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ORIGINAL ARTICLE

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Biology of bone and how it orchestrates the form and function of the skeleton

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Abstract The principal role of the skeleton is to provide structural support for the body. While the skeleton also serves as the body's mineral reservoir, the mineralized structure is the very basis of posture, opposes muscular contraction resulting in motion, withstands functional load bearing, and protects internal organs. Although the mass and morphology of the skeleton is defined, to some extent, by genetic determinants, it is the tissue's ability to remodel – the local resorption and formation of bone – which is responsible for achieving this intricate balance between competing responsibilities. The aim of this review is to address bone's form–function relationship, beginning with extensive research in the musculoskeletal disciplines, and focusing on several recent cellular and molecular discoveries which help understand the complex interdependence of bone cells, growth factors, physical stimuli, metabolic demands, and structural responsibilities. With a clinical and spine-oriented audience in mind, the principles of bone cell and molecular biology and physiology are presented, and an attempt has been made to incorporate epidemiologic data and therapeutic implications. Bone research remains interdisciplinary by nature, and a deeper understanding of bone biology will ultimately lead to advances in the treatment of diseases and injuries to bone itself.

Keywords Bone · Skeleton · Orthopedic · Growth Factors · Morphology · Osteoblasts · Osteoclasts · Osteocytes · Remodeling

Introduction

The skeleton's principal role as a structure has predisposed bone to the unfortunate reputation of being an inert and static material. Given bone tissue's ability to adapt its mass and morphology to functional demands, its ability to repair itself without leaving a scar, and its capacity to rapidly mobilize mineral stores on metabolic demand, it is in fact the ultimate "smart" material [43] and a dynamic example of "form follows function" in biological systems [45]. Considering the ever-growing number of patients who suffer from devastating disorders of the skeleton and the ever-increasing opportunities inherent in the post-genomics era to treat diseases and injuries to bone [44], it is critical for both the physician and the scientist to more fully understand the biology of bone and how its ability to form and resorb tissue ultimately orchestrates the structural and metabolic successes of the skeleton.

Cells

Three distinctly different cell types can be found within bone: the matrix-producing osteoblast, the tissue-resorbing osteoclast, and the osteocyte, which accounts for 90% of all cells in the adult skeleton. Osteocytes can be viewed as highly specialized and fully differentiated osteoblasts;

similarly, osteoblasts have recently been described as sophisticated fibroblasts [19]. Fibroblasts, osteoblasts, osteocytes, and adipocytes derive from pluripotent mesenchymal stem cells [3], whereas osteoclasts are of hematopoietic descent and their precursors are located in the monocytic fraction of the bone marrow [22].

Osteoblasts

Functionally, osteoblasts are the cells within bone that lay down the extracellular matrix and regulate its mineralization. Morphologically, these cells are cuboidal in shape and located at the bone surface together with their precursors, where they form a tight layer of cells. Osteoblasts are highly anchorage dependent and rely on extensive cell–matrix and cell–cell contacts via a variety of transmembranous proteins (integrins, connexins, cadherins) and specific receptors (for cytokines, hormones, growth factors) to maintain cellular function and responsiveness to metabolic and mechanical stimuli [21,29].

The lifespan of an osteoblast ranges between 3 days in young rabbits up to 8 weeks in humans, during which time it lays down 0.5–1.5 μm osteoid per day [27,36]. Eventually, some osteoblasts may become "trapped" in their own calcified matrix, changing their phenotype and developing into osteocytes. These cells continue to thrive, but considerably reduce their cell organelles and the production of matrix proteins. They remain connected with other similar cells but also with bone-lining cells (inactive osteoblasts) at the bone's surface, creating an extensive network of intercellular communication. There is accumulating evidence for a functional role of these cellular connections in sensing the need for and directing the site of new bone formation [15,33].

