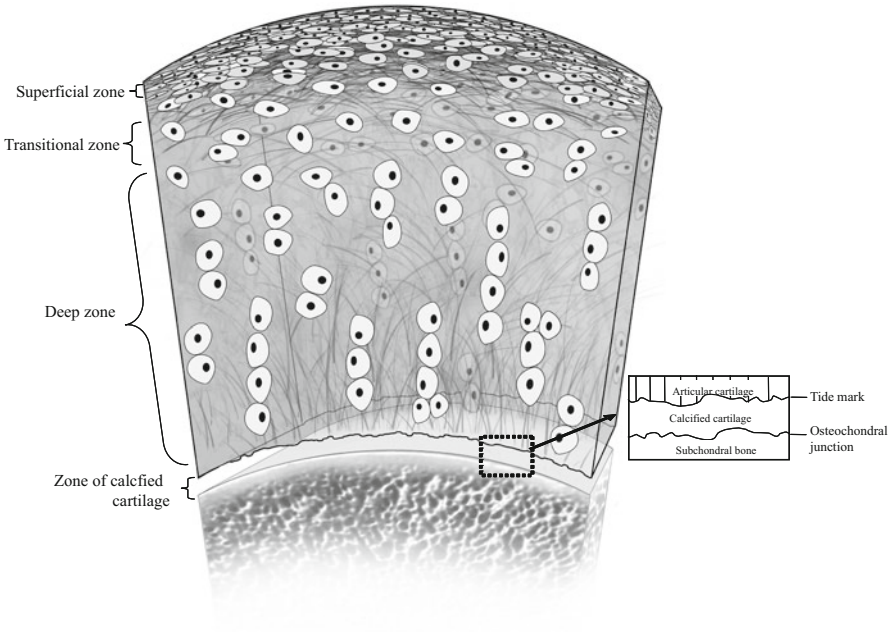


**Fig. 10.1** Structure and composition of cartilage at different depths from the articular surface

subchondral bone. The deep and the calcified zones are separated by the *tide mark*. It is widely believed that the calcified zone of articular cartilage and the *tide mark* present barriers for solute diffusion via the subchondral bone and therefore nutrition is solely from the synovial fluid, via the articular surface (Honner and Thompson 1971; McKibbin and Holdsworth 1966). Evidence does exist, however to suggest the contrary, in that molecules can travel across to the articular cartilage. Notably, most of these studies have used immature synovial joint, and it is generally accepted that the route for nutrient delivery to the articular cartilage is affected by skeletal maturity (Honner and Thompson 1971). Compared to the deep zones, cells in the calcified zone have a smaller volume, and are associated with fewer Golgi membranes and endoplasmic reticula in the cytoplasm, thus suggesting a reduced metabolic activity (Buckwalter and Mankin 1997).

### *10.1.4 Cartilage Biomechanics*

Mechanically, a healthy articular cartilage acts to limit the contact stresses acting on the underlying bone and provide an extremely efficient low wear bearing surface for smooth movement (Kempson et al. 1970; Mow et al. 1992). For these reasons, cartilage is more deformable than bone, and thus when loaded, can provide a considerable area of contact to support joint loads (Weightman and Kempson 1979).

Interactions between the two main solid components of the ECM have crucial roles in the tissues ability to sustain an applied load (Maroudas 1976; Wong et al. 2000). For example, PG exhibits a swelling capacity, resulting from the negatively charged GAG molecules repelling each other while attracting water and mobile cations. Therefore PG molecules impede the loss of water in the matrix by reducing the tissue's permeability (Quinn et al. 2001). When not loaded, the associated osmotic pressure is balanced by the hydrostatic pressure resulting from the tensile stresses within the network of collagen fibers.

#### 10.1.4.1 Cartilage Loading

When cartilage is loaded, there is a short-lived response that alters the balance between the osmotic and hydrostatic pressures. The internal pressures increase within the joints, producing pressure gradients. Consequently, fluid flows away from the tissue, resulting in an increased in PG concentration (Weightman and Kempson 1979). To minimize this displacement, tensile stresses builds up in the collagen network. As the load is removed from the joint, fluid flows back into the cartilage and it regains its original shape. This response varies with the magnitude and type of load applied (Herzog et al. 1998).

During prolonged loading of cartilage, fluid flows out from the tissue and over time, there is a loss of volume, resulting in a time-dependent creep response. During static loading such as squatting and maintaining a 90° bend, the load transmission is confined to a relatively smaller area of the joint, the contact stress and deformation in this region is considerably greater than anywhere else the joint. Despite the loading rate being lower than that in knee bending exercises, the cartilage is loaded continuously at a local site over a long period, and this can lead to creep-behavior (Eckstein et al. 2000).

#### 10.1.4.2 Creep

The mechanical properties of cartilage can be measured either in creep or stress relaxation. Creep is the slow time-dependent deformation process which occurs after the immediately, elastic deformation of cartilage during load application (Fig. 10.2a). This is then followed by a slow, time dependent increased deformation. The initial deformation is brought about by the tissues' matrix, thus there is no net change to its volume. Moreover, the tissues resistance to deformation is due to the network of collagen fibers. However, the time-dependent deformation, which occurs as the load is maintained, results directly from the imbibition of water from the tissues matrix. As the fluid leaves cartilage, the applied load is transferred from the matrix fluid to the solid components. An equilibrium is established when the load is totally transferred unto the matrix fibers. For creep measurement of cartilage, the tissue is compressed with a constant load and the resulting deformation is recorded.

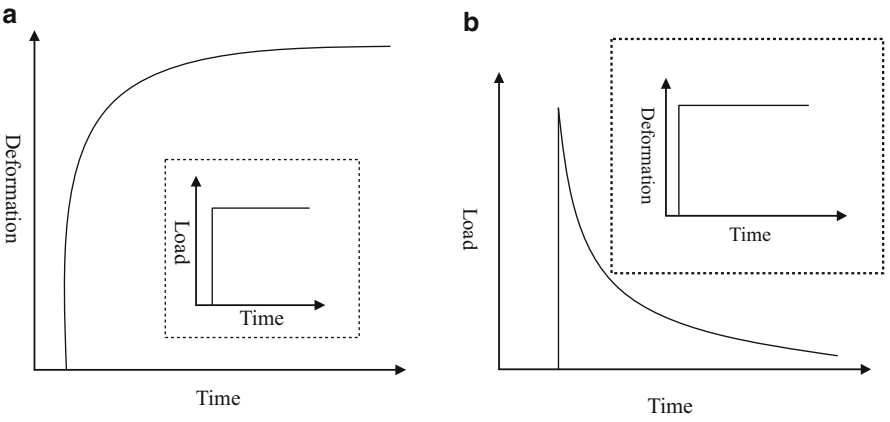


**Fig. 10.2** (**a**) Creep and (**b**) load relaxation measurements of cartilage

#### 10.1.4.3 Load Relaxation

In load relaxation, cartilage is compressed to a constant deformation and the load is measured (Fig. 10.2b). Initially, the load required to maintain a constant deformation is high. This is necessary in order to pressurize the matrix fluid. As the fluid begins to leave the tissue, the load required to maintain the deformation decreases and tend towards a plateau. At this stage, the matrix is compacted and the interfibrillar pore space is reduced. Equilibrium is then established when fluid is no longer exiting the cartilage, and the remaining fluid is redistributed within the tissue. Both the time-dependent creep and load relaxation of cartilage is largely due to the fluid flow, whereas the equilibrium is controlled by the solid matrix. In fact, the equilibrium stiffness of articular cartilage has been tied to the tissues PG content (Jurvelin et al. 1988; Mow et al. 1980).

#### 10.1.4.4 *In Vitro* Mechanical Testing

Three common methods used for determining the mechanical properties of cartilage are confined compression, unconfined compression and indentation testing. In confined compression (Fig. 10.3a), cartilage is placed a non-porous chamber and compressed with a porous platen, so fluid is forced out only via the porous platen. During unconfined compression (Fig. 10.3b) however, cartilage is compressed between two non-porous platens and fluid exits laterally. For indentation tests (Fig. 10.3c), cartilage is compressed with an indenter that is either porous or non-porous. In cases where a porous indenter is used, fluid expelled from the cartilage may flow laterally or axially. However, non-porous indenters impede axial fluid flow.

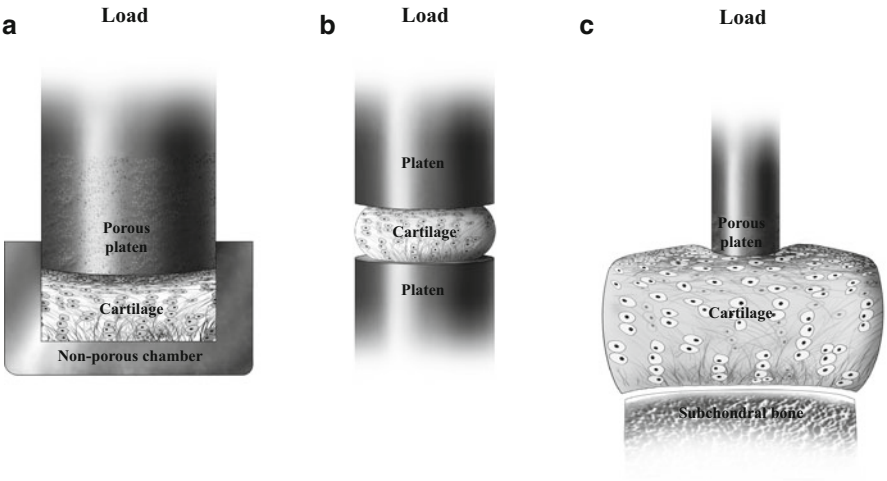


**Fig. 10.3** Schematic representation of experimental setup used for the (**a**) confined, (**b**) unconfined compressive and (**c**) indentation testing of cartilage explants

Although common mechanical parameters may be obtained using any of the three strategies, it has been recognized that the values of mechanical properties are dependent on the measurement technique employed. For example, Hurtig and co-workers (Korhonen et al. 2002) reported that values of compressive stiffness and poisson's ratio of bovine cartilage derived from confined compression were slightly higher than values derived from unconfined compression tests, and values derived from indentation testing were significantly higher than both the confined and unconfined values. This technique dependence of mechanical properties is due to the inhomogeneous structure and anisotropic mechanical properties of cartilage.

#### 10.1.4.5 In Vivo Mechanical Testing

The ability to monitor the health status of an intact cartilage, predict or diagnose osteoarthritis, and monitor the healing process of the tissue after a treatment had necessitated in vivo strategies, be it simple observation, or qualitative or quantitative measurements. Earlier techniques were based on magnetic resonance imaging (MRI). To this extent, Eckstein and co-workers (1999) analyzed the deformation and recovery, as indicated by interstitial fluid flow rate in seven healthy patellae joints. Similarly, O'Byrne et al. (2003) assessed the biochemical composition of cartilage in goat knees, in response to papain injection. The authors were able to demonstrate a compromise of the tissues collagen integrity with the magnetic resonance technique. This dose-dependent degradation was confirmed by post-mortem biochemistry and histology.

High-frequency ultrasound and mechanical indentation in now commonly combined to measure both structural and mechanical parameters, such as stiffness, and thickness, respectively. In an example, Kiviranta et al. (2008) compared the dynamic stiffness of healthy and degenerated patella cartilage, thereby diagnosing early stages of OA. In a similar study, Nishitani et al. (2008) were able to arthroscopically determine the thickness and surface roughness of ten male athletes while undergoing mosaicplasty for osteochondritis dissecans.

### *10.1.5 Modelling Theories for Articular Cartilage*

During indentation tests, after a sudden application of constant load on cartilage, a rapid compression takes place, which is then followed by a slow creep process towards equilibrium at a rate which is governed by the applied load and test conditions (Mow et al. 1984). Early explanations for this viscoelastic behavior did not take into account the interstitial fluid flow and internal redistribution of the organic matrix and the compaction within the cartilage specimen. Although the possible influence of the multiphasic nature of cartilage on its deformational characteristics was realized by Hirsch (1944) as early as 1944, the role of fluid flow on the dynamic deformational behavior of articular cartilage was not recognized until later. One of these studies (Elmore et al. 1963) showed that the creep response observed in indentation testing of cartilage was largely due to the efflux of interstitial fluid from the tissue. They also observed that upon removal of the load, complete recovery of the tissue occurred only if sufficient fluid was available to re-imbibe into the tissue. Indeed, Linn and Sokoloff (1965) recorded a positive correlation between creep response and the amount of fluid exuded from cartilage tissue. Such studies stimulated a range of models describing both physicochemical and mechanical properties of cartilage.

#### 10.1.5.1 Biphasic Theory

The biphasic model depicts cartilage as a soft, porous and permeable material comprising 20 % (wt/vol) of elastic solid, and filled with an incompressible fluid (Mow et al. 1980; Torzilli and Mow 1976). The model accounts for the effect of the drag forces arising from the relative motion between the fluid and solid phases. It incorporates all existing known mechanical properties of cartilage, namely, inhomogeneity, anisotropy, stress-strain non-linearity, interstitial fluid flow and finite deformation. However, several assumptions are associated with the theory (Mow et al. 1992), namely,

- The solid matrix is porous, permeable, and elastic.
- The solid matrix and interstitial fluid are intrinsically incompressible; i.e. volume change of the tissue as a whole is possible only if there is fluid exudation or imbibition.

- Frictional drag is directly proportional to the relative velocity between the interstitial fluid and the porous-permeable solid matrix – the proportionality coefficient is the drag coefficient [*K*], which may be strain-dependent.
- The frictional drag of the interstitial fluid flow is the dominant mechanism controlling tissue viscoelasticity in compression.

A modified, general form is the Kuei, Lai and Mow biphasic theory for cartilage. This form differs to the previous by the addition of more constitutive assumptions, such as an infinitesimal strain, linear, isotropy, constant elastic coefficients, and constant or strain-dependent permeability. However, some authors have associated the biphasic theory with inherent flaws (Brown and Singerman 1986). In particular; the theory relies on the ability to define the distinct phases, which is problematic as there are no distinctive barriers between the matrix and the fluid components. When applied to the prediction of creep behavior of an isotropic, homogeneous and linearly elastic material undergoing small strain deformation the biphasic theory was found to be inadequate. For example, it was incapable of modelling the substantial portion of the transient phase of cartilage response when load under a slow rate in unconfirmed compression.

#### 10.1.5.2 Triphasic Theory

It has been observed that when unloaded cartilage specimens are soaked in a sodium chloride (NaCl) solution at constant temperature, the tissue dimensions decrease exponentially with increasing NaCl concentration. The influence of ionic movements in cartilage on its swelling and deformational behavior has long been recognized (Maroudas 1979). This has led to the development of the triphasic theory. The theory couples both the physicochemical aspects of cartilage swelling and the biphasic view of solid matrix deformation and interstitial fluid flow. The theory describes the equilibrium free swelling and confined compression behavior of cartilage and other soft hydrated tissues. In this theory, cartilage is considered as a mixture of three phases: an *incompressible solid phase*, which is the matrix, consisting of collagen and PG, *an incompressible fluid phase*, which is the interstitial water, and an *ionic phase* of two species of a single salt, the cations and the anions. The theory can be applied to equilibrium as well as transient problems, and has been found capable of predicting the stress-strain fields in the solid matrix, the interstitial fluid flow along with the distribution of the ions, and fluid pressure (Gu et al. 1997; Lai et al. 1991).

#### 10.1.5.3 Poroviscoelastic and Poroelastic Theories

Both the biphasic and triphasic theories fail to incorporate the anisotropy and viscoelasticity of cartilage, which are of great importance when determining cartilage mechanical properties. To this extent, several models exist, whose details are

beyond the scope of the present review. More relevant is the consideration of the interfibrillar pores in cartilage, which control the transport of soluble nutrients and the flow-independent viscoelasticity of cartilage mechanical and physicochemical properties. These are described by the poroelastic and the poroviscoelastic theories.

The poroviscoelastic model describes the viscoelasticity exhibited by cartilage with a combination of a fluid flow-dependent, fluid flow-independent mechanisms and the intrinsic viscoelasticity of the solid matrix (Mak 1986). In the poroelastic model of cartilage, the tissue is modelled as an isotropic solid matrix containing fluid-saturated pores, entrapped by a fibrillar network. Both the solid and the fluid phases are assumed to be incompressible. The structure is defined by the Young's modulus, Poisson's ratio of the matrix and the hydraulic permeability. The model assumes that the hydraulic permeability depends on the dilatation of the bulk material. The fibrils are evenly distributed in the radial, circumferential and axial directions forming an elastic constituent attached to the porous matrix and that the stiffness of the fibrillar network depends on the longitudinal strain of the fibrils. These fibrils have no resistance to compression and the effect of lateral deformation of every single fibril is neglected (Li et al. 1999).

## *10.1.6 Pathologies*

### 10.1.6.1 Mechanical

Single and multiple blunt impacts on cartilage yielding 20 % strains at strain rate of 6.7 %.s$^{-1}$ have been found to cause destruction of bovine metacarpal cartilage. Moreover, strains of 40 % and above have evidently caused surface defects, correlating to collagen network failure and cell death. However, cartilage has been shown to survive impacts yielding less than 10 % strain, with no injury to chondrocytes on their ECM (Radin et al. 1970; Repo and Finlay 1977). On the other hand, low impact may lead to cell death despite structural integrity being maintained (Duda et al. 2001).

Defects of articular cartilage may or may not reach the surface of the underlying bone. In care of the latter, these are termed chondral, or partial thickness defects. Some of these superficial lesions result from surgical procedures (Rosenberg 1971; Thompson 1975). Full thickness lesions, also termed osteochondral defects (Fig. 10.4), cross the tidemark of articular cartilage and violate the underlying subchondral bone. In doing so, they have access to cells in the bone marrow cavities.

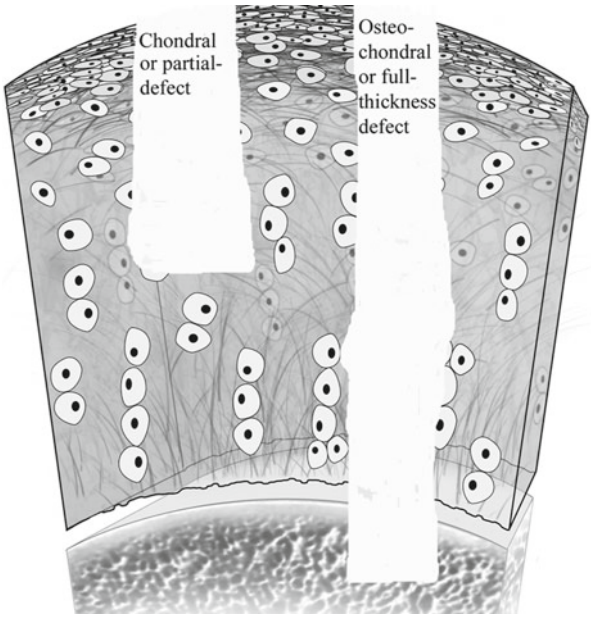


**Fig. 10.4** Schematic representation of full and partial thickness defects in articular cartilage

#### 10.1.6.2 Degenerative and Non-Degenerative Diseases

Common diseases, which affect the health and functionality of the joint, are osteoarthritis (OA), rheumatoid arthritis (RA), chondromalacia and disuse atrophy. OA is a slowly progressive disorder of unknown cause (Mankin 1974a), which generally occurs later in life, principally affecting major weight-bearing joints. It is characterized clinically, by pain, deformity and reduced mobility, and pathologically, by features including focal erosive lesion, cartilage destruction, subchondral sclerosis, cyst formation, and large osteophytes at the margins of the joints. With the progression of OA, cartilage exhibits histological, biochemical and metabolic changes, although their precise nature frequently depends on the underlying abnormality and the duration of the disease progression. At the early stages of the disease, the tissue erodes, disappearing completely from the focal areas of the surface, leaving a denuded, sclerotic and eburnated bone. Type II collagen degrades beneath the articular surface, and their organization is disrupted. Consequently, the tissue depletes in stiffness and strength and fibrillation follows (Mow et al. 1992).

RA typically affects many different joints and can be chronic in nature. This systemic disease affects the entire body and is one of the most common forms of arthritis. It is characterized by the inflammation of the membrane lining the joint, causing pain, stiffness, warmth, redness, and swelling. In a similar manner to OA, there is degradation of type II collagen, particularly around chondrocytes in the deep zones, rather than directly beneath the articular surfaces (Mow et al. 1992). PGs are also degraded, but can be partly replaced. Eventual cartilage thickness is reduced due to its exposure of migrating cytokines, produced in the adjacent subchondral bone, resulting in the erosion of underlying calcified cartilage and bone.

Pathological diseases of the articular cartilage are not necessarily confined to the elderly. Indeed, any form of joint immobilization, for example following an injury or surgery, will lead to tissue atrophy and joint stiffness. These conditions can be reversed with joint remobilization, starting with gentle exercise, which gradually increase in intensity. Another non-degenerative disease is chondromalacia patella, which is often caused by trauma, overuse, part misalignment or muscle weakness. Instead of gliding smoothly, the patella translates across the femur, thereby roughening the cartilage underneath the patella. The damage may range from a slight abnormality to a complete wear of the associated cartilage surface. Traumatic chondromalacia occurs when a blow to the patella bone tears off either a small piece of articular cartilage or a large fragment containing a piece of bone. The latter is termed an osteochondral fracture. Clinically, the process results in mild to moderate pain and stiffness. The resulting changes resemble those of mild OA, with fibrillation, surface irregularities and cartilage erosion (Mankin 1974b).

## 10.2 Repair and Regeneration Strategies

### *10.2.1 Response to Injuries*

The effects of mechanical injuries to articular cartilage vary considerably, depending on its nature and severity. Its response to superficial defects, which violate neither its calcified layers nor the underlying bone typically lack inflammation of the cartilage, and has limited potential for self-repair (Buckwalter 1998; Mankin 1982). Characteristically, there is minimal attempt on the part of the cartilage to elicit cellular or matrix repair (Calandruccio and Gilmer 1962; Campbell 1969; DePalma et al. 1966). However, cartilage responds to lacerative injuries with an enhanced mitotic activity adjacent to the defect margins. This is associated with increased synthesis of the matrix components (Mankin 1962).

When a cartilage defect affects the vasculature of the subchondral bone, an enhanced biological response is elicited. This repair response is equivalent to that of other vascularized tissues in the body (Mankin 1982), filling the whole defect cavity with blood. In the proceeding events, a blood clot is formed, which contains both red and white blood cells, undifferentiated cells and marrow elements (DePalma et al. 1966). However, only the bone defect is filled with the new bone, and is fused

with the cartilage defect, with its edges united by the vascular fibrous tissue (Calandruccio and Gilmer 1962; DePalma et al. 1966). As observed with superficial defects, brief synthetic activities take place in the remaining cartilage, during which a small amount of cells and matrix is produced, replacing some of that lost to the initial damage (Mankin 1962, 1982).

The quality of the repaired cartilage is dependent on the initial defect size. For example, defects less than 3 mm in diameter often repair completely after 3 months and are difficult to locate after 9 months (Convery et al. 1972). However, defects 9 mm or larger may not completely repair. It has also been demonstrated that the site of an old osteochondral laceration may clearly be visible years after injury as a slightly discolored, roughened pit, or linear grooves on the otherwise smooth surface adjacent to the defect site (Bennett and Bauer 1935; Campbell 1969; Key 1931).

### *10.2.2 Non-invasive Therapies*

Different interventions exist for the management of cartilage damage. The most topical of these are lifestyle changes, pharmacological and surgical methods. The emphasis on lifestyle becomes highly relevant due to the high contributions of obesity, and abnormal loading on the development and progression of osteoarthritis. Acute joint injuries, fractures of articular surface, along with tears of the meniscus and ligaments are all linked with osteoarthritis. Occupation and nutrition have also been deemed strong factors in degenerative cartilage diseases (Cooper et al. 1992; Felson and Zhang 1998; Lievense et al. 2001). For example, strong evidence exists, which suggests that the risk of OA doubles after 10 years of farming (Jensen 2008). Additionally, occupations which involve kneeling, squatting or heavy lifting also accelerates cartilage degeneration. Therefore, strategies such as weight control, recreational exercise, and injury prevention are all common interventions adopted as least-invasive therapies. More specific, exercises such as quadriceps strengthening; stretching and aerobic exercises are commonly prescribed for treatment of hip and knee OA (Bukowski et al. 2006; Hochberg et al. 2012; Jansen et al. 2011; Roddy et al. 2005). Other examples are ultrasound (Soren 1965; Welch et al. 2001) and acupuncture (Brinkhaus et al. 2007; Lin and Chen 2009; Reinhold et al. 2008).

Pharmacological interventions play a vital role in pain relief to OA patients. For mild or moderate pain, acetaminophen (paracetamol) is a common choice recommended by physicians (Towheed et al. 2006; Wegman et al. 2004). In the 2014 Osteoarthritis Research Society International (OARSI) guidelines for the non-surgical management of knee osteoarthritis, acetaminophen treatment is deemed appropriate as a short-term analgesic for knee OA pain, however conservative dosing and treatment duration consistent with approved prescribing limits is recommended (McAlindon et al. 2014). Other non-steroidal anti-inflammatory drugs (NSAID) such as naproxen and ibuprofen used for patients with either hip or knee OA have been found to be superior to paracetamol, in bringing pain relief, albeit,

at a higher health risks. However, both analgesics have been associated with discomfort, perforation, and bleeding of the gastrointestinal tracts (Chou et al. 2011; Zhang et al. 2004). Both paracetamol and NSAIDs work by inhibiting the actions of cyclo.oxygenase-1 and -2, thereby, relieving the patients of pain. As the disease progresses and the pain persists, intra-articular injection of corticosteroids can lead to a significant short-term decrease in pain (Bannuru et al. 2009; Bellamy et al. 2006). Other pharmacological interventions include chondroitin and glucosamine (Dahmer and Schiller 2008; Matsuno et al. 2009; Owens et al. 2004; Sawitzke et al. 2008). These glycosaminoglycans are taken as food supplements either alone or in combination with each other. However, it's beneficial effect both in terms as pain relief drug and disease-modifying osteoarthritis drug (DMOAD) is controversial and under constant debate (Henrotin et al. 2014) and they are labelled as having an uncertain appropriateness as analgesia for knee OA and not recommended as disease modifying OA treatment by the OARSI (McAlindon et al. 2014) nor by the American College of Rheumatology (ACR) (Hochberg et al. 2012). Although the benefits towards pain and physical function in knee OA of intra-articular injection of hyaluronic acid is controversial and currently its use for knee OA treatment is considered uncertain by the OARSI (McAlindon et al. 2014).

### *10.2.3 Surgical Interventions*

In cases where non-invasive therapies are not possible, due to substantial cartilage damage, or detachment of cartilage fragments, surgical procedures are undertaken. These include joint lavage, subchondral stimulation, autogenic and allogenic transplantation and cell transplantation, performed either arthroscopically or with an open joint surgical approach.

#### 10.2.3.1 Arthroscopic Cleaning

Arthroscopic procedures, such as lavage, involve thorough rinsing of the joint cavity with Ringer solution, lactate and sodium chloride solutions. Such a palliative approach is designed to reduce the degree of pain experienced by the patient. In the main, this strategy is successful, although the biological reasoning for pain relief is not established (Anderson et al. 1993; Chang et al. 1993; Gillespie and O'Connell 1992; Livesley et al. 1991). However, there are limits to its application, particularly with OA patients whose pain relief is generally considered to be a result of a placebo effect (Gibson et al. 1992; Moseley et al. 1996).

Other arthroscopic strategies include chondral shaving and debridement also called chondroplasty. The aim is to remove loose and unstable remains of damaged and fibrillated articular cartilage to a smoother surface while avoiding any damage to the healthy surrounding cartilage. As with lavage, the biological rationale behind each of these two procedures remains unclear. Indeed, cell loss along the lesion

borders of the remaining cartilage has been reported to follow chondral shaving, which is counter-productive for cartilage repair (Kim et al. 1991; Mitchell and Shepard 1987; Tew et al. 2000). In addition, debridement has been reported to be associated with skeletal misalignment and shown clinically to exacerbate the osteoarthritic condition (Messner et al. 2000). Both procedures can be carried out using a gentle cutting instrument incorporating laser light at a specific wavelength. Although the laser is useful for welding and fusing the tissue, performing a chondral shaving or a debridement using laser offers little advantages over mechanical cutting method (Vangsness and Smith 1995).

#### 10.2.3.2 Subchondral Stimulation

A common repair strategy recommended for superficial defects, involves surgically accessing the adjacent bone-marrow spaces along with the bone and the vascular spaces so that residing bone marrow mesenchymal stromal cells can migrate into the cartilage defect. Examples of such procedures include Pridie drilling, abrasion arthroplasty and microfracture techniques. The three procedures are very similar, and start with a chondroplasty followed by a procedure to access the bone marrow. Pridie pioneered the drilling procedure by drilling with a Kirschner wire (K-wire) in the subchondral plate at the cartilage lesion (Insall 1967). Abrasion arthroplasty is similar to Pridie drilling, but instead of using a drill or wire, a high speed burr is used to reach the subchondral bone marrow space. The microfracture technique introduced by Steadman and his team (Steadman et al. 2003, 1999), is a refinement of the Pridie drilling. The approach starts with the debridement to a stable cartilage margin followed by a careful removal of the calcified cartilage layer while taking care of not damaging the underlying subchondral bone. Finally, using a sharp instrument, called an awl, subchondral bone perforations are made over the entire cartilage lesion approximately 3 mm apart to a depth of 4 mm. This should result in a defect filling with a well-anchored mesenchymal clot. The rehabilitation protocol, which includes quick mobilization of the joint after surgery by continuous passive motion, is an important part of the microfracture procedure (Steadman et al. 2003). Moreover, the holes are relatively small (1.0–2.0 mm diameter) when compared to Pridie drilling who recommended using wires of a quarter inch (6.35 mm) in diameter (Insall 1967).