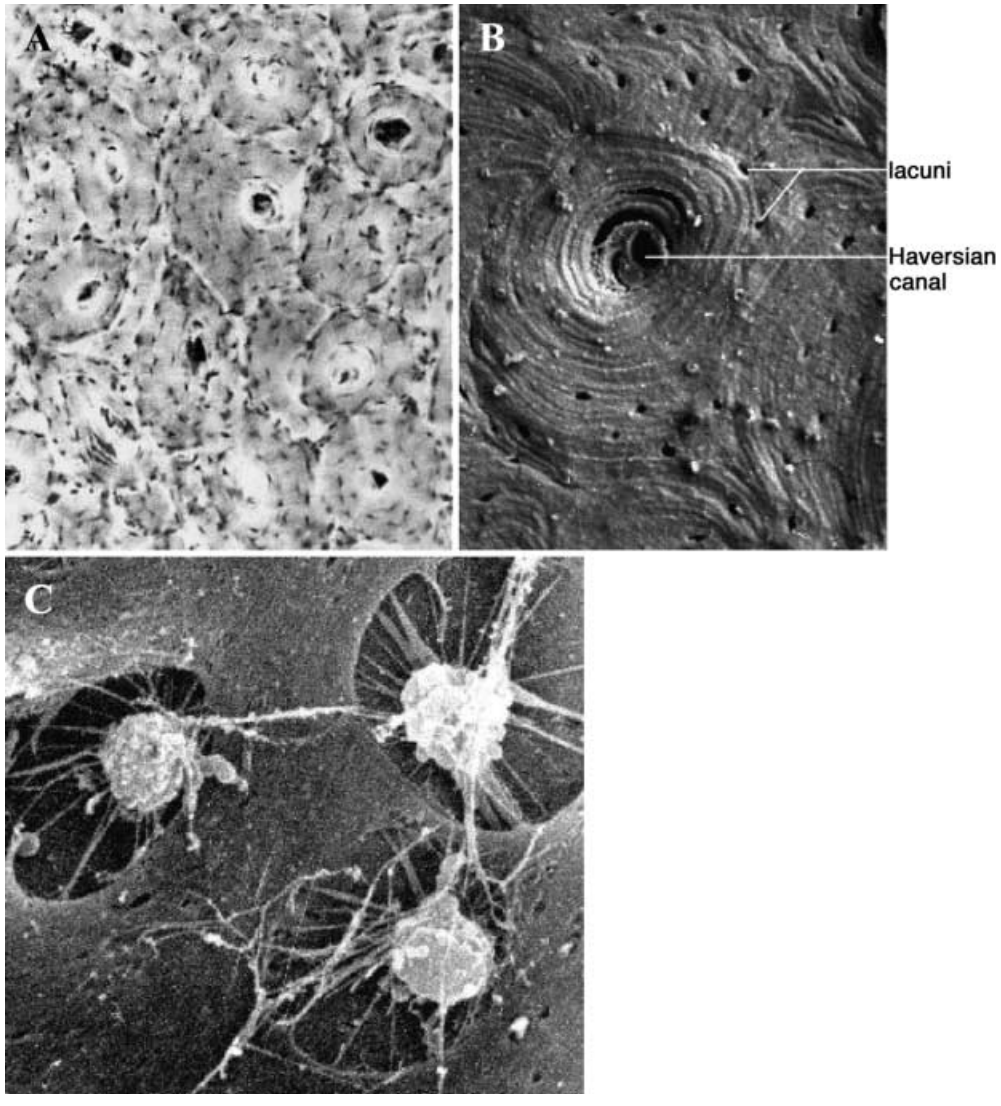

Fig. 1A–C Ultrastructure of bone. **A** Light microscope image of a ground section of compact bone. Osteons or Haversian systems can be seen. The central dark circle is the Haversian canal, which contains a nutrient artery in vivo. It is surrounded by concentric lamellae of calcified bone matrix. The dark spots visible within the compacta are the lacuni in which osteocytes become entrapped. ×350. **B** Scanning electron micrograph (SEM) of a Haversian system. ×800. **C** SEM at higher magnification reveals individual osteocytes with cellular processes reaching out towards the lacunar wall and interconnecting cells in an intricate network. ×1600. (Reproduced with permission from the Dept. of Functional Anatomy of the University of Glasgow, http://www.anatomy.gla.ac.uk/fab/)

Osteoclasts

The main feature of osteoclasts is their ability to resorb fully mineralized bone at sites called Howship's lacunae. Both macrophages and osteoclasts are derived from hematopoietic stem cells and, similar to macrophages, osteoclasts are highly migratory, multinucleated, and polarized cells which carry an arsenal of lysosomal enzymes [46]. They have to be highly specialized to fulfill their task and possess several unique ultrastructural characteristics, such as pleomorphic mitochondria, vacuoles, and lysosomes [47]. Probably the most intriguing feature is the apical membrane, which is able to form a tight seal with the calcified matrix. A resorption bay is formed underneath the cell into which the lytic enzymes are secreted. In addition, proton pumps lower the pH in this subosteoclastic space to values between 2 and 4, activating the secreted enzymes such as tartrate-resistant acid phosphatase [7]. An activated osteoclast is able to resorb 200,000 μm^3/day, an amount of bone formed by seven to ten generations of osteoblasts with an average lifespan of 15–20 days [1].

Osteocytes

Derived from osteoblasts yet distinctly different in morphology and function, osteocytes are the most abundant cells in bone. They are smaller in size than osteoblasts, contain less cell organelles such as ribosomes and endoplasmatic reticula, and have an increased nucleus to cytoplasm ratio. There is a higher number of filopodia, or cytoplasmatic extensions, which serve to interconnect the osteocytes and to connect them with the bone-lining cells, creating a veritable three-dimensional syncitium (Fig. 1), the function of which is beginning to emerge [12]. Considering that it is osteocytes that are the principal cell in adult bone and that neither osteoclasts nor osteoblasts are evident in any significant numbers in a skeleton with low turnover, it appears that this osteocyte construct may actually orchestrate the spatial and temporal recruitment of the cells that form and resorb bone [9].