By penetrating the subchondral bone beneath the defect, the void is immediately filled with a fibrin clot which, within 2 days adheres to the bony compartments of the wound, as opposed to the cartilaginous tissue. By the fifth day, mesenchymal stem cells have penetrated and completely resorbed the fibrin clot, filling the void. Thereafter, between days 10 and 14, the cells differentiate into chondrocytes and lay down a PG-rich matrix. By 8 weeks, the repair tissue begins to resemble normal cartilage and forms a continuous surface with the surrounding native tissue by approximately 6 months. However, by 12 months, there is generally evidence of degradation of repair tissue (Hunziker 1999; Wyre and Downes 2000).

Arthroscopic microfracture has increasingly replaced subchondral drilling as marrow stimulation technique in the clinical situation. However, it has to be noted that microfracture does not restore normal hyaline cartilage but primarily results in fibrous or hybrid repair cartilage tissue with variable repair tissue volume (Mithoefer et al. 2009). A long-term follow-up study by Steadman's team also indicates, that the success rate of the technique is dependent on the age of the patients and improved functional outcome and less pain is mainly seen in patients under the age of 35 years treated for isolated full-thickness chondral defects (Steadman et al. 2003). Two different routes are currently under investigation to improve the outcome of the bone marrow stimulation technique. On the one hand, research is directed to optimize the technique of drilling. Especially the drill hole size and drill depth are being addressed. The aim is to have ample access to the bone marrow, while drill hole diameters better mimic the normal physiological trabecular distance (Benthien and Behrens 2013; Eldracher et al. 2014; Min et al. 2013). On the other hand, the procedure of subchondral stimulation in combination with defect filling with a scaffold, to offer the infiltrating cells a substrate from where to repopulate the defect area, is another hot research topic (Sharma et al. 2013; Zantop and Petersen 2009).

There is an inherent discontinuity between the repair tissue and the surrounding cartilage, as the collagen fibrils within the two compartments fail to integrate. Additionally, some PGs in the cartilage matrix exhibit anti-adhesive properties, and hinder the bonding between the repair and the native cartilage tissues. The employment of abrasion chondroplasty for cartilage defects in rabbits and dogs have resulted in the formation of cartilage-like tissue, which originated from the subchondral bone (Altman et al. 1992; Kim et al. 1991), though other studies report the presence of significant quantities of fibrous cartilage (Furukawa et al. 1980). It has also been reported that the, repaired full-thickness cartilage lesion in rabbits are more durable following the Pridie drilling when compared to the abrasion chondroplasty strategy (Menche et al. 1996). Indeed the Pridie approach has been reported to be of great benefit to patients with conditions such as osteochondritis dissecans and gonathrosis (Pedersen et al. 1995), yielding both pain relief and restored joint function (Beiser and Kanat 1990; Goldman et al. 1997). The microfracture technique, being a minimally invasive arthroscopic procedure is relatively less disruptive to the subchondral bone. Nonetheless, its employment in treating young athletes and horses has resulted in an improved joint function and pain relief (Frisbie et al. 1999; Sledge 2001).

#### 10.2.3.3 Tissue Grafting

The transplantation of cartilage into defect sites has been a viable strategy for several decades (Cohen and Lacroix 1955). The transplanted cartilage may be sourced autologously or extracted from human cadavers. In autologous cartilage transplantation, plugs of cartilage biopsy are extracted either from adjacent to the defect (periosteal) or from the rib (perichondral). These are either sutured or glued to the defect floor, such that the defect may be stimulated to form repair cartilage that

binds to the transplant, forming a continuous neo-tissue over the entire defect (Ohlsen 1976). Another more common autologous grafting procedure is the osteochondral autograft transplantation (OATS). When multiple small cylindrical autogenous osteochondral plugs are fitted together in the defect, the term autologous osteochondral mosaicplasty is used. These autologous biopsies are retrieved from low-weight-bearing areas and transferred to the defect. In contrast to marrow stimulation procedures, which result in fibrocartilaginous tissue, OATS aims to restore functional hyaline cartilage. With this technique, joint function and pain relieve have been reported to reach 80 % of cases (Bouwmeester et al. 1997; Homminga et al. 1990; Korkala and Kuokkanen 1991; Moran et al. 1992). Moreover, these strategies are advantageous because they minimize disease transfer and immunological rejection, which are commonplace with allografts from another donor. For these reasons, autografts have produced treatments with survival rates up to 70 % at 2–5 years (Temenoff and Mikos 2000). To minimize donor side morbidities, these explants are taken from non-load-bearing region of cartilage. When implanted in the defect the cartilage is often unable to withstand forces imparted at joint surfaces. Due to its lack of mechanical integrity, the matrix of the implant and cartilage in the vicinity of the defect breaks down to the extent that the implant and associated regions later exhibit signs of osteoarthritis. Additionally, this breakdown also occurs at the donor site (Kim et al. 1991; Mitchell and Shepard 1987), often necessitating undesirable and expensive second operation. The amount of autograft that can be harvested is limited, thus the technique is often unsuitable for clinical-sized defects.

Alternately, allogenic osteochondral grafts obtained from human cadavers have been used to fill cartilage defects. Unlike autologous grafts, no biological interaction is predicted between the transplant and its surrounding cartilage, such that the primary role of the transplant is to fill the defect site and replace the lost tissue volume. This approach has benefited patients with large osteochondral defects, particularly caused by trauma and osteo-necrosis. The benefits of osteochondral resurfacing in the human knee joint has been observed to last for many years (Bakay et al. 1998; Bell et al. 1994), with reported success rates around 80–85 % after 10 years (Levy et al. 2013; Mahomed et al. 1992; Meyers et al. 1989). Fresh osteochondral allografting is associated with inherent challenges related to availability of suitable donor tissue and donor tissue retrieval and storage. Although, adverse immunological reactions are associated with this procedure, the survival of allogenic transplants may be prolonged with the use of immunosuppression and histocompatibility techniques (Hickey et al. 1994; Stevenson 1987; Stevenson et al. 1989). General potential limitations related to both autologous and allogenic osteochondral grafting include differences in orientation, thickness, and mechanical properties between donor and recipient cartilage. In addition, absence of fill and the potential dead space between cylindrical grafts may limit the quality and integrity of the repair (Bedi et al. 2010).

The perichondrium, which is a dense membrane composed of fibrous connective tissue that closely wraps cartilage (except for the articular cartilage, which is covered by the synovial membrane) has been implanted unto cartilage defects in the human joints (Homminga et al. 1990; Kwan et al. 1989). These autologous

scaffolds were advantageous because they naturally contain autogeneous cells that are useful for cartilage repair. However, in addition to the limited availability of harvest sites, the neo-cartilage formation resulting from these grafts have been deemed unsatisfactory in patients over the age of 40 (Seradge et al. 1984). Moreover, regenerates formed from these scaffolds do not completely fill the defect and tend to detach and ossify (Hendrickson et al. 1994; Homminga et al. 1990).

#### 10.2.3.4 Cell Transplantation

Isolated chondrocytes have been transplanted into articular cartilage defects for its repair. However, such an approach typically has a success rate of less than 40 %, as the cells are not retained within the defect site for sufficient period to produce neo-ECM (Temenoff and Mikos 2000). On the other hand, mesenchymal stem cells from the skeletal muscle of adult rabbits, seeded onto porous polyglycolic acid (PGA) mats have also been implanted into non-weight bearing defects in the rabbits femoropatella groove. The PGA matrix biodegrades and the stem cells remain in situ, producing a cartilage-like tissue containing type II collagen and subchondral bone that is morphologically similar to native tissue (Grande et al. 1997; Martin et al. 1999). However, in a similar approach using mesenchymal stem cells and collagen gel for cartilage defects in osteoarthritic human knees limited clinical improvement was observed after 42 weeks (Wakitani et al. 2002).

#### 10.2.3.5 Autologous Chondrocyte Implantation (ACI)

Since its first clinical application for treating deep articular cartilage defects in the knee (Brittberg et al. 1994), ACI has been a fairly successful approach for treating cartilage defects (Peterson et al. 2010). The technique involves harvesting a healthy portion of cartilage, usually from a non-load bearing region of the patient, and enzymatically degrading the tissue to isolate the cell population. These cells are expanded in vitro to a sufficient density for implantation. In the first generation ACI, a periosteal patch is sutured over the debrided cartilage defect and the cells are injected in the defect. The injection site is closed with a suture and covered with fibrin glue (Peterson et al. 2010). Presently a collagen membrane is used as a cover, minimizing peri-operative morbidity and eliminating hypertrophy of the periosteal flap (Benthien and Behrens 2011). The cells used in the repair may either originate from the chondrocytes in the host-extracted cartilage, its precursor cells from the periosteum or possibly mesenchymal stem cells of the subchondral bone (of the defect site) had this been injured. The use of ACI has resulted in an improved joint function for at least 72 % of patients at 1 year post-operatively (Bentley et al. 2003; Minas 1998) and 84 % of patients at 3 years post-operatively (Micheli et al. 2001). In a 10 years follow-up study of cartilage knee lesions treated with ACI, 26 % of the patients experienced graft failure at a mean of 5,7 years after ACI. Of the 73 patients that did not fail, 88 % had an excellent to good outcome 10-years post-implantation.

It is known that the clinical results of ACI as the primary articular cartilage repair technique are superior to the results obtained when ACI is used as a salvage option after failure of marrow-stimulating techniques. This could account for the relative high failure rate in this 10-year follow-up study (Biant et al. 2014). ACI has been used for treating defects in other joints such as hips and ankles (Giannini et al. 2001; Romeo et al. 2002). The use of ACI as an alternative treatment to surgical excursion, allogenic grafting and autografting (Peterson et al. 2003) has been discussed to provide long-term joint restoration and pain relief for patients with osteochondritis dissecans.

Although quite successful, the ACI technique has been constantly optimized to overcome some of the surgical and biological short-comings of the procedure. Since the late 1990s matrix-assisted autologous chondrocyte transplantation (MACT) was introduced in the clinics (Behrens et al. 2006; Schneider et al. 2011). In this procedure, the cells are no longer injected as a suspension in the defect, but seeded onto a biomaterial that fills the defect. The surgeon no longer needs to worry about handling and retaining the chondrocyte cell suspension under the leakage preventing periosteal seal. The cells will colonize the biomaterial in vitro and will start to produce their own matrix prior to implantation. Some used biomaterials even promote cartilage regeneration (Filardo et al. 2011; Zeifang et al. 2010). ACI and MACT will not result in true native tissue regeneration, but in pain relief and formation of fibrocartilage and/or articular cartilage and therefore delay OA and its adverse effects (Ringe et al. 2012).

### *10.2.4 Tissue Engineering*

Despite the numerous strategies available for treating cartilage defects, there is yet to be a standardized solution for restoring long term function, especially due to the large variability of defects to be treated. This limitation has encouraged a more sophisticated tissue-engineered approach (Ringe and Sittinger 2009). Tissue engineering combines the principles of cell and molecular biology with material technology, to create a new tissue, which has the potential to physically and biologically mimic its predecessor and restore function to the damaged tissue. Key activities in this approach are the attainment and expansion of cells and the development of scaffolds that act as carriers for the cells.

#### 10.2.4.1 Chondrocytes

An important step in tissue engineering is the isolation and expansion of cells that are to be transplanted. The cells must be both appropriate for the intended tissue and of sufficient quantity to treat clinical-sized defects (LeBaron and Athanasiou 2000), whilst being free of pathogens and contamination. Cells sources can be either autologous, allogenic or xenogenic, the latter being derived from a different animal species.

Each approach has specific benefits and shortcomings (Breinan et al. 2001; Ma et al. 2005; Masuoka et al. 2005; Ostrander et al. 2001; Pavesio et al. 2003). For example, although autologous cells are free from immuno-related problems, they are relatively few in numbers and cell harvesting could lead to morbidity at the donor site. Also the age of the chondrocyte needs to be considered, since chondrocytes from older patients are metabolically less active in vitro (Dehne et al. 2009). Thus the autologous approach does not effectively lead to a readily available off-the-shelf solution.

Allogenic and xenogenic cells may be extractible in large numbers and are available off-the-shelf, but these are associated with immunological problems and in the case of xenogenic cells, there is often the possibility of animal virus transmission (Sirlin et al. 2001). Tissue-engineered constructs derived from these cells require additional steps to incorporate immune acceptance. In general one of the major drawbacks is that chondrocyte expansion in a monolayer is characterized by dedifferentiation of the cells to a fibroblast-like phenotype, causing a decreased proteoglycan synthesis and collagen type II expression and an increase in type I collagen (Goessler et al. 2005; Minegishi et al. 2013).

#### 10.2.4.2 Stem and Progenitor Cells

**A chondroprogenitor population** resides in articular cartilage and has been shown to possess superior migration abilities (Schminke and Miosge 2014; Seol et al. 2012). Upon in vitro chondrogenic differentiation in 3D pellet culture, there is no expression of hypertrophic markers nor of calcification (Williams et al. 2010). The surface marker CD166 has been identified as a marker for this chondrogenic progenitor population that predominantly resides in the superficial and middle zone of articular cartilage (Pretzel et al. 2011).

**Multipotent stem cells** have been proposed to be a vital source of cells for tissue engineering applications. In a similar manner to differentiated cells, stem cells may either be autologous, allogenic or xenogenic in nature. Since mesenchymal stromal cells (MSC) show immunosuppressive properties they are being applied allogeneically in clinical settings today without the need of immunosuppression treatment. Stem cells offer the benefits of being able to be multiplied extensively, yielding high cell number; from which, the desired number may be extracted and differentiated into chondrocytes. The remaining stem cells may be further multiplied for future use. The intervention is simple, but cell preparation is expensive. As an example, mesenchymal stem cells derived either from the bone marrow and other adult connective tissues (Friedenstein et al. 1976) may differentiate to a selected range of cells including chondrocytes, osteoblasts, tenocytes or myocytes, irrespective of their origin (Jones et al. 2002; Minguell et al. 2001; Pittenger et al. 1999; Yoo et al. 1998). The most obvious stem cell source for articular cartilage regeneration are the MSC population that reside in the bone marrow. Moreover clinical trials are also underway to look at the use of umbilical cord derived MSCs and adipose

tissue MSCs. Currently 26 clinical studies are registered in the ClinicalTrial.gov database with a focus on articular cartilage and mesenchymal stem cells. One of them, has reported on a 2 year follow-up of intra-articular injections of bone marrow-derived MSCs for the treatment of knee osteoarthritis. Based on a small patient cohort (12 patients) their preliminary results reaffirm that autologous MSC may be a valid alternative for AO treatment because it attains effective and durable pain relief and objective cartilage improvement (Orozco et al. 2014). The same group also looked at the efficacy of using allogenic MSCs in 15 knee OA patients and compared the treatment against intra-articular hyaluronic acid injections. Although the procedure resulted in significant relief of pain and disability, and quantitative MRI evidence indicated partial articular cartilage healing, the effects appeared to be somewhat smaller than those reported for treatment with autologous MSCs (Vega et al. 2015). Besides the bone marrow, also other tissues in the joint harbor mesenchymal stem cells that have the potential to differentiate into chondrocytes and could contribute to the healing of articular cartilage lesions, including the synovium, the synovial fluid and the infrapatellar fat pad (Chang et al. 2013; Felimban et al. 2014; Suzuki et al. 2012).