Interaction of bone-forming and bone-resorbing cells

Although it was suggested for many years that crosstalk between osteoblasts and osteoclasts must exist to coordinate processes of bone formation and resorption, it was not until 1997 that a molecular basis for this paradigm was discovered in the form of osteoprotegerin (OPG) and, shortly after, its cognate ligand OPG-L, a transmembranous receptor expressed on osteoblasts and immune cells. Both of these molecules can bind to RANK (receptor/activator of NF-κB), a transmembranous receptor expressed on osteoclast precursor cells. Interaction between OPG-L and RANK initiates a signaling and gene expression cascade resulting in the promotion of osteoclast formation from the precursor pool. In this setting, OPG, which is secreted by osteoblasts, but also expressed in many other tissues, acts as a soluble competitive binding partner for RANK-L, which inhibits osteoclast formation and, consequentially, bone resorption [24] (Fig. 2). This crosstalk mechanism also appears to be an endpoint for the action of several calciotropic hormones and cytokines such as 1,25-$(OH)_2D_3$, parathyroid hormone (PTH), estrogen, prostaglandin E_2 (PGE_2), interleukins, and tumor necrosis factor (TNF)-α. As a result of these findings, and a mere 3 years after its discovery, OPG has already entered clinical trials as a promising therapeutic agent for osteoporosis [4,23].

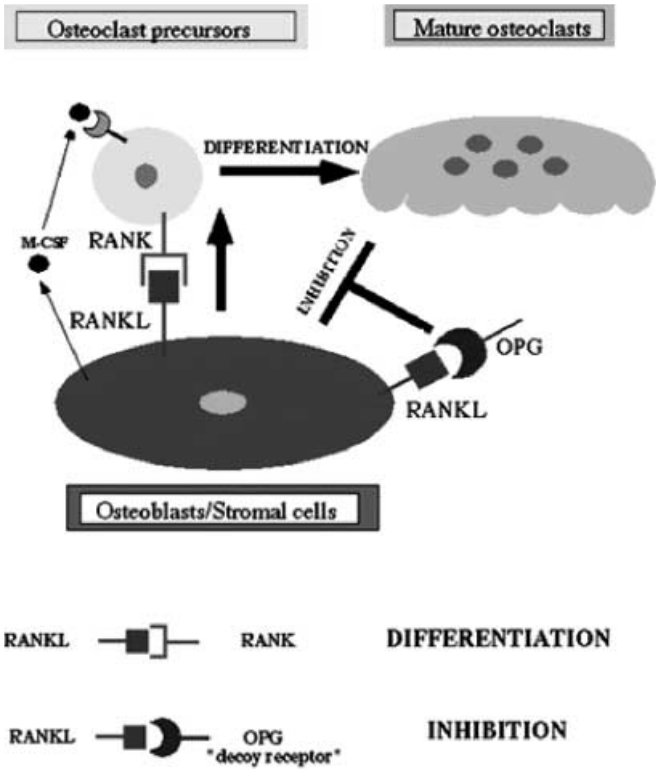

Fig. 2 Schematic of osteoblast–osteoclast interaction via RANK/RANK-L and the soluble protein osteoprotegerin (*OPG*). RANK-L, a transmembranous receptor on the surface of mature osteoblasts, interacts with the transmembranous RANK receptor on osteoblast precursor cells. This interaction induces proliferation and differentiation of osteoclasts in the presence of the permissive factor macrophage colony-stimulating factor (M-CSF) and can be inhibited by OPG. (Reproduced with permission from [4])

Extracellular matrix

Calcified bone contains about 25% organic matrix, including cells (2–5%), 5% water, and 70% inorganic mineral (hydroxylapatite). Osteoid, the freshly synthesized matrix prior to its mineralization, consists primarily (approx. 94%) of collagen. Other proteins, some of them unique to bone, such as osteocalcin, are embedded in the

extracellular matrix and may have important signaling functions (bone morphogeneic proteins, growth factors, cytokines, adhesion molecules) or play a role during the mineralization process (osteopontin, osteonectin, matrix-gla protein). The use of knockout mice lacking the ability to synthesize these proteins has shed light on the individual functions of some of these proteins. Osteocalcin-deficient mice, for example, display increased bone formation [18], whereas mice lacking osteonectin are osteopenic due to reduced bone remodeling [14].

Most of the non-collagenous proteins in bone consist of proteoglycans, the function of which was regarded until recently as structural. Recent findings, however, using transgenic mouse models show that at least some of these molecules such as perlecan and biglycan, in addition to their role in defining the spatial organization of the extracellular matrix (ECM), can also have unique functions at a biochemical level. In the case of perlecan, for example, synthesis of proteoglycan is essential for survival of these animals, possibly due to roles in facilitating cellular signaling and/or interactions with growth factors during development [2].

Ten to 15 days after the organic matrix has been laid down, it begins to mineralize. During this period, the mineral content suddenly increases to 70% of its final amount, whereas deposition of the final 30% takes several months. While the actual process of mineralization remains poorly understood, several investigators believe that the initiators of this process are small, round, extracellular, lipid bilaminar organelles which bud from hypertrophic chondrocytes, or osteoblasts. These matrix vesicles contain phosphatases, phospholipids, and calcium ions. At a point of supersaturation, mineral crystalization begins and as the matrix vesicles disintegrate, the mineral is exposed to the matrix where the process of mineralization proceeds in a self-perpetuating manner. During this process, collagen fibrils, fibronectin, and glycoproteins such as osteonectin and osteopontin determine the orientation and organization of the bone mineral crystal [11]. Other glycoproteins such as matrix-gla protein and glycosaminoglycans appear to play a role in the inhibition of excessive mineralization [50].

Bone mineral is generically referred to as hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], a plate-like crystal 20–80 nm in length and 2–5 nm thick. Because it is four times smaller than naturally occurring apatites and less perfect in structure, it is more reactive and soluble and facilitates chemical turnover [48]. In other words, a more “perfect” crystal would be difficult to resorb, and thus repair of the matrix would be hindered. Typically, the degree of mineralization of bone, or bone mineral density (BMD), is estimated in the clinic via dual-energy X-ray absorptiometry (DXA) or quantitative computed tomography (qCT) and is the principal diagnostic tool for osteoporosis [38].

Development

The vertebrate skeleton is the product of complex, coordinated, and synergistic interaction between three distinctly different cell lines. Cells derived from the neural crest are responsible for the development of the branchial arches and, ultimately, the craniofacial skeleton; sclerotome cells, a subdivision of the somites and of mesodermal origin, give rise to the axial skeleton; and the lateral plate mesoderm is the starting point for limb bud formation and long bone development [6].

Two mechanisms of bone formation can be observed during morphogenesis. One option involves mesenchymal cells differentiating directly into osteoblasts, which then proceed to form bone. This membranous or intramembranous bone formation is found during skull development, but also in maxilla and mandibula morphogenesis. If differentiation of mesenchymal cells proceeds via chondrocytes, which then form cartilaginous templates or so-called anlagen of the future bones, the process is termed endochondral ossification. The cartilage anlagen develop by interstitial and appositional growth and are at some point replaced by invading osteoblasts, which replace the hypertrophic cartilage and allow ossification of the structure [35].

The axial skeleton begins to develop in humans at 4 weeks postgestation, when cells from the paraxial mesoderm condense to form somites and subsequently sclerotomes. After differentiating into chondrocytes and migrating ventral, dorsal, and lateral to the neural tube, the cartilage anlagen for the vertebral body, neural arches, and ribs or transverse processes, respectively, are formed (Fig. 3).

A key aspect during development of the vertebral column is to create a flexible enclosure to allow continuous growth of the neural components, which develop slower and later. During the precartilaginous stage (week 4–6), the vertebral anlage is formed by the sclerotomal mesenchyme surrounding the notochord. Each sclerotome has two components, of which the cranial loose cells fuse with the next segment, whereas the caudal dense cells form the fibrous ring of the intervertebral disk and surround the notochord, which eventually forms the nucleus pulposus. The caudalmost cells then fuse with the cranial cells from the next segment and so on. During the cartilaginous stage, the mesenchymal anlagen are replaced by cartilage (week 7) and finally, during the bony stage of vertebral development (week 7 to year 25), by three primary ossification centers from within the cartilaginous vertebrae. The two dorsal ones form the two vertebral arches, which do not fuse until age 3–5 years, whereas the central and more ventral ossification center forms the vertebral body. Vertebral development is not completed until puberty, as the secondary ossification centers on the vertebral body and facets are formed.

This lengthy process of spine development is under tight and complex genetic control and regulation. A mas-