**Pluripotent stem cells** such as embryonic stem cells (ESC), derived from the inner cell mass of the embryonic blastocyst and induced-pluripotent stem cells (iPSC) offer great potentials for tissue engineering. Directing human ESC through a step wise differentiation protocol over intermediate developmental stages, allows for a successful end-differentiation into chondrocytes. Aggregates of these ESC–derived chondrocytes produced a collagen type II and sulfated GAG rich matrix without the evidence of hypertrophy (Oldershaw et al. 2010). However, there are ethical and legal concerns with using human embryonic cells. For this reason, much of the research has been conducted on animals (Fuchs et al. 2005; Kramer et al. 2006). iPSC are generated by transducing adult somatic cells with reprogramming factors (c-MYC, KLF4,OCT3/4 and SOX2) to make them pluripotent and as such rejuvenate somatic cells (Takahashi and Yamanaka 2006). It was shown that after 21 days of in vitro chondrogenic differentiation of human iPSC cells a significantly higher GAG content and gene expression of collagen type II and aggrecan was detected compared to human bone marrow-derived MSCs and the expression of hypertrophic and osteogenic markers was very low. Implantation of these 21 day differentiated iPCS cells in a cartilage lesion in immuno-deficient rats resulted after 12 weeks in good restoration of the articular surface, albeit with a reduced amount of proteoglycans compared to the adjacent healthy tissue (Ko et al. 2014). The use of viral vectors to incorporate these reprogramming factors causes a major concern towards their clinical application. Optimization of the transfection step is ongoing to generate transient expression of the reprogramming factors (Tsumaki et al. 2015). Although possessing a tremendous potential as cell sources for tissue regeneration, iPSC and hESC applications currently are not a realistic clinical option in the foreseeable future because of ethical and regulatory issues and the potential of teratoma formation (Ringe et al. 2012).

#### 10.2.4.3 Stimulatory Biochemical Factors

Several cytokines, hormones and growth factors are known to influence chondrocyte behavior and chondrogenesis and have been incorporated in various cartilage tissue engineering strategies. Especially the members of the transforming growth factor (TGF) superfamily such as TGFβ1, TGFβ2 and TGFβ3 induce chondrocyte proliferation and promote ECM production and TGFβ1 and TGFβ3 promote chondrogenesis of MSCs. Also certain bone morphogenic proteins (BMP), especially BMP-2 and BMP-7, promote chondrogenesis of MSCs and increase matrix production by chondrocytes and MSCs. Insuline growth factor-1 (IGF-1) enhances proteoglycan and type II collagen production, while fibroblast growth factor-2 (FGF-2) is added to the culture medium to stimulate the expansion of chondrocytes (Barry et al. 2001; Fukumoto et al. 2003; Hicks et al. 2007; Kock et al. 2012). However, the dose and administration timing does play an important role in governing chondrogenesis.

Recent developments in the tissue engineering domain focus on the delivery of chemokines at the side of injury to mobilize endogenous stem cells and as such stimulate tissue repair. The body possesses an inherent mechanism to guide stem cells to sites of tissue injury, however this process is often insufficient to achieve full tissue repair. The chemokine CXCL12 also referred to as stromal cell-derived factor-1 alpha (SDF-1α) is a prominent stem cell homing factor and is transiently up-regulated upon injury in the bone to promote subsequent recruitment of MSCs (Andreas et al. 2014). A collagen scaffold releasing CXCL12 has been employed in vivo to recruit endogenous MSCs in partial-thickness cartilage defects in rabbit (Zhang et al. 2013). Cell-free chemoattractant-based therapies are likely to become more important in the future, since they could offer a convenient off-the-shelf product as a therapeutic tool for regenerative therapies. However additional research is need to be sure that no detrimental cells such as immune cells or fibroblasts are recruited to the defect side.

Furthermore, both for the growth factors and chemokines application there is a need to present these factors at the defect side in an appropriate delivery vehicle. These biochemical signaling molecules possess a short half-live and are prone to protease cleavage and will diffuse rapidly upon bolus injection at the defect side, so in order to keep them at the side of tissue repair an appropriate scaffold delivery vehicle is required (Andreas et al. 2014).

#### 10.2.4.4 Scaffold Technology

Cells and growth factors are commonly transplanted into the body with the support of a carrier scaffold. These carriers function to retain the cells at the defect site, allow them to multiply and synthesize their own ECM. Therefore, such scaffolds must provide a number of design properties including: (1) Biocompatibility: To prevent undesirable immune or biological responses. (2) Permeability: to demonstrate sufficient porosity to enable good nutrient supply to cells at all regions of the

construct, allow transport of signaling molecules between cells, permit removal of waste products and allow ingrowth of host tissue. (3) Biodegradability, where appropriate, to enable the scaffold to degrade in a controlled temporal manner, into non-toxic by-products as a neo-tissue is developed. In addition, this property may enable the controlled release of morphogens and/or pharmacological agents to encourage cellular activity. To date, a wide range of natural and synthetic materials are available for use as scaffolds for tissue engineered cartilage constructs (Barnewitz et al. 2006; Ossendorf et al. 2007; Perka et al. 2000; Risbud and Sittinger 2002; Sittinger et al. 1994, 2004).

**Natural polymers** can be subdivided into protein-based such as collagen, fibrin and silk or carbohydrate-based such as alginate, agarose, hyaluronan, chondroitin sulfate and chitosan. Many of these are hydrogels, which makes them appropriate for cartilage regeneration, since their highly hydrated polymer networks mimic a similar high water content as in the native cartilage ECM (Kock et al. 2012).

Encapsulation of chondrocytes within agarose and alginate hydrogels is a well-established protocol for in vitro cartilage models (Benya et al. 1988; Freeman et al. 1994; Lee and Bader 1995; Naqvi and Buckley 2015) and has been used to deliver autologous chondrocytes articular cartilage lesions in human patients (Selmi et al. 2008). These in vitro systems have demonstrated their value in studying the response of chondrocytes to many external stimuli while excluding the coupled influences of other factors that are also implicated within the native cartilage. Examples of such studies include the effects of dynamic mechanical stimulation on chondrocyte metabolism (Chowdhury et al. 2001, 2003; Lee and Bader 1997) and chondrocyte deformation (Buschmann et al. 1995; Knight et al. 1998). In a similar manner to many hydrogels, however, cell-seeded agarose or alginate constructs are limited by their poor resorption rate and their inferior mechanical and biochemical properties, making them unsuitable for load-bearing applications. The potential of fibrin based scaffolds as carriers of cells and growth factors for cartilage regeneration was investigated (Hendrickson et al. 1994). Although this natural clot-forming polymer produces a neo-tissue that is histologically similar to natural cartilage, it has poor mechanical properties and often evokes an immune response (Kawabe and Yoshinao 1991). The use of collagen-based scaffolds for delivering cell and growth factors to defect sites is extensive. As collagen naturally occurs in skeletal tissues, it promotes attachment of cells unto its surface. Accordingly, it has been used either cell-free, seeded with chondrocytes or MSC, in many animal studies (Russlies et al. 2002; Sams et al. 1995; Samuel et al. 2002). Chondrocytes seeded onto dense collagen scaffolds, implanted into rabbit femoral trochlea for up to 24 weeks has demonstrated to have produced a hyaline-like cartilage that was biochemically and mechanically similar to its surrounding cartilage (Frenkel et al. 1997). By contrast, other in vivo studies reported that although the repair appears adequate at earlier time point, subsequent thinning of the repair tissue occurs with time (Wakitani et al. 1994). Hyaluronan is a non-sulphated GAG that is essential for the aggregation of large proteoglycans such as aggrecans in articular cartilage. It has been used to

deliver mesenchymal stem cells to caprine chondral defects (Butnariu-Ephrat et al. 1996), and stabilize chondrocytes and osteochondral progenitor cells for cartilage defects in rabbits (Grigolo et al. 2001; Solchaga et al. 2002). Although the newly developed tissues exhibit good integration with the host cartilage, they are typically thinner and often induce the breakdown of cartilage matrix. Chitosan has been used to deliver cells and growth factors to the defect site. Chitosan, is derived from the exoskeleton from arthropods and is structurally similar to the glycosaminoglycans found in cartilage (Berger et al. 2004). Chitosan can form into thermo reversible hydrogels, offers the combined advantages of an implant with a uniform distribution of cells and direct injectable into the defect (Chenite et al. 2000). Autologous chondrocytes encapsulated in injectable chitosan hydrogels repaired non-weight bearing defects in adolescent sheep, with good integration with the surrounding tissue (Hao et al. 2010).

**Synthetic polymers** used in cartilage tissue engineering are mainly poly-α-hydroxyesters (especially polylactic acid (PLA), polyglycolic acid (PGA), Poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL)) (Dahlin et al. 2014; Mooney et al. 1996) but also poly(vinyl alcohol) (PVA), poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO). Compared to natural scaffolds, the mechanical and biochemical properties of synthetic scaffolds are readily modified to suit specific applications. PLA and PGA have been demonstrated to support chondrogenesis (Haisch et al. 2005). Moreover, their degradation products are naturally occurring metabolites that can be cleared from the body through the metabolic mechanism and because of their biodegradability there have been approved for certain clinical applications by the FDA and EMA. However, PGA was found to be weaker than most synthetic scaffolds, and degrades very fast, often releasing acidic byproducts of degradation into its immediate environment, which may prove cytotoxic (Grande et al. 2003). The uses of PLA/PGA copolymers as scaffolds allow improved control of the degradation rate. Indeed success was demonstrated by Cohen et al., who observed good histological and biochemical response, after 12-week implantation of the co-polymer into rabbit-chondral-defects (Cohen et al. 2003). An exhaustive range of copolymers have been proposed for cartilage repair. These include PLA/PEG (Tamai et al. 2005), and nanofibrous forms of PLA/PCL (Li et al. 2005), the latter has been shown to elicit differentiation of human mesenchymal stem cells into chondrocytes exhibiting similar zonal morphology to that of native cartilage. Other synthetic copolymers include Poly(ethylene oxide)-terephthalate/poly(butylene-terephthalate) (PEOT/PBT) which have been used as filler of the donor side during mosaicplasty in humans (Bartha et al. 2013; Rey-Rico et al. 2015).

**Hybrid composite scaffolds** combing both synthetic and natural polymers are also tested in the cartilage engineering field. This allows to combine the tailorable mechanical and degradation properties of synthetic polymers with delivering tissue-specific clues of naturally occurring polymers. A macroporous PCL scaffold with desired mechanical properties was coated with hyaluronic acid to provide a

hydrophilic surface and chondroactive properties and showed 24 weeks after implantation in a cartilage full-thickness defect in rabbits a well-organized hyaline cartilage in the defect lesions (Lebourg et al. 2014). Hybrid composite scaffolds allow for the construction of scaffolds with a biomimetic microarchitecture. A study combining type-II collagen and Chitosan-PCL as main components enabled to create a layered scaffold with an altered average pore-size, porosity, swelling index and compressive modulus from one layer to layer in a gradient manner and a decreased collagen content from the top layer to the bottom layer (Zhu et al. 2014).

Multiphase implants consisting of PGA, Bioglass and calcium phosphates have been examined in osteochondral defects in goats (Niederauer et al. 2000). The PGA fibers were seeded with autologous chondrocytes and the calcium phosphates were used to modulate the construct stiffness at specific regions of the implants.

## 10.3 The Limiting Factor: What Lies Beneath

### *10.3.1 Subchondral Considerations in Cartilage Disease*

Although little is known about the relationship between bone and cartilage in the etiology of osteoarthritis, an abnormal growth of the subchondral bone resulting in thickened subchondral bone plate, increased stiffness, and bone mineral density have been tagged with the progression of the disease (Fazzalari and Parkinson 1997; Grynpas et al. 1991; Li and Aspden 1997). Having observed these, and a decreased energy absorbing capacity Radin and co-workers proposed that stiffening of the subchondral plate was an initiating factor in osteoarthritis (Radin et al. 1970). They later hypothesized that trabecular microfracture due to impulsive loading initiates bone remodeling in the subchondral plate. This leads to localized stiffening that in turn produces increased shear stress in the cartilage, culminating in cartilage breakdown (Pugh et al. 1974).

It had been an ongoing debate that the calcified cartilage layer and the tide mark was an impenetrable structure, separating the articular cartilage from its underlying subchondral bone. However, microcracks and micro channels between the subchondral region and the uncalcified cartilage have been demonstrated (Clark and Huber 1990; Holmdahl and Ingelmark 1950). It is therefore conceivable that these microcracks, and the vascularization in the subchondral bone plate, could facilitate molecular transport from the subchondral region to the basal layer of cartilage. Evidence to support this transportation comes from the discovery of hepatocyte growth factor (HGF) within the deep zone of normal cartilage, and an elevated level in osteoarthritic cartilage (Pfander et al. 1999); despite it not being produced by chondrocytes, but by the osteoblasts in the subchondral region (Guevremont et al. 2003). It has therefore been proposed that, following its synthesis by subchondral osteoblasts, HGF can reach the deep layers of articular cartilage via these microcracks, and/or the vascularized subchondral plate, and promote cartilage breakdown

and/or enhances matrix remodeling. The association of HGF with Osteoarthritis comes from its incitement of MMP-13 production (Reboul et al. 2001); an enzyme present in the lower intermediate and deep layers of osteoarthritic cartilage. Other evidence for the role of subchondral bone in cartilage degradation are TGF-ß, Cathepsin K, and PGE2/LTB4, which are all produced by osteoarthritic subchondral bone cells, and yet found at the deep layers of osteoarthritic cartilage (Konttinen et al. 2002; Moldovan et al. 1997; Nakase et al. 2000).

### *10.3.2 Subchondral Considerations in Cartilage Healing*

Although clinical studies have reported favorable results with osteochondral autografts at short and mid-term follow-up, animal studies 3 months after grafting found signs of degeneration, evidenced by chondrocyte clustering and hyper-cellularity in cartilage (Tibesku et al. 2004). Answering the question of whether the observed degradation may be detected histologically, Kleemann et al. (2007) characterized the mechanical competence and morphology of cartilage in osteochondral autografts. The ensuing study demonstrated that grafted tissues seem to undergo in a short period of time, where both substantial degenerative and regenerative processes occur. The compressive stiffness of the grafted cartilage was about 58 % of that of healthy tissue at 3 months, and rose to 82 % at 6 months. Fibrillation, hypercellularity, and cell clustering were observed at the edges of the grafts. Both the cartilage and the underlying bone were observed to be degrading, raising doubts as to their long term repair. Events such as disrupted nutrition (Malinin and Ouellette 2000), physical damage during the extraction, and transplantation of the graft (Buckwalter and Mankin 1998; Duda et al. 2001; Huntley et al. 2005; Redman et al. 2004; Whiteside et al. 2005) were thought to be contributing factors. Despite this, the intensity of type II collagen staining of the healthy and the grafted cartilage tissue were identical.