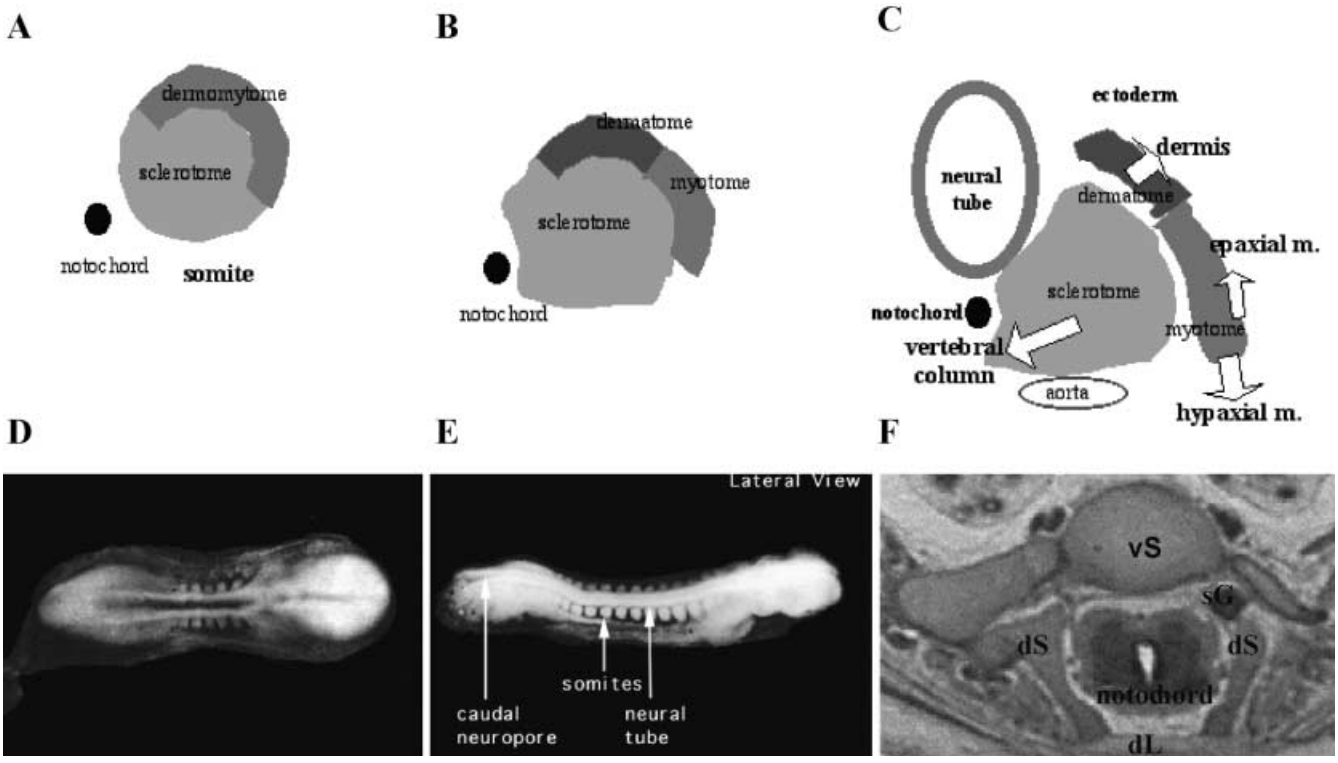

Fig. 3A–F Development of the verterbral column. **A** Somitogenesis begins during week 4 with condensation in the paraxial mesoderm. **B** Cells within the somites further differentiate, and the cells surrounding the notochord then proceed to form the sclerotome. **C** Sclerotome cells then differentiate into chondrocytes that form the anlagen of vertebral bodies. **D,E** Somite formation is clearly visible in a human embryo at day 22.5. (Courtesy of Prof. Kohei Shiota, Congenital Anomaly Research Center, Kyoto University Faculty of Medicine). **F** Section through the cartilaginous anlage of vertebral body Th1 in a human embryo at day 55. The ventral sclerotome (*vS*) forming the vertebral body and the two dorsal sclerotomes (*dS*) forming the vertebral arches, which will fuse after birth, are clearly visible. *dL*, dorsal lamina; *sG*, spinal ganglion. (Courtesy of Dr. Mark Hill, Cell Biology Lab, School of Anatomy, University of New South Wales, Sydney)

ter gene for development of the vertebral column is the secreted cytokine sonic hedgehog, for example. Mice carrying inactivated alleles of this gene do not form a spine and lack the posterior parts of their ribs [10]. Sonic hedgehog and a number of highly conserved homeobox transcription factors, which have been under intense investigation for the last 4–5 years, are equally important during limb formation, where they control dorsal–ventral, proximal–distal, and posterior–anterior patterning [25].

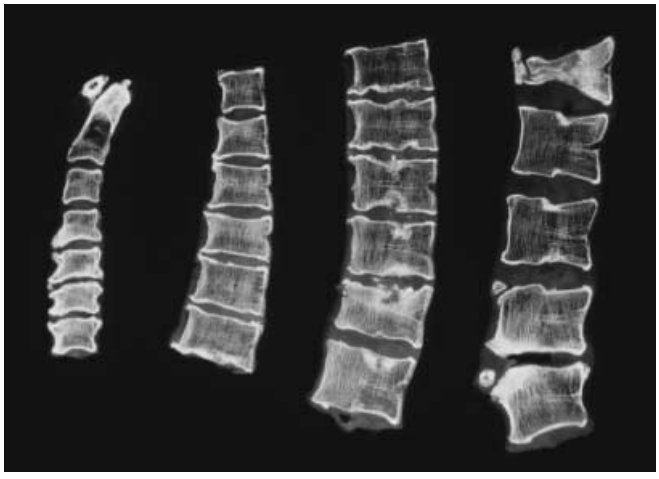

Fig. 4 Contact radiography of a cervical, thoracic, and lumbar human spine. The trabecular architecture within the vertebral body and the orientation of trabeculi preferably in the direction of axial loading are shown. Note the multiple degenerative changes such as C1/C2 fusion with the formation of osteophytes, or the osteoporotic compression fracture of L1. (Courtesy of Dr. M. Amling, Dept. of Trauma and Reconstructive Surgery, University of Hamburg, Germany)

Architecture

Morphology

Bones are exceptionally well suited for the structural demands placed on them. At the gross morphological level, as hollow tubes they provide great strength and durability against axial compression forces while at the same time minimizing weight to efficiently accomplish this task. The ultimate tensile strength of bone approaches that of cast iron, and its capacity to absorb and release energy is twice that of oak, yet the weight of bone is only one third that of

steel [31]. On the next level, the morphology of cortical and cancellous bone is strategically arranged to accommodate input of stresses and strains during weight-bearing. The trabecular cascades of the proximal femur, for example, readily distribute the forces and moments to the cortical shell of the diaphysis. The vertebral body distributes axial compressive forces throughout a tightly woven network of trabecular bone, thus minimizing fracture risk even under extreme conditions (Fig. 4).

Microscopically, bone is made up of two distinct phenotypes: woven and lamellar. As mentioned earlier, woven bone is characteristic of embryonic and fetal development, but it is also found in the healthy adult skeleton at ligament and tendon insertions and under pathologic conditions, such as osteogenic tumor and metastasis formation or in the temporary callus of a healing fracture, where it is usually resorbed and replaced by lamellar bone within a few weeks of deposition. Architecturally, it has an irregular, disorganized pattern of collagen fiber orientation and osteocyte distribution. Mechanical stimulation can cause rapid production of woven bone, which ultimately remodels into dense, lamellar bone [39], indicating that the woven bone response is a strategic means of rapidly responding to changes in functional activity.

Lamellar or mature bone is found in both cortical and trabecular bone. The structural subunits, the lamellae, run parallel to the trabeculae or, as is the case in cortical bone, are arranged in osteons, which are composed of up to 20 concentric lamellar plates forming a cylinder with a diameter of 200–300 μm. A central capillary runs through the osteon, and up to seven concentric rings of osteocytes are incorporated into its wall. A distinction is made between primary osteons, which form de novo, e.g., during woven bone consolidation, and secondary osteons or Haversian systems, which form via resorption of preexisting bone and account for most of the adult human bone tissue [1].

Modeling and remodeling

Modeling is the processes whereby bone is laid down onto surfaces without necessarily being preceded by resorption. In the case of remodeling, osteoclastic resorption of bone leaves pockets that are then filled by osteoblast activity. A classic example of modeling occurs during longitudinal growth of long bones at the metaphysis and diaphysis. To increase the girth of the diaphysis, bone is laid onto the periosteal and endosteal surfaces. As bone length increases, the wider metaphysis has to be remodeled into a leaner diaphyseal shape by periosteal resorption and endosteal apposition of bone. This process is generally referred to as metaphyseal reshaping [20]. In a similar fashion, the sagittal curvature of a femur adapts during growth to accommodate the increasing length of the bone; this is done on the posterior surface through the highly coupled resorption of the periosteal surface and apposition on the endosteal surface and vice versa on the anterior surface by resorption of the endosteal surface and formation on the periosteal surface. This process results in the central section of the bone "drifting" dorsally, a process known as cortical drift [42].

Remodeling as an etiologic factor in skeletal disorders

In the adult skeleton, remodeling is by far the more active process, reflecting the process of "real-time" tissue replacement during bone turnover and repair. In some places, either as bone-lining cells on a trabeculum or as infilling after an osteoclastic cutting cone in cortical bone, osteoblasts lay down new bone; in others, osteoclasts resorb the mineralized matrix. This cyclic sequence is also called the activation–resorption–reversal–formation (ARRF) sequence and takes about 3–6 months to be completed in humans. Remodeling is not only required to replace dead or damaged tissue, it also gives bone the capacity to adapt to changes in loading and to respond to nutritional and/or metabolic changes [5,37].

Ultimately, the pathologies inherent in bone diseases are reflected by this physiologic remodeling sequence, either by influencing bone formation (induction of osteoblast activity or inhibition of osteoclast activity) or resorption (induction of osteoclast activity or inhibition of osteoblast activity). According to this paradigm, osteoporosis is generally viewed as the inability of osteoblasts to fully repair the resorptive defects during normal osteoclast resorption, since mean wall thickness and porosity in cortical bone are generally elevated and trabecular spacing in cancellous bone is increased [13].

The spine consists primarily (75%) of trabecular bone, and the intertrochanteric region of the femur has a cancellous bone content of 50%. Despite the relatively small net amount of cancellous bone (only 15% of the total bone in the body), remodeling events within these parts of the skeleton therefore largely determine whether osteoporotic fractures occur. Bone mass peaks at about 35 years of age. Since a decline in bone mass with age is evident within the entire population, failure of the skeletal structures mentioned above is the result of a host of additional systemic and local factors. These can include perimenopausal decline in estrogen production, heritable, nutritional, and environmental factors, and the absence or reduction of mechanical stimuli, which alone or in combination tend to further aggravate the resorptive component of the bone remodeling equation [34].

Systemic regulation of bone remodeling

Perhaps the principal responsibility of systemic peptide or steroid hormones is to regulate mineral homeostasis rather

than locally control skeletal morphology. Nevertheless, PTH, for example, as the main regulator of serum calcium, has significant effects on bone remodeling. By indirectly stimulating osteoclast activity via an increase in OPG-L on the osteoblast membrane and/or inhibition of OPG secretion, PTH is able to release calcium and phosphate into the bloodstream while at the same time inducing net bone resorption [30].