A bottom-upwards approach by Schell et al., had aimed to first support the reconstruction of the subchondral bone plate in an osteochondral defect, and thereby improving the mechanical and histological quality of the repaired cartilage (Schell et al. 2007). The authors transplanted crushed bone graft together with a collagen membrane into osteochondral defects, 8.3 mm in diameter and 10 mm in depth. Comparing its healing with unfilled control groups, they observed no difference in healing outcome between the two groups after 6 months. All defects, whether filled or not, showed an irregular, more or less advanced cartilage repair. However, the articular surface was not restored in any case.

A similar endeavor had attempted to encourage osteochondral healing through mechanical straining (Duda et al. 2005). Bone resorption and formation were observed at the base, and at the circumference of the defects, respectively. Defect filling, cartilage formation, and trabecular structures were observed for up to 12 weeks. Although their defects were completely filled, the neo-tissue mainly comprised of fibrous cartilage, and only partially with hyaline-like cartilage.

The importance of the subchondral bone in cartilage healing is undisputed. When a cartilage lesion is deep enough, the penetrated subchondral bone is prompted into action. Often, in cases such as abrasion chondroplasty and microfracture, it is strategically penetrated surgically for its input into the healing process to be realized. It is now a topical discussion that the state of the underlying bone itself, be it mechanical, physiological, or otherwise, is actually important for the quality of cartilage regenerated.

### *10.3.3 Subchondral Considerations in Cartilage Tissue Engineering*

The functioning of articular cartilage is believed to be dependent on the mechanical support by the subchondral bone. In fact, the steep stiffness gradient in the subchondral bone is suggested to be responsible for the initiation and progression of cartilage damage (Radin and Rose 1986). Moreover, the stiffened subchondral bone associated with osteoarthritis (Radin et al. 1970) is said to cause transverse stresses at the base of the articular cartilage, potentially resulting in deep horizontal splits therein. Given their apparent differences, tissue-engineered solutions either favors cartilage repair, or bone regeneration, and seldom satisfy both tissues. Osteochondral repair strategies now aim to concurrently mimic the physiological properties and structure of the cartilage and bone using cell-seeded constructs. The resulting hybrid is an engineered scaffold consisting of both a cartilage-optimized phase and a subchondral bone-optimized phase (Temenoff and Mikos 2000). Principally, the two phases are produced separately, under their appropriate conditions, and with the appropriate cellular disseminations, and are later united prior to implantation. On this front, two kinds of hybrid scaffolds have been developed by Hutmacher and co-workers, using a combination of fibrin, polycaprolactone (PCL), and a PCL-TCP combination. In one instance, the fibrin served as the cartilage phase while the PCL scaffold substitutes for the subchondral phase. On another occasion, their hybrid consisted of PCL and PCL-TCP. The top PCL region promotes cartilage regeneration while the underlying PCL-TCP serves as the subchondral bone phase. Having been seeded with pre-cultured MSCs, the biphasic constructs were implanted into New Zealand white rabbits for up to 6 months. The researchers found that in terms of cartilage regeneration, PCL bettered the fibrin constructs; stipulating that the mechanical support provided by the fibrin was insufficient for cellular development, and its subsequent secretion of the essential ECM products. In fact, the fibrin degrades rapidly, while the porous PCL scaffold degraded slowly, providing an effective mechanical support (Swieszkowski et al. 2007).

Along a similar line, Schlichting et al. evaluated the healing of osteochondral defects using polylactide-co-glycolide scaffolds of differing stiffness, hypothesizing that a stiff scaffold creates sufficiently stable conditions necessary for subchondral bone formation and consequently cartilage regeneration compared with a softer

scaffold or to untreated controls (Schlichting et al. 2008). The stiff scaffold was found to improve the regeneration of subchondral bone, while the soft scaffolds provided less support, and consequently the surrounding subchondral bone became more sclerotic. Indeed, the regenerated cartilage that was formed over, the stiff scaffold exhibited higher elastic and dynamic moduli at 3 months than did the soft scaffold group. However these mechanical properties were not dissimilar for both groups at 6 months. Moreover, these values were inferior to that of native articular cartilage. These findings led to the conclusions that Materials used to fill subchondral defects should have a comparable stiffness to that of healthy subchondral bone rather than being too flexible. When this is not the case, degradation or resorption of filling materials will lead to loss of stiffness, and may compromise the defect healing.

## 10.4 Summary

The present review has looked at the current challenges faced when trying to regenerate cartilage. Most of these issues have been related to the structure, composition, and mechanical features of the tissue. In light of the topics discussed above, the following statements may summarize the current challenges associated with cartilage regeneration:

Cartilage is a complex tissue, with at least three phases. Moreover, cartilage illness may be systemic, local, acute or chronic. Current treatment options aim to reduce pain. By large, there is as of yet no solution that is all-encompassing, and can regenerate all the different types of cartilage defects. Despite the ongoing debate over the separation of articular cartilage from its subchondral bone by the tide mark, there exists an overwhelming amount of evidence to link the two regions, particularly at the onset of OA. Therefore, a good strategy for cartilage regeneration ought not to neglect the underlying subchondral tissue. Principally, a successful clinical outcome will have re-established both the damaged cartilage and its underlying subchondral bone.

## References

Altman RD, Kates J, Chun LE, Dean DD, Eyre D (1992) Preliminary observations of chondral abrasion in a canine model. Ann Rheum Dis 51:1056–1062

Anderson MA, Payne JT, Kreeger JM, Wagner-Mann CC, Schmidt DA, Mann FA (1993) Effects of intra-articular chlorhexidine diacetate lavage on the stifle in healthy dogs. Am J Vet Res 54:1784–1789

Andreas K, Sittinger M, Ringe J (2014) Toward in situ tissue engineering: chemokine-guided stem cell recruitment. Trends Biotechnol 32:483–492

Ateshian GA, Wang H (1997) Rolling resistance of articular cartilage due to interstitial fluid flow. Proc Inst Mech Eng 211:419–424

Ayad S, Kwan AP, Grant ME (1987) Partial characterization of type X collagen from bovine growth-plate cartilage. Evidence that type X collagen is processed in vivo. FEBS Lett 220:181–186

Bakay A, Csonge L, Papp G, Fekete L (1998) Osteochondral resurfacing of the knee joint with allograft. Clinical analysis of 33 cases. Int Orthop 22:277–281

Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE (2009) Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum 61:1704–1711

Barnewitz D, Endres M, Kruger I, Becker A, Zimmermann J, Wilke I, Ringe J, Sittinger M, Kaps C (2006) Treatment of articular cartilage defects in horses with polymer-based cartilage tissue engineering grafts. Biomaterials 27:2882–2889

Barry F, Boynton RE, Liu BS, Murphy JM (2001) Chondrogenic differentiation of mesenchymal stem cells from bone marrow: differentiation-dependent gene expression of matrix components. Exp Cell Res 268:189–200

Bartha L, Hamann D, Pieper J, Peters F, Riesle J, Vajda A, Novak PK, Hangody LR, Vasarhelyi G, Bodo L et al (2013) A clinical feasibility study to evaluate the safety and efficacy of PEOT/PBT implants for human donor site filling during mosaicplasty. Eur J Orthop Surg Traumatol: Orthop Traumatol 23:81–91

Bedi A, Feeley BT, Williams RJ (2010) Management of articular cartilage defects of the knee. J Bone Joint Surg Am 92A:994–1009

Behrens P, Bitter T, Kurz B, Russlies M (2006) Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI) - 5-year follow-up. Knee 13:194–202

Beiser IH, Kanat IO (1990) Subchondral bone drilling: a treatment for cartilage defects. J Foot Surg 29:595–601

Bell RS, Davis A, Allan DG, Langer F, Czitrom AA, Gross AE (1994) Fresh osteochondral allografts for advanced giant cell tumors at the knee. J Arthroplast 9:603–609

Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G (2006) Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev (Online), CD005328

Bennett GA, Bauer W (1935) Further studies concerning the repair of articular cartilage in dog joints. J Bone Joint Surg Am 17:141–150

Benthien JP, Behrens P (2011) The treatment of chondral and osteochondral defects of the knee with autologous matrix-induced chondrogenesis (AMIC): method description and recent developments. Knee Surg Sport Tr A 19:1316–1319

Benthien JP, Behrens P (2013) Reviewing subchondral cartilage surgery: considerations for standardised and outcome predictable cartilage remodelling. Int Orthop 37:2139–2145

Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM, Skinner JA, Pringle J (2003) A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg 85:223–230

Benya PD, Brown PD, Padilla SR (1988) Microfilament modification by dihydrocytochalasin B causes retinoic acid-modulated chondrocytes to reexpress the differentiated collagen phenotype without a change in shape. J Cell Biol 106:161–170

Berger J, Reist M, Mayer JM, Felt O, Gurny R (2004) Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. Eur J Pharm Biopharm 57:35–52

Biant LC, Bentley G, Vijayan S, Skinner JA, Carrington RWJ (2014) Long-term results of autologous chondrocyte implantation in the knee for chronic chondral and osteochondral defects. Am J Sport Med 42:2178–2183

Boot-Handford RP, Tuckwell DS, Plumb DA, Rock CF, Poulsom R (2003) A novel and highly conserved collagen (pro(alpha)1(XXVII)) with a unique expression pattern and unusual molecular characteristics establishes a new clade within the vertebrate fibrillar collagen family. J Biol Chem 278:31067–31077

Bouwmeester SJ, Beckers JM, Kuijer R, van der Linden AJ, Bulstra SK (1997) Long-term results of rib perichondrial grafts for repair of cartilage defects in the human knee. Int Orthop 21:313–317

Breinan HA, Minas T, Hsu HP, Nehrer S, Shortkroff S, Spector M (2001) Autologous chondrocyte implantation in a canine model: change in composition of reparative tissue with time. J Orthop Res 19:482–492

Brinkhaus B, Witt CM, Jena S, Linde K, Streng A, Hummelsberger J, Irnich D, Hammes M, Pach D, Melchart D et al (2007) Physician and treatment characteristics in a randomised multicentre trial of acupuncture in patients with osteoarthritis of the knee. Complement Ther Med 15:180–189

Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L (1994) Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 331:889–895

Brown TD, Singerman RJ (1986) Experimental determination of the linear biphasic constitutive coefficients of human fetal proximal femoral chondroepiphysis. J Biomech 19:597–605

Buckwalter JA (1998) Articular cartilage: injuries and potential for healing. J Orthop Sports Phys Ther 28:192–202

Buckwalter JA, Mankin HJ (1997) Articular cartilage. Part I: tissue design and chondrocyte-matrix interactions. J Bone Joint Surg (Am) 79A:600–611

Buckwalter JA, Mankin HJ (1998) Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. Instr Course Lect 47:487–504

Buckwalter JA, Rosenberg LC, Ungar R (1987) Changes in proteoglycan aggregates during cartilage mineralization. Calcif Tissue Int 41:228–236

Buckwalter JA, Mankin HJ, Grodzinsky AJ (2005) Articular cartilage and osteoarthritis. Instr Course Lect 54:465–480

Bukowski EL, Conway A, Glentz LA, Kurland K, Galantino ML (2006) The effect of iyengar yoga and strengthening exercises for people living with osteoarthritis of the knee: a case series. Int Q Community Health Educ 26:287–305

Buschmann MD, Gluzband YA, Grodzinsky AJ, Hunziker EB (1995) Mechanical compression modulates matrix biosynthesis in chondrocyte/agarose culture. J Cell Sci 108(Pt 4):1497–1508

Butnariu-Ephrat M, Robinson D, Mendes DG, Halperin N, Nevo Z (1996) Resurfacing of goat articular cartilage by chondrocytes derived from bone marrow. Clin Orthop Relat Res 330:234–243

Calandruccio RA, Gilmer WSJR (1962) Proliferation, regeneration, and repair of articular cartilage of immature animals. J Bone Joint Surg Am 44:431–455

Campbell CJ (1969) The healing of cartilage defects. Clin Orthop Relat Res 64:45–63

Chang RW, Falconer J, Stulberg SD, Arnold WJ, Manheim LM, Dyer AR (1993) A randomized, controlled trial of arthroscopic surgery versus closed-needle joint lavage for patients with osteoarthritis of the knee. Arthritis Rheum 36:289–296

Chang CB, Han SA, Kim EM, Lee S, Seong SC, Lee MC (2013) Chondrogenic potentials of human synovium-derived cells sorted by specific surface markers. Osteoarthr Cartilage 21:190–199

Cheifetz S, Bassols A, Stanley K, Ohta M, Greenberger J, Massague J (1988) Heterodimeric transforming growth factor beta. Biological properties and interaction with three types of cell surface receptors. J Biol Chem 263:10783–10789

Chenite A, Chaput C, Wang D, Combes C, Buschmann MD, Hoemann CD, Leroux JC, Atkinson BL, Binette F, Selmani A (2000) Novel injectable neutral solutions of chitosan form biodegradable gels in situ. Biomaterials 21:2155–2161

Chou R, McDonagh MS, Nakamoto E, Griffin J (2011) In: Analgesics for osteoarthritis: an update of the 2006 comparative effectiveness review. Agency for Healthcare Research and Quality, Rockville

Chowdhury TT, Bader DL, Lee DA (2001) Dynamic compression inhibits the synthesis of nitric oxide and PGE(2) by IL-1beta-stimulated chondrocytes cultured in agarose constructs. Biochem Biophys Res Commun 285:1168–1174

Chowdhury TT, Bader DL, Shelton JC, Lee DA (2003) Temporal regulation of chondrocyte metabolism in agarose constructs subjected to dynamic compression. Arch Biochem Biophys 417:105–111

Clark JM, Huber JD (1990) The structure of the human subchondral plate. J Bone Joint Surg 72:866–873

Clarke IC (1971) Articular cartilage: a review and scanning electron microscope study. 1. The interterritorial fibrillar architecture. J Bone Joint Surg 53:732–750

Cohen J, Lacroix P (1955) Bone and cartilage formation by periosteum; assay of experimental autogenous grafts. J Bone Joint Surg Am 37-A:717–730

Cohen SB, Meirisch CM, Wilson HA, Diduch DR (2003) The use of absorbable co-polymer pads with alginate and cells for articular cartilage repair in rabbits. Biomaterials 24:2653–2660

Comper WD (1996) Extracellular matrix. Harwood Academic Publishers, Amsterdam

Convery FR, Akeson WH, Keown GH (1972) The repair of large osteochondral defects. An experimental study in horses. Clin Orthop Relat Res 82:253–262

Cooper C, Cushnaghan J, Kirwan JR, Dieppe PA, Rogers J, McAlindon T, McCrae F (1992) Radiographic assessment of the knee joint in osteoarthritis. Ann Rheum Dis 51:80–82