Osteoprotegerin and its ligand also seem to be involved in the action of vitamin D or calcitriol (1,25-$(OH)_2D_3$), as its active metabolite is generally referred to. While adequate levels of it are necessary to provide calcium for bone formation via intestinal reabsorption, supraphysiologic levels induce bone resorption by stimulation of osteoclast differentiation. An increase in OPG-L gene expression in osteoblasts seems to be the mechanism of this effect on bone resorption [32].

As an example of induction of bone formation via the same effector pathway, estrogen, or more correctly 17β-estradiol, protects bone by increasing OPG levels in osteoblasts, thus inhibiting osteoclast differentiation and activation and promoting osteoclast apoptosis. Using the same effector mechanism, namely OPG/OPG-L interaction, many cytokines and calciotropic hormones therefore seem to exert what are sometimes dual effects on bone formation and/or resorption [24].

In addition to these hormonal systemic regulatory mechanisms, exciting data have recently been presented postulating a central control mechanism for bone mass control via the hypothalamus. In this model, leptin not only regulates body mass, but also – and at much lower serum concentrations – has an inhibitory effect on bone mass. This effect is apparently not mediated via a direct effect on bone cells and is also independent of endocrine organs such as the pituitary gland, the parathyroid, or adrenal glands, but rather suggests an additional control of bone mass solely by the central nervous system [17].

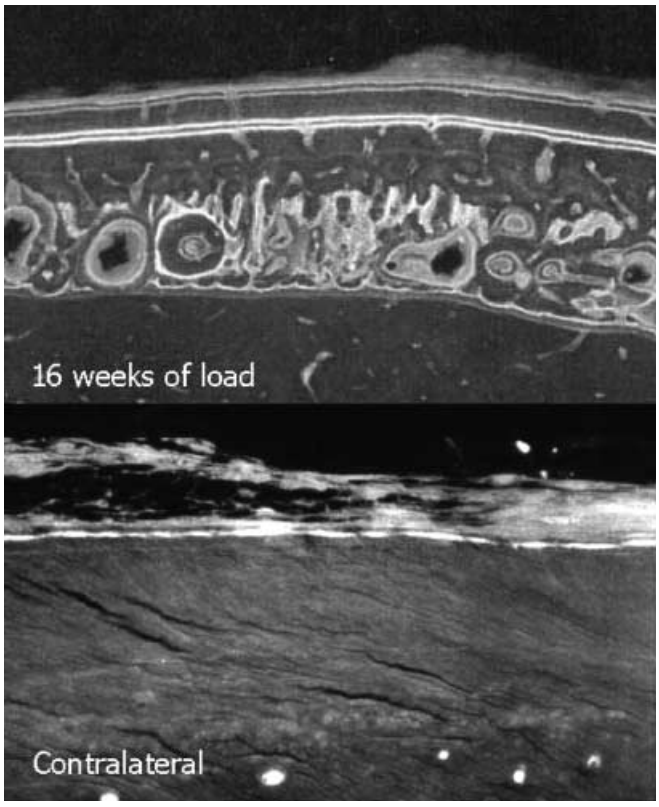

Fig. 5 A fluorescent photomicrograph of the periosteal surface of a turkey ulna diaphysis following 16 weeks of a mechanical regimen sufficient to cause a peak of 2000 microstrain. Remnants of the original woven response can be seen serving as interstitial elements of primary and secondarily remodeled bone. In essence, the woven bone response has served as a strategic stage in the achievement of a structurally appropriate increase in bone mass. Mechanical stimuli are certainly strong, site-specific growth factors. (Reproduced with permission from [28])

Structural adaptation in bone

A great deal of bone's structural success is derived from its ability to constantly redefine its mass and morphology to accommodate subtle changes in mechanical and metabolic demands. It is therefore reasonable to speculate about the signals that regulate the modeling and remodeling processes. Regardless of the genetic predetermination of the shape and structure (i.e., cancellous vs. cortical) of each individual bone in the skeleton, a bone's shape, anatomy, and mechanical properties, such as mechanical strength, stiffness, and toughness, are adapted to mechanical stimuli happens throughout the lifetime of an individual. The "form follows function" concept as it pertains to mechanical adaptation in bone was first proposed in 1892; it is one of the oldest in modern medicine and is widely referred to as Wolff's law [49]. A century later, the parameters in the functional environment that bone is actually responding to still remain unclear. For example, several research teams are strong advocates of the theory that strain magnitude is the key regulatory factor in bone adaptation. However, it is important to emphasize that axial loading accounts for only a small percentage of the total strain measured at the bone surface, with well over 80% of measured strain caused by bending moments. Much smaller strains would certainly be achieved (or much less bone material required) if all strains were a product of axial loads. As it is, though, at most only one small area of the bone is subject to high strains, yet the remodeling of bone correlates only weakly with this area most likely to be subject to microcracks or other forms of damage or extreme signals. Equally surprisingly, it does not appear to be the aim of long bone curvature or cross-sectional geometries to minimize bending moments, but in some cases these morphologic features even accentuate the strain signals [40].