Dahlin RL, Kinard LA, Lam J, Needham CJ, Lu S, Kasper FK, Mikos AG (2014) Articular chondrocytes and mesenchymal stem cells seeded on biodegradable scaffolds for the repair of cartilage in a rat osteochondral defect model. Biomaterials 35:7460–7469

Dahmer S, Schiller RM (2008) Glucosamine. Am Fam Physician 78:471–476

Dehne T, Karlsson C, Ringe J, Sittinger M, Lindahl A (2009) Chondrogenic differentiation potential of osteoarthritic chondrocytes and their possible use in matrix-associated autologous chondrocyte transplantation. Arthritis Res Ther 11:R133

DePalma AF, McKeever CD, Subin DK (1966) Process of repair of articular cartilage demonstrated by histology and autoradiography with tritiated thymidine. Clin Orthop Relat Res 48:229–242

Duda GN, Eilers M, Loh L, Hoffman JE, Kaab M, Schaser K (2001) Chondrocyte death precedes structural damage in blunt impact trauma. Clin Orthop Relat Res 393:302–309

Duda GN, Maldonado ZM, Klein P, Heller MO, Burns J, Bail H (2005) On the influence of mechanical conditions in osteochondral defect healing. J Biomech 38:843–851

Eckstein F, Tieschky M, Faber S, Englmeier KH, Reiser M (1999) Functional analysis of articular cartilage deformation, recovery, and fluid flow following dynamic exercise in vivo. Anat Embryol 200:419–424

Eckstein F, Lemberger B, Stammberger T, Englmeier KH, Reiser M (2000) Patellar cartilage deformation in vivo after static versus dynamic loading. J Biomech 33:819–825

Eldracher M, Orth P, Cucchiarini M, Pape D, Madry H (2014) Small subchondral drill holes improve marrow stimulation of articular cartilage defects. Am J Sport Med 42:2741–2750

Elmore SM, Sokoloff L, Norris G, Carmeci P (1963) Nature of "imperfect" elasticity of articular cartilage. J Appl Physiol 18:393–396

Eyre DR (2004) Collagens and cartilage matrix homeostasis. Clin Orthop Relat Res 427:S118–S122

Eyre DR, Jiann-Jiu W, Woods P (1992) Cartilage-specific collagens, structural studies. In: Kuettner KE, Schleyerbach R, Peyron JG, Hascall VC (eds) Articular cartilage and osteoarthritis. Ravens Press Ltd, New York

Fazzalari NL, Parkinson IH (1997) Fractal properties of subchondral cancellous bone in severe osteoarthritis of the hip. J Bone Miner Res 12:632–640

Felimban R, Ye K, Traianedes K, Di Bella C, Crook J, Wallace GG, Quigley A, Choong PFM, Myers DE (2014) Differentiation of stem cells from human infrapatellar fat pad: characterization of cells undergoing chondrogenesis. Tissue Eng A 20:2213–2223

Felson DT, Zhang Y (1998) An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 41:1343–1355

Filardo G, Kon E, Di Martino A, Iacono F, Marcacci M (2011) Arthroscopic second-generation autologous chondrocyte implantation a prospective 7-year follow-up study. Am J Sport Med 39:2153–2160

Freeman PM, Natarajan RN, Kimura JH, Andriacchi TP (1994) Chondrocyte cells respond mechanically to compressive loads. J Orthop Res 12:311–320

Frenkel SR, Toolan B, Menche D, Pitman MI, Pachence JM (1997) Chondrocyte transplantation using a collagen bilayer matrix for cartilage repair. J Bone Joint Surg 79:831–836

Friedenstein AJ, Gorskaja JF, Kulagina NN (1976) Fibroblast precursors in normal and irradiated mouse hematopoietic organs. Exp Hematol 4:267–274

Frisbie DD, Trotter GW, Powers BE, Rodkey WG, Steadman JR, Howard RD, Park RD, McIlwraith CW (1999) Arthroscopic subchondral bone plate microfracture technique augments healing of large chondral defects in the radial carpal bone and medial femoral condyle of horses. Vet Surg 28:242–255

Fuchs JR, Hannouche D, Terada S, Zand S, Vacanti JP, Fauza DO (2005) Cartilage engineering from ovine umbilical cord blood mesenchymal progenitor cells. Stem Cells (Dayton, Ohio) 23:958–964

Fukumoto T, Sperling JW, Sanyal A, Fitzsimmons JS, Reinholz GG, Conover CA, O'Driscoll SW (2003) Combined effects of insulin-like growth factor-1 and transforming growth factor-beta 1 on periosteal mesenchymal cells during chondrogenesis in vitro. Osteoarthr Cartilage 11:55–64

Furukawa T, Eyre DR, Koide S, Glimcher MJ (1980) Biochemical studies on repair cartilage resurfacing experimental defects in the rabbit knee. J Bone Joint Surg Am 62:79–89

Giannini S, Buda R, Grigolo B, Vannini F (2001) Autologous chondrocyte transplantation in osteochondral lesions of the ankle joint. Foot Ankle Int/Am Orthop Foot Ankle Soc Swiss Foot Ankle Soc 22:513–517

Gibson JN, White MD, Chapman VM, Strachan RK (1992) Arthroscopic lavage and debridement for osteoarthritis of the knee. J Bone Joint Surg 74:534–537

Gillespie WJ, O'Connell DL (1992) Arthroscopic lavage of osteoarthritic knees. J Bone Joint Surg 74:787–788; author reply 788–789

Goessler UR, Bieback K, Bugert P, Naim R, Schafer C, Sadick H, Hormann K, Riedel F (2005) Human chondrocytes differentially express matrix modulators during in vitro expansion for tissue engineering. Int J Mol Med 16:509–515

Goldman RT, Scuderi GR, Kelly MA (1997) Arthroscopic treatment of the degenerative knee in older athletes. Clin Sports Med 16:51–68

Grande DA, Halberstadt C, Naughton G, Schwartz R, Manji R (1997) Evaluation of matrix scaffolds for tissue engineering of articular cartilage grafts. J Biomed Mater Res 34:211–220

Grande DA, Mason J, Light E, Dines D (2003) Stem cells as platforms for delivery of genes to enhance cartilage repair. J Bone Joint Surg Am 85-A(Suppl 2):111–116

Grant ME, Ayad S, Kwan APL, Bates GP, Thomas JT JM, Grant ME, Ayad S, Kwan APL, Bates GP, Thomas JT JM (1988) The structure and synthesis of cartilage collagens. In: Glauert AM, Glauert AM (eds) Control of tissue damage. Elsevier Science Publishers, Amsterdam, pp 3–28

Grigolo B, Roseti L, Fiorini M, Fini M, Giavaresi G, Aldini NN, Giardino R, Facchini A (2001) Transplantation of chondrocytes seeded on a hyaluronan derivative (hyaff-11) into cartilage defects in rabbits. Biomaterials 22:2417–2424

Grynpas MD, Alpert B, Katz I, Lieberman I, Pritzker KP (1991) Subchondral bone in osteoarthritis. Calcif Tissue Int 49:20–26

Gu WY, Lai WM, Mow VC (1997) A triphasic analysis of negative osmotic flows through charged hydrated soft tissues. J Biomech 30:71–78

Guevremont M, Martel-Pelletier J, Massicotte F, Tardif G, Pelletier JP, Ranger P, Lajeunesse D, Reboul P (2003) Human adult chondrocytes express hepatocyte growth factor (HGF) isoforms but not HgF: potential implication of osteoblasts on the presence of HGF in cartilage. J Bone Miner Res 18:1073–1081

Guilak F, Mow VC (2000) The mechanical environment of the chondrocyte: a biphasic finite element model of cell-matrix interactions in articular cartilage. J Biomech 33:1663–1673
Guilak F, Jones WR, Ting-Beall HP, Lee GM (1999) The deformation behavior and mechanical properties of chondrocytes in articular cartilage. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 7:59–70
Haisch A, Groger A, Gebert C, Leder K, Ebmeyer J, Sudhoff H, Jovanovic S, Sedlmaier B, Sittinger M (2005) Creating artificial perichondrium by polymer complex membrane macroencapsulation: immune protection and stabilization of subcutaneously transplanted tissue-engineered cartilage. Eur Arch Otorhinolaryngol 262:338–344
Hao T, Wen N, Cao JK, Wang HB, Lu SH, Liu T, Lin QX, Duan CM, Wang CY (2010) The support of matrix accumulation and the promotion of sheep articular cartilage defects repair in vivo by chitosan hydrogels. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 18:257–265
Hardingham TE, Fosang AJ (1992) Proteoglycans: many forms and many functions. FASEB J 6:861–870
Hendrickson DA, Nixon AJ, Grande DA, Todhunter RJ, Minor RM, Erb H, Lust G (1994) Chondrocyte-fibrin matrix transplants for resurfacing extensive articular cartilage defects. J Orthop Res 12:485–497
Henrotin Y, Marty M, Mobasheri A (2014) What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis? Maturitas 78:184–187
Herzog W, Diet S, Suter E, Mayzus P, Leonard TR, Muller C, Wu JZ, Epstein M (1998) Material and functional properties of articular cartilage and patellofemoral contact mechanics in an experimental model of osteoarthritis. J Biomech 31:1137–1145
Hickey MJ, Ohta I, Shigetomi M, Hurley JV, Kuwata N, O'Brien BM (1994) Vascularized heterotopic osteochondral allografts in a rat model following long-term immunosuppression. J Reconstr Microsurg 10:255–260
Hicks DL, Sage AB, Shelton E, Schumacher BL, Sah RL, Watson D (2007) Effect of bone morphogenetic proteins 2 and 7 on septal chondrocytes in alginate. Otolaryngol Head Neck 136:373–379
Hirsch CA (1944) Contribution to the pathogenesis of chondromalacia of the patella. Acta Chir Scaninavica 83:1–106
Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P (2012) American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 64:465–474
Holmdahl DE, Ingelmark BE (1950) The contact between the articular cartilage and the medullary cavities of the bone. Acta Orthop Scand 20:156–165
Homminga GN, Bulstra SK, Bouwmeester PS, van der Linden AJ (1990) Perichondral grafting for cartilage lesions of the knee. J Bone Joint Surg 72:1003–1007
Honner R, Thompson RC (1971) The nutritional pathways of articular cartilage. An autoradiographic study in rabbits using 35S injected intravenously. J Bone Joint Surg Am 53:742–748
Huber S, Winterhalter KH, Vaughan L (1988) Isolation and sequence analysis of the glycosaminoglycan attachment site of type IX collagen. J Biol Chem 263:752–756
Huntley JS, Bush PG, McBirnie JM, Simpson AH, Hall AC (2005) Chondrocyte death associated with human femoral osteochondral harvest as performed for mosaicplasty. J Bone Joint Surg Am 87:351–360
Hunziker EB (1999) Biologic repair of articular cartilage. Defect models in experimental animals and matrix requirements. Clin Orthop Relat Res 367:S135–S146
Insall JN (1967) Intra-articular surgery for degenerative arthritis of the knee. A report of the work of the late K. H. Pridie. J Bone Joint Surg 49:211–228
Jansen MJ, Viechtbauer W, Lenssen AF, Hendriks EJM, de Bie RA (2011) Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: a systematic review. J Physiother 57:11–20

Jensen LK (2008) Hip osteoarthritis: influence of work with heavy lifting, climbing stairs or ladders, or combining kneeling/squatting with heavy lifting. Occup Environ Med 65:6–19
Jones EA, Kinsey SE, English A, Jones RA, Straszynski L, Meredith DM, Markham AF, Jack A, Emery P, McGonagle D (2002) Isolation and characterization of bone marrow multipotential mesenchymal progenitor cells. Arthritis Rheum 46:3349–3360
Jurvelin J, Saamanen AM, Arokoski J, Helminen HJ, Kiviranta I, Tammi M (1988) Biomechanical properties of the canine knee articular cartilage as related to matrix proteoglycans and collagen. Eng Med 17:157–162
Kawabe N, Yoshinao M (1991) The repair of full-thickness articular cartilage defects. Immune responses to reparative tissue formed by allogeneic growth plate chondrocyte implants. Clin Orthop Relat Res 268:279–293
Kempson GE, Muir H, Swanson SA, Freeman MA (1970) Correlations between stiffness and the chemical constituents of cartilage on the human femoral head. Biochim Biophys Acta 215:70–77
Key JA (1931) Experimental arthritis: the changes in joints produced by creating defects in the articular cartilage. J Bone Joint Surg Am 13:725–739
Kim HK, Moran ME, Salter RB (1991) The potential for regeneration of articular cartilage in defects created by chondral shaving and subchondral abrasion. An experimental investigation in rabbits. J Bone Joint Surg Am 73:1301–1315
Kim YJ, Sah RL, Grodzinsky AJ, Plaas AH, Sandy JD (1994) Mechanical regulation of cartilage biosynthetic behavior: physical stimuli. Arch Biochem Biophys 311:1–12
Kiviranta P, Lammentausta E, Toyras J, Kiviranta I, Jurvelin JS (2008) Indentation diagnostics of cartilage degeneration. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 16:796–804
Kleemann RU, Schell H, Thompson M, Epari DR, Duda GN, Weiler A (2007) Mechanical behavior of articular cartilage after osteochondral autograft transfer in an ovine model. Am J Sports Med 35:555–563
Knight MM, Lee DA, Bader DL (1998) The influence of elaborated pericellular matrix on the deformation of isolated articular chondrocytes cultured in agarose. Biochim Biophys Acta 1405:67–77
Knudson CB, Knudson W (2001) Cartilage proteoglycans. Semin Cell Dev Biol 12:69–78
Ko JY, Kim KI, Park S, Im GI (2014) In vitro chondrogenesis and in vivo repair of osteochondral defect with human induced pluripotent stem cells. Biomaterials 35:3571–3581
Kock L, van Donkelaar CC, Ito K (2012) Tissue engineering of functional articular cartilage: the current status. Cell Tissue Res 347:613–627
Konttinen YT, Mandelin J, Li TF, Salo J, Lassus J, Liljestrom M, Hukkanen M, Takagi M, Virtanen I, Santavirta S (2002) Acidic cysteine endoproteinase cathepsin K in the degeneration of the superficial articular hyaline cartilage in osteoarthritis. Arthritis Rheum 46:953–960
Korhonen RK, Laasanen MS, Toyras J, Rieppo J, Hirvonen J, Helminen HJ, Jurvelin JS (2002) Comparison of the equilibrium response of articular cartilage in unconfined compression, confined compression and indentation. J Biomech 35:903–909
Korkala O, Kuokkanen H (1991) Autogenous osteoperiosteal grafts in the reconstruction of full-thickness joint surface defects. Int Orthop 15:233–237
Kramer J, Bohrnsen F, Schlenke P, Rohwedel J (2006) Stem cell-derived chondrocytes for regenerative medicine. Transplant Proc 38:762–765
Kwan AP, Sear CH, Grant ME (1986) Identification of disulphide-bonded type X procollagen polypeptides in embryonic chick chondrocyte cultures. FEBS Lett 206:267–272
Kwan MK, Coutts RD, Woo SL, Field FP (1989) Morphological and biomechanical evaluations of neocartilage from the repair of full-thickness articular cartilage defects using rib perichondrium autografts: a long-term study. J Biomech 22:921–930
Lai WM, Hou JS, Mow VC (1991) A triphasic theory for the swelling and deformation behaviors of articular cartilage. J Biomech Eng 113:245–258
Lane JM, Weiss C (1975) Review of articular cartilage collagen research. Arthritis Rheum 18:553–562