Perhaps contrary to a "static material"-based interpretation of Wolff's concept, it appears that the ultimate goal of bone adaptation is not to minimize strain. Instead, skeletal morphology and functional load-bearing apparently conspire to strive toward a certain type of strain. Peak strain magnitudes measured in a wide range of adult species are remarkably similar, ranging from 2000 to 3500 microstrain (where the yield strain of bone is approximately 7000 microstrain, and the ultimate strain is 25,000 microstrain). This generic peak strain environment has been termed "dynamic strain similarity" and is one argument for the concept of bone working toward achieving a favorable strain environment rather than to reduce it as far as possible [41] (Fig. 5).

Although the cellular and molecular mechanisms have yet to be fully established, there is increasing evidence for the concept of a mechanosensory cell system, such as the osteocyte syncytium, that is able to communicate information to bone-forming and/or bone-resorbing cells. The interspecies similarity in strain magnitudes further suggests the existence of a generic cellular mechanism that strives toward a common structural and beneficial goal.

There are many examples of this structure–function relationship, including the 35% increase in cortical thickness on the humerus of the playing arm of professional tennis players [26] or the striking bone resorption that results from immobilization or space flight; it is thus clear that bone can quickly identify changes in its functional milieu and respond to these changes structurally [16, 26].

Attempts to identify the parameters that bone is sensitive to in terms of an adaptive response have shown that parameters such as strain distribution, gradients, cycle number, and rate critically influence bone mass, turnover, and remodeling. Nevertheless, no single parameter has been shown to reliably predict bone adaptation under all naturally observed or experimentally created conditions [8]. Perhaps we should be more hesitant to presume that skeletal morphology is merely a product of dominant strain parameters with the structural goal of minimizing strain. Instead, incorporating the biological principles that guide the homeostasis of a living tissue, the cellular advantages for a tissue exposed to a dynamic functional milieu such as increased perfusion and nutrition have to be considered in concert with the advantages of an effective structural material.

Whatever the signal transduction pathway of transforming physical information to something the cell population can perceive and respond to, it is clear that the capacity of bone tissue to adapt to the functional demands placed on it is critical to the skeleton's structural success. Indeed, as we attempt to evaluate the cellular mechanisms responsible for the positive control of bone mass, the osteogenic potential of physical stimuli cannot be ignored.

Conclusion

By providing a brief overview of the anatomical, structural, and physiological aspects of bone's form–function relationship, it is hoped that this manuscript has provided at least an appreciation of the great complexity of bone tissue. An exhaustive review of bone biology and its ability to orchestrate the mass and morphology of the skeleton is obviously not possible, not only because of space constraints, but because there is so much about this "smart material" that we still do not understand. In reviewing the means by which bone integrates the fundamental tasks of providing skeletal structure while managing the metabolic responsibilities of an organ under endocrine, and possibly central, control, it is hoped that, at the same time, the physician and scientist will have gained some insight into the challenges – and opportunities – which musculoskeletal science is faced with. Through transgenic approaches, the contributions of individual proteins within bone to its structural and functional integrity can and will continue to be determined. Similarly, cell–cell and cell–matrix interactions within bone are being elucidated on a molecular level using signal transduction studies. The advent of the molecular tools capable of genome-wide gene expression analyses, the search for single nucleotide polymorphisms (SNP), and proteomics will certainly lead to discoveries identifying the responsible genes and proteins for many diseases affecting the bone phenotype. Advances in new biocompatible materials, both osteoconductive and osteoinductive, will also aid in the treatment of bone disorders, while new diagnostic modalities will aid in identifying those at risk of disease perhaps before symptoms are evident.

Other problems, e.g., questions concerning mechanotransduction, a mechanosensory system, and the details of regulation of bone adaptation, are still less clear, even though considerable progress has been made in identifying some of the responsible parameters of bone's functional milieu and the means by which bone can respond to it in terms of modeling and remodeling. An improved understanding of how bone perceives and responds to mechanical signals will certainly aid in accelerating the healing of fractures, augmenting osseointegration into implants, and ensuring that diseases such as osteoporosis can be adequately addressed.

The basic biology of bone is obviously also of concern to the clinician and spine surgeon. Even in a field of medicine where hands-on experience cannot be overestimated, new treatment modalities for diseases and problems of the musculoskeletal system are certain to be derived from the above-mentioned studies. For example, local gene delivery systems to achieve spinal fusion between hypermobile segments in spondylolisthesis are conceivable; tissue engineering approaches to replace and augment bone, cartilage, and muscle are receiving a great deal of attention; and many of the drugs to treat arthritis, osteoporosis, and

other diseases of the musculoskeletal system will be based on SNP and complex gene interactions. These are undoubtedly exciting times for everyone working in the bone field, and the interdisciplinary nature of the research that has brought us tremendous insight into bone's complexity on a structural and functional level will serve us well in the future.

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