LeBaron RG, Athanasiou KA (2000) Ex vivo synthesis of articular cartilage. Biomaterials 21:2575–2587
Lebourg M, Martinez-Diaz S, Garcia-Giralt N, Torres-Claramunt R, Ribelles JLG, Vila-Canet G, Monllau JC (2014) Cell-free cartilage engineering approach using hyaluronic acid-polycaprolactone scaffolds: a study invivo. J Biomater Appl 28:1304–1315
Lee DA, Bader DL (1995) The development and characterization of an in vitro system to study strain-induced cell deformation in isolated chondrocytes. In Vitro Cell Dev Biol 31:828–835
Lee DA, Bader DL (1997) Compressive strains at physiological frequencies influence the metabolism of chondrocytes seeded in agarose. J Orthop Res 15:181–188
Lee DA, Reisler T, Bader DL (2003) Expansion of chondrocytes for tissue engineering in alginate beads enhances chondrocytic phenotype compared to conventional monolayer techniques. Acta Orthop Scand 74:6–15
Levy YD, Gortz S, Pulido PA, McCauley JC, Bugbee WD (2013) Do fresh osteochondral allografts successfully treat femoral condyle lesions? Clin Orthop Relat Res 471:231–237
Li B, Aspden RM (1997) Composition and mechanical properties of cancellous bone from the femoral head of patients with osteoporosis or osteoarthritis. J Bone Miner Res 12:641–651
Li LP, Soulhat J, Buschmann MD, Shirazi-Adl A (1999) Nonlinear analysis of cartilage in unconfined ramp compression using a fibril reinforced poroelastic model. Clin Biomech (Bristol, Avon) 14:673–682
Li WJ, Tuli R, Huang X, Laquerriere P, Tuan RS (2005) Multilineage differentiation of human mesenchymal stem cells in a three-dimensional nanofibrous scaffold. Biomaterials 26:5158–5166
Lievense A, Bierma-Zeinstra S, Verhagen A, Verhaar J, Koes B (2001) Influence of work on the development of osteoarthritis of the hip: a systematic review. J Rheumatol 28:2520–2528
Lin JG, Chen WL (2009) Review: acupuncture analgesia in clinical trials. Am J Chin Med 37:1–18
Linn FC, Sokoloff L (1965) Movement and composition of interstitial fluid of cartilage. Arthritis Rheum 8:481–494
Lipshitz H, Etheredge R 3rd, Glimcher MJ (1976) Changes in the hexosamine content and swelling ratio of articular cartilage as functions of depth from the surface. J Bone Joint Surg Am 58:1149–1153
Livesley PJ, Doherty M, Needoff M, Moulton A (1991) Arthroscopic lavage of osteoarthritic knees. J Bone Joint Surg 73:922–926
Lusse S, Claassen H, Gehrke T, Hassenpflug J, Schunke M, Heller M, Gluer CC (2000) Evaluation of water content by spatially resolved transverse relaxation times of human articular cartilage. Magn Reson Imaging 18:423–430
Ma HL, Chen TH, Low-Tone Ho L, Hung SC (2005) Neocartilage from human mesenchymal stem cells in alginate: implied timing of transplantation. J Biomed Mater Res A 74:439–446
Mahomed MN, Beaver RJ, Gross AE (1992) The long-term success of fresh, small fragment osteochondral allografts used for intraarticular post-traumatic defects in the knee joint. Orthopedics 15:1191–1199
Mak AF (1986) The apparent viscoelastic behavior of articular cartilage – the contributions from the intrinsic matrix viscoelasticity and interstitial fluid flows. J Biomech Eng 108:123–130
Malinin T, Ouellette EA (2000) Articular cartilage nutrition is mediated by subchondral bone: a long-term autograft study in baboons. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 8:483–491
Mankin HJ (1962) Localization of tritiated thymidine in articular cartilage of rabbits: II. Repair in immature cartilage. J Bone Joint Surg Am 44:688–698
Mankin HJ (1974a) The reaction of articular cartilage to injury and osteoarthritis (first of two parts). N Engl J Med 291:1285–1292
Mankin HJ (1974b) The reaction of articular cartilage to injury and osteoarthritis (second of two parts). N Engl J Med 291:1335–1340

Mankin HJ (1982) The response of articular cartilage to mechanical injury. J Bone Joint Surg Am 64:460–466
Maroudas A (1976) Transport of solutes through cartilage: permeability to large molecules. J Anat 122:335–347
Maroudas A (1979) Physicochemical properties of articular cartilage. In: Freeman MAR (ed) Adult articular cartilage. Pitman Medical Publishing Co. Ltd, Kent, pp 215–290
Martin I, Obradovic B, Freed LE, Vunjak-Novakovic G (1999) Method for quantitative analysis of glycosaminoglycan distribution in cultured natural and engineered cartilage. Ann Biomed Eng 27:656–662
Masuoka K, Asazuma T, Ishihara M, Sato M, Hattori H, Ishihara M, Yoshihara Y, Matsui T, Takase B, Kikuchi M et al (2005) Tissue engineering of articular cartilage using an allograft of cultured chondrocytes in a membrane-sealed atelocollagen honeycomb-shaped scaffold (ACHMS scaffold). J Biomed Mater Res B Appl Biomater 75:177–184
Matsuno H, Nakamura H, Katayama K, Hayashi S, Kano S, Yudoh K, Kiso Y (2009) Effects of an oral administration of glucosamine-chondroitin-quercetin glucoside on the synovial fluid properties in patients with osteoarthritis and rheumatoid arthritis. Biosci Biotechnol Biochem 73:288–292
McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H et al (2014) OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthr Cartilage 22:363–388
McCutchen CW (n.d.) The frictional properties of animal joints. Wear 5:1–17
McKibbin B, Holdsworth FW (1966) The nutrition of immature joint cartilage in the lamb. J Bone Joint Surg 48:793–803
Meachim G, Stockwell RA (1979) The matrix. In: Freeman MAR (ed) Adult articular cartilage. Pitman Medical Publishing Co. Ltd, Kent, pp 600–610
Meisenberg G, Simmons WH (1998) Principles of medical biochemistry. Mosby Inc, St. Louis
Menche DS, Frenkel SR, Blair B, Watnik NF, Toolan BC, Yaghoubian RS, Pitman MI (1996) A comparison of abrasion burr arthroplasty and subchondral drilling in the treatment of full-thickness cartilage lesions in the rabbit. Arthroscopy 12:280–286
Messner K, Fahlgren A, Ross I, Andersson B (2000) Simultaneous changes in bone mineral density and articular cartilage in a rabbit meniscectomy model of knee osteoarthrosis. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 8:197–206
Meyers MH, Akeson W, Convery FR (1989) Resurfacing of the knee with fresh osteochondral allograft. J Bone Joint Surg Am 71:704–713
Micheli LJ, Browne JE, Erggelet C, Fu F, Mandelbaum B, Moseley JB, Zurakowski D (2001) Autologous chondrocyte implantation of the knee: multicenter experience and minimum 3-year follow-up. Clin J Sport Med 11:223–228
Min BH, Choi WH, Lee YS, Park SR, Choi BH, Kim YJ, Jin LH, Yoon JH (2013) Effect of different Bone Marrow Stimulation Techniques (BSTs) on MSCs mobilization. J Orthop Res 31:1814–1819
Minas T (1998) Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life. Am J Orthop (Belle Mead NJ) 27:739–744
Minegishi Y, Hosokawa K, Tsumaki N (2013) Time-lapse observation of the dedifferentiation process in mouse chondrocytes using chondrocyte-specific reporters. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 21:1968–1975
Minguell JJ, Erices A, Conget P (2001) Mesenchymal stem cells. Exp Biol Med 226:507–520
Mitchell N, Shepard N (1987) Effect of patellar shaving in the rabbit. J Orthop Res 5:388–392
Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR (2009) Clinical efficacy of the microfracture technique for articular cartilage repair in the knee an evidence-based systematic analysis. Am J Sport Med 37:2053–2063
Moldovan F, Pelletier JP, Hambor J, Cloutier JM, Martel-Pelletier J (1997) Collagenase-3 (matrix metalloprotease 13) is preferentially localized in the deep layer of human arthritic cartilage in situ: in vitro mimicking effect by transforming growth factor beta. Arthritis Rheum 40:1653–1661

Mollenhauer J, Bee JA, Lizarbe MA, von der Mark K (1984) Role of anchorin CII, a 31,000-mol-wt membrane protein, in the interaction of chondrocytes with type II collagen. J Cell Biol 98:1572–1579

Mooney DJ, Baldwin DF, Suh NP, Vacanti JP, Langer R (1996) Novel approach to fabricate porous sponges of poly(D, L-lactic-co-glycolic acid) without the use of organic solvents. Biomaterials 17:1417–1422

Moran ME, Kim HK, Salter RB (1992) Biological resurfacing of full-thickness defects in patellar articular cartilage of the rabbit. Investigation of autogenous periosteal grafts subjected to continuous passive motion. J Bone Joint Surg 74:659–667

Moseley JB Jr, Wray NP, Kuykendall D, Willis K, Landon G (1996) Arthroscopic treatment of osteoarthritis of the knee: a prospective, randomized, placebo-controlled trial. Results of a pilot study. Am J Sports Med 24:28–34

Mow VC, Kuei SC, Lai WM, Armstrong CG (1980) Biphasic creep and stress relaxation of articular cartilage in compression? Theory and experiments. J Biomech Eng 102:73–84

Mow VC, Holmes MH, Lai WM (1984) Fluid transport and mechanical properties of articular cartilage: a review. J Biomech 17:377–394

Mow VC, Ratcliffe A, Poole AR (1992) Cartilage and diarthrodial joints as paradigms for hierarchical materials and structures. Biomaterials 13:67–97

Muir H (1980) The chemistry of the ground substance of joint cartilage. In: Sokolff L (ed) The joints and synovial fluid II. Academic, New York, pp 27–94

Muir H (1995) The chondrocyte, architect of cartilage. Biomechanics, structure, function and molecular biology of cartilage matrix macromolecules. Bioessays 17:1039–1048

Muir H, Bullough P, Maroudas A (1970) The distribution of collagen in human articular cartilage with some of its physiological implications. J Bone Joint Surg 52:554–563

Nakase T, Kaneko M, Tomita T, Myoui A, Ariga K, Sugamoto K, Uchiyama Y, Ochi T, Yoshikawa H (2000) Immunohistochemical detection of cathepsin D, K, and L in the process of endochondral ossification in the human. Histochem Cell Biol 114:21–27

Naqvi SM, Buckley CT (2015) Differential response of encapsulated nucleus pulposus and bone marrow stem cells in isolation and coculture in alginate and chitosan hydrogels. Tissue Eng A 21:288–299

Niederauer GG, Slivka MA, Leatherbury NC, Korvick DL, Harroff HH, Ehler WC, Dunn CJ, Kieswetter K (2000) Evaluation of multiphase implants for repair of focal osteochondral defects in goats. Biomaterials 21:2561–2574

Nishida K, Inoue H, Murakami T (1995) Immunohistochemical demonstration of fibronectin in the most superficial layer of normal rabbit articular cartilage. Ann Rheum Dis 54:995–998

Nishitani K, Nakagawa Y, Gotoh T, Kobayashi M, Nakamura T (2008) Intraoperative acoustic evaluation of living human cartilage of the elbow and knee during mosaicplasty for osteochondritis dissecans of the elbow: an in vivo study. Am J Sports Med 36:2345–2353

O'Byrne E, Pellas T, Laurent D (2003) Qualitative and quantitative in vivo assessment of articular cartilage using magnetic resonance imaging. Novartis Found Symp 249:190–198; discussion 198-202, 234-198, 239-141

O'Conor CJ, Leddy HA, Benefield HC, Liedtke WB, Guilak F (2014) TRPV4-mediated mechanotransduction regulates the metabolic response of chondrocytes to dynamic loading. Proc Natl Acad Sci U S A 111:1316–1321

Ohlsen L (1976) Cartilage formation from free perichondrial grafts: an experimental study in rabbits. Br J Plast Surg 29:262–267

Oldershaw RA, Baxter MA, Lowe ET, Bates N, Grady LM, Soncin F, Brison DR, Hardingham TE, Kimber SJ (2010) Directed differentiation of human embryonic stem cells toward chondrocytes. Nat Biotechnol 28:1221–U1280

Orozco L, Munar A, Soler R, Alberca M, Soler F, Huguet M, Sentis J, Sanchez A, Garcia-Sancho J (2014) Treatment of knee osteoarthritis with autologous mesenchymal stem cells: two-year follow-up results. Transplantation 97:e66–e68

Ossendorf C, Kaps C, Kreuz PC, Burmester GR, Sittinger M, Erggelet C (2007) Treatment of posttraumatic and focal osteoarthritic cartilage defects of the knee with autologous polymer-based three-dimensional chondrocyte grafts: 2-year clinical results. Arthritis Res Ther 9:R41

Ostrander RV, Goomer RS, Tontz WL, Khatod M, Harwood FL, Maris TM, Amiel D (2001) Donor cell fate in tissue engineering for articular cartilage repair. Clin Orthop Relat Res 389:228–237

Owens S, Wagner P, Vangsness CT Jr (2004) Recent advances in glucosamine and chondroitin supplementation. J Knee Surg 17:185–193

Pavesio A, Abatangelo G, Borrione A, Brocchetta D, Hollander AP, Kon E, Torasso F, Zanasi S, Marcacci M (2003) Hyaluronan-based scaffolds (Hyalograft C) in the treatment of knee cartilage defects: preliminary clinical findings. Novartis Found Symp 249:203–217; discussion 229-233, 234-208, 239-241

Pedersen MS, Moghaddam AZ, Bak K, Koch JS (1995) The effect of bone drilling on pain in gonarthrosis. Int Orthop 19:12–15

Perka C, Schultz O, Spitzer RS, Lindenhayn K, Burmester GR, Sittinger M (2000) Segmental bone repair by tissue-engineered periosteal cell transplants with bioresorbable fleece and fibrin scaffolds in rabbits. Biomaterials 21:1145–1153

Peterson L, Minas T, Brittberg M, Lindahl A (2003) Treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: results at two to ten years. J Bone Joint Surg Am 85-A(Suppl 2):17–24

Peterson L, Vasiliadis HS, Brittberg M, Lindahl A (2010) Autologous chondrocyte implantation a long-term follow-up. Am J Sport Med 38:1117–1124

Pfander D, Cramer T, Weseloh G, Pullig O, Schuppan D, Bauer M, Swoboda B (1999) Hepatocyte growth factor in human osteoarthritic cartilage. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 7:548–559

Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR (1999) Multilineage potential of adult human mesenchymal stem cells. Science 284:143–147

Poole CA (1997) Articular cartilage chondrons: form, function and failure. J Anat 191(Pt 1):1–13

Poole AR, Pidoux I, Reiner A, Rosenberg L (1982) An immunoelectron microscope study of the organization of proteoglycan monomer, link protein, and collagen in the matrix of articular cartilage. J Cell Biol 93:921–937

Pretzel D, Linss S, Rochler S, Endres M, Kaps C, Alsalameh S, Kinne RW (2011) Relative percentage and zonal distribution of mesenchymal progenitor cells in human osteoarthritic and normal cartilage. Arthritis Res Ther 13:R64(1–15)

Pugh JW, Radin EL, Rose RM (1974) Quantitative studies of human subchondral cancellous bone. Its relationship to the state of its overlying cartilage. J Bone Joint Surg Am 56:313–321

Pulkkinen L, Kainulainen K, Krusius T, Makinen P, Schollin J, Gustavsson KH, Peltonen L (1990) Deficient expression of the gene coding for decorin in a lethal form of Marfan syndrome. J Biol Chem 265:17780–17785

Quinn TM, Morel V, Meister JJ (2001) Static compression of articular cartilage can reduce solute diffusivity and partitioning: implications for the chondrocyte biological response. J Biomech 34:1463–1469

Radin EL, Rose RM (1986) Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop Relat Res 213:34–40

Radin EL, Paul IL, Lowy M (1970) A comparison of the dynamic force transmitting properties of subchondral bone and articular cartilage. J Bone Joint Surg Am 52:444–456

Ratcliffe A, Mow VC (1976) Structure and function of articular cartilage. In: Comper WD (ed) Extracellular matrix Harwood Academic Publisher, pp 234–302

Reboul P, Pelletier JP, Tardif G, Benderdour M, Ranger P, Bottaro DP, Martel-Pelletier J (2001) Hepatocyte growth factor induction of collagenase 3 production in human osteoarthritic cartilage: involvement of the stress-activated protein kinase/c-Jun N-terminal kinase pathway and a sensitive p38 mitogen-activated protein kinase inhibitor cascade. Arthritis Rheum 44:73–84

Redman SN, Dowthwaite GP, Thomson BM, Archer CW (2004) The cellular responses of articular cartilage to sharp and blunt trauma. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 12:106–116

Reinhold T, Witt CM, Jena S, Brinkhaus B, Willich SN (2008) Quality of life and cost-effectiveness of acupuncture treatment in patients with osteoarthritis pain. Eur J Health Econ 9:209–219
Repo RU, Finlay JB (1977) Survival of articular cartilage after controlled impact. J Bone Joint Surg Am 59:1068–1076
Rey-Rico A, Venkatesan JK, Sohier J, Moroni L, Cucchiarini M, Madry H (2015) Adapted chondrogenic differentiation of human mesenchymal stem cells via controlled release of TGF-beta1 from poly(ethylene oxide)-terephtalate/poly(butylene terepthalate) multiblock scaffolds. J Biomed Mater Res A 103:371–383
Ringe J, Sittinger M (2009) Tissue engineering in the rheumatic diseases. Arthritis Res Ther 11:211
Ringe J, Burmester GR, Sittinger M (2012) Regenerative medicine in rheumatic disease-progress in tissue engineering. Nat Rev Rheumatol 8:493–498
Risbud MV, Sittinger M (2002) Tissue engineering: advances in in vitro cartilage generation. Trends Biotechnol 20:351–356
Roddy E, Zhang W, Doherty M (2005) Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis 64:544–548
Romeo AA, Cole BJ, Mazzocca AD, Fox JA, Freeman KB, Joy E (2002) Autologous chondrocyte repair of an articular defect in the humeral head. Arthroscopy 18:925–929
Rosenberg L (1971) Chemical basis for the histological use of safranin O in the study of articular cartilage. J Bone Joint Surg Am 53:69–82
Ruoslahti E, Yamaguchi Y (1991) Proteoglycans as modulators of growth factor activities. Cell 64:867–869
Russlies M, Behrens P, Wunsch L, Gille J, Ehlers EM (2002) A cell-seeded biocomposite for cartilage repair. Ann Anat 184:317–323
Ryan MC, Sandell LJ (1990) Differential expression of a cysteine-rich domain in the amino-terminal propeptide of type II (cartilage) procollagen by alternative splicing of mRNA. J Biol Chem 265:10334–10339
Salter DM (1993) Tenascin is increased in cartilage and synovium from arthritic knees. Br J Rheumatol 32:780–786
Sams AE, Minor RR, Wootton JA, Mohammed H, Nixon AJ (1995) Local and remote matrix responses to chondrocyte-laden collagen scaffold implantation in extensive articular cartilage defects. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 3:61–70
Samuel RE, Lee CR, Ghivizzani SC, Evans CH, Yannas IV, Olsen BR, Spector M (2002) Delivery of plasmid DNA to articular chondrocytes via novel collagen-glycosaminoglycan matrices. Hum Gene Ther 13:791–802
Sawitzke AD, Shi H, Finco MF, Dunlop DD, Bingham CO 3rd, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG et al (2008) The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. Arthritis Rheum 58:3183–3191
Schell H, Lienau J, Kleemann RU, Schlichting K, Taylor WR, Weiler A, Duda GN (2007) Crushed bone grafts and a collagen membrane are not suitable for enhancing cartilage quality in the regeneration of osteochondral defects – an in vivo study in sheep. J Biomech 40(Suppl 1):S64–S72
Schlichting K, Schell H, Kleemann RU, Schill A, Weiler A, Duda GN, Epari DR (2008) Influence of scaffold stiffness on subchondral bone and subsequent cartilage regeneration in an ovine model of osteochondral defect healing. Am J Sports Med 36:2379–2391
Schminke B, Miosge N (2014) Cartilage repair in vivo: the role of migratory progenitor cells. Curr Rheumatol Rep 16:461
Schneider U, Rackwitz L, Andereya S, Fensky F, Reichert J, Loer I, Barthel T, Rudert M, Noth U (2011) A prospective multicenter study on the outcome of type I collagen hydrogel-based autologous chondrocyte implantation (CaReS) for the repair of articular cartilage defects in the knee. Am J Sport Med 39:2558–2565
Selmi TA, Verdonk P, Chambat P, Dubrana F, Potel JF, Barnouin L, Neyret P (2008) Autologous chondrocyte implantation in a novel alginate-agarose hydrogel: outcome at two years. J Bone Joint Surg 90:597–604

Seol D, McCabe DJ, Choe H, Zheng HJ, Yu Y, Jang K, Walter MW, Lehman AD, Ding L, Buckwalter JA et al (2012) Chondrogenic progenitor cells respond to cartilage injury. Arthritis Rheum 64:3626–3637

Seradge H, Kutz JA, Kleinert HE, Lister GD, Wolff TW, Atasoy E (1984) Perichondrial resurfacing arthroplasty in the hand. J Hand Surg 9:880–886

Sharma B, Fermanian S, Gibson M, Unterman S, Herzka DA, Cascio B, Coburn J, Hui AY, Marcus N, Gold GE et al (2013) Human cartilage repair with a photoreactive adhesive-hydrogel composite. Sci Transl Med 5:167ra6(1–11)

Sirlin CB, Brossmann J, Boutin RD, Pathria MN, Convery FR, Bugbee W, Deutsch R, Lebeck LK, Resnick D (2001) Shell osteochondral allografts of the knee: comparison of mr imaging findings and immunologic responses. Radiology 219:35–43

Sittinger M, Bujia J, Minuth WW, Hammer C, Burmester GR (1994) Engineering of cartilage tissue using bioresorbable polymer carriers in perfusion culture. Biomaterials 15:451–456

Sittinger M, Hutmacher DW, Risbud MV (2004) Current strategies for cell delivery in cartilage and bone regeneration. Curr Opin Biotechnol 15:411–418

Sledge SL (2001) Microfracture techniques in the treatment of osteochondral injuries. Clin Sports Med 20:365–377

Solchaga LA, Gao J, Dennis JE, Awadallah A, Lundberg M, Caplan AI, Goldberg VM (2002) Treatment of osteochondral defects with autologous bone marrow in a hyaluronan-based delivery vehicle. Tissue Eng 8:333–347

Soren A (1965) Treatment of musculoskeletal disorders with ultrasound. J Occup Med 7:434–438

Steadman JR, Rodkey WG, Briggs KK, Rodrigo JJ (1999) The microfracture technique to treat full thickness articular cartilage defects of the knee. Orthopade 28:26–32

Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG (2003) Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. Arthrosc J Arthrosc Relat Surg 19:477–484

Stevenson S (1987) The immune response to osteochondral allografts in dogs. J Bone Joint Surg Am 69:573–582

Stevenson S, Dannucci GA, Sharkey NA, Pool RR (1989) The fate of articular cartilage after transplantation of fresh and cryopreserved tissue-antigen-matched and mismatched osteochondral allografts in dogs. J Bone Joint Surg Am 71:1297–1307

Stockwell RA, Meachim G (1979) The chondrocyte. In: Freeman MAR (ed) Adult articular cartilage. Pitman Medical Publishing Co. Ltd, Kent, pp 600–610

Suzuki S, Muneta T, Tsuji K, Ichinose S, Makino H, Umezawa A, Sekiya I (2012) Properties and usefulness of aggregates of synovial mesenchymal stem cells as a source for cartilage regeneration. Arthritis Res Ther 14:R136(1–13)

Swieszkowski W, Tuan BHS, Kurzydlowski KJ, Hutmacher DW (2007) Repair and regeneration of osteochondral defects in the articular joints. Biomol Eng 24:489–495

Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126:663–676

Tamai N, Myoui A, Hirao M, Kaito T, Ochi T, Tanaka J, Takaoka K, Yoshikawa H (2005) A new biotechnology for articular cartilage repair: subchondral implantation of a composite of interconnected porous hydroxyapatite, synthetic polymer (PLA-PEG), and bone morphogenetic protein-2 (rhBMP-2). Osteoarthr Cartilage/OARS Osteoarthr Res Soc 13:405–417

Temenoff JS, Mikos AG (2000) Review: tissue engineering for regeneration of articular cartilage. Biomaterials 21:431–440

Tew SR, Kwan AP, Hann A, Thomson BM, Archer CW (2000) The reactions of articular cartilage to experimental wounding: role of apoptosis. Arthritis Rheum 43:215–225

Thompson RC Jr (1975) An experimental study of surface injury to articular cartilage and enzyme responses within the joint. Clin Orthop Relat Res 239–248

Tibesku CO, Szuwart T, Kleffner TO, Schlegel PM, Jahn UR, Van Aken H, Fuchs S (2004) Hyaline cartilage degenerates after autologous osteochondral transplantation. J Orthop Res 22:1210–1214

Torzilli PA, Mow VC (1976) On the fundamental fluid transport mechanisms through normal and pathological articular cartilage during function – I. The formulation. J Biomech 9:541–552
Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G (2006) Acetaminophen for osteoarthritis. Cochrane database of systematic reviews (Online) CD004257
Tsumaki N, Okada M, Yamashita A (2015) iPS cell technologies and cartilage regeneration. Bone 70:48–54
Vangsness CT, Smith CF (1995) Arthroscopic shoulder surgeyr with three different laser systems: An evaluation of laser applications. Arthrosc: J Arthrosc Relat Surg 11:696–700
Vega A, Martin-Ferrero MA, Del Canto F, Alberca M, Garcia V, Munar A, Orozco L, Soler R, Fuertes JJ, Huguet M et al (2015) Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. Transplantation 99(8):1681–1690
Vogel KG, Paulsson M, Heinegard D (1984) Specific inhibition of type I and type II collagen fibrillogenesis by the small proteoglycan of tendon. Biochem J 223:587–597
Wakitani S, Goto T, Pineda SJ, Young RG, Mansour JM, Caplan AI, Goldberg VM (1994) Mesenchymal cell-based repair of large, full-thickness defects of articular cartilage. J Bone Joint Surg Am 76:579–592
Wakitani S, Imoto K, Yamamoto T, Saito M, Murata N, Yoneda M (2002) Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. Osteoarthr Cartilage/OARS Osteoarthr Res Soc 10:199–206
Wegman A, van der Windt D, van Tulder M, Stalman W, de Vries T (2004) Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. J Rheumatol 31:344–354
Weightman B, Kempson GE (1979) Load cartilage. In: Freeman MAR (ed) Adult articular cartilage. Pitman Medical Publishing Co. Ltd, Kent, pp 291–331
Welch V, Brosseau L, Peterson J, Shea B, Tugwell P, Wells G (2001) Therapeutic ultrasound for osteoarthritis of the knee. Cochrane database of systematic reviews (Online) CD003132
Whiteside RA, Jakob RP, Wyss UP, Mainil-Varlet P (2005) Impact loading of articular cartilage during transplantation of osteochondral autograft. J Bone Joint Surg 87:1285–1291
Williams R, Khan IM, Richardson K, Nelson L, McCarthy HE, Analbelsi T, Singhrao SK, Dowthwaite GP, Jones RE, Baird DM et al (2010) Identification and clonal characterisation of a progenitor cell sub-population in normal human articular cartilage. PLoS One 5:e13246(1–14)
Wilusz RE, Sanchez-Adams J, Guilak F (2014) The structure and function of the pericellular matrix of articular cartilage. Matrix Biol: J Int Soc Matrix Biol 39:25–32
Wong M, Ponticiello M, Kovanen V, Jurvelin JS (2000) Volumetric changes of articular cartilage during stress relaxation in unconfined compression. J Biomech 33:1049–1054
Wyre RM, Downes S (2000) An in vitro investigation of the PEMA/THFMA polymer system as a biomaterial for cartilage repair. Biomaterials 21:335–343
Yoo JU, Barthel TS, Nishimura K, Solchaga L, Caplan AI, Goldberg VM, Johnstone B (1998) The chondrogenic potential of human bone-marrow-derived mesenchymal progenitor cells. J Bone Joint Surg Am 80:1745–1757
Zantop T, Petersen W (2009) Arthroscopic implantation of a matrix to cover large chondral defect during microfracture. Arthroscopy 25:1354–1360
Zeifang F, Oberle D, Nierhoff C, Richter W, Moradi B, Schmitt H (2010) Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation: a randomized clinical trial. Am J Sports Med 38:924–933
Zhang W, Jones A, Doherty M (2004) Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. Ann Rheum Dis 63:901–907
Zhang W, Chen JL, Tao JD, Jiang YZ, Hu CC, Huang L, Ji JF, Ouyang HW (2013) The use of type 1 collagen scaffold containing stromal cell-derived factor-1 to create a matrix environment conducive to partial-thickness cartilage defects repair. Biomaterials 34:713–723
Zhu Y, Wan Y, Zhang J, Yin D, Cheng W (2014) Manufacture of layered collagen/chitosan-polycaprolactone scaffolds with biomimetic microarchitecture. Colloids Surf B: Biointerfaces 113:352–360