Overviews of Biomimetic Medical Materials

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1.1 General Introduction

The term 'biomimetics' was coined by renowned American biophysicist Otto Herbert Schmitt in the 1950s (Julian et al. 2006). Biomimetics originates from the Greek words 'bios' and 'mimesis' which mean "life" and "to imitate," respectively (Bar-Cohen 2006). Scientist Janine Benyus defined 'Biomimicry' in her book 'Biomimicry: Innovation Inspired by Nature' as an "innovative science that observes nature's models and formerly duplicates or takes inspiration from those designs and procedures to solve human problems" (Benyus 1997; Bello et al. 2013). Benyus suggests that by treating nature as a 'model, measure and mentor,' biomimicry can offer advantages relating to 'leading edge opportunities' (Benyus 1997). One important example of biomimicry can be observed in the field of medical materials. Biomimetic medical materials are biocompatible and/or biodegradable materials designed by careful observation of nature's models and then developed by imitating natural architectures and methods for use in the medical industry (e.g., biosensing, tissue engineering and regenerative medicine, biosignals and drug/protein delivery) (Fig. 1.1). The method involves the development of composite materials that mimic the characteristics and/or structures of diverse materials found in nature. Examples of natural structures serving as inspiration include the honeycomb organization of a beehive, the fibrous structure of wood, spider webs, nacre, bone, hedgehog quills, and so on (Bello et al. 2013). The rapid development of biomaterials for medical applications is emerging as a promising interdisciplinary research field between materials science and biology. Advances in the biomedical field create an ever-increasing demand for novel biomaterials with precise and definite host interactions (Bello et al. 2013; Eggermont 2008; Nagarajan 2008), and recent progress within materials research encourages further inquiry into how to best emulate the structures of natural materials in biomimetic materials (Bello et al. 2013; Erik and Stephen 2002; Hengstenberg et al. 2001). The emerging field of biomimetics deals with new technologies generated from biologically stimulated engineering at nano- to macro- levels and 3D-bioprinting. Improved understandings of biological functions and human anatomy are critical to achieving more varied and efficient biomedical applications through the development of: (1) more effective biomimetic materials and (2) approaches to best leverage advanced technologies.

This book focuses on the development of diverse biomimetic medical materials with intellectual properties for biomedical applications. It contains eight sections: (1) introduction,

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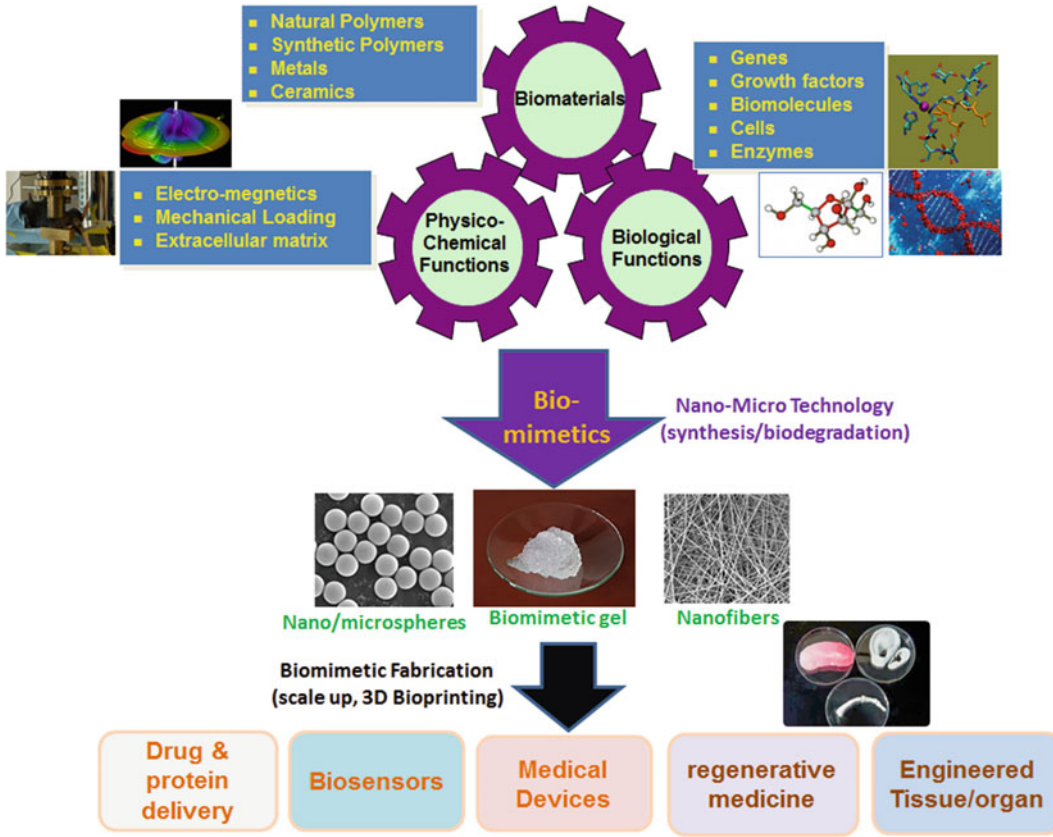

Fig. 1.1 Overview of biomimetic medical materials

(2) nanomaterials as emerging biomimetic materials, (3) biomimetic materials in tissue engineering, (4) biomimetic materials and stem cell, (5) 3-D bioprinting materials, (6) immune responses of biomaterials, (7) functional biomaterials, and (8) intellectual properties of biomimetic materials. This chapter provides a general overview of important developments in the field of biomimetic medical materials (e.g., key properties and potential applications). Chapters 2, 3, 4, 5, 6, 7, and 8 provide more details and the current statuses of individual topics.

1.2 Nanomaterials: A Promising Class of Biomimetic Medical Materials

Progress made in the fields of nanoscience and nanotechnology have directly led to advancements of functional materials with biomedical applications. Examples of important nanomaterials include graphene, carbon nanotubes, fullerenes, polymeric nanoparticles, nanogels, metal organic nanomaterials, and supramolecular nanostructures (Bhattacharya et al. 2014). The distinctive physico-chemical properties (e.g., size, shape, surface charge and chemical composition) drive their potential utility in sensors, protein cages, drug delivery, bioimaging, tissue engineering, and so on (Bhattacharya et al. 2014). The remarkable variety of potential roles for biomimetic nanomaterials arises from the observation that humans are fabricated by nanoscale interactions, specifically the efficient self-assembly of biological molecules (Bhattacharya et al. 2014). Recent noteworthy advancements in the field of biomimetic materials include organs-on-chips, smart robotic devices, nanomaterials for tissue

engineering and orthopaedic implants (Bhattacharya et al. 2014).

1.2.1 Protein Cages

Protein cages are artificial, symmetrical, multifunctional constructions with three discrete interfaces (Fig. 1.2): (1) interior, (2) exterior, and (3) intra-subunit (Uchida et al. 2007; Chen et al. 2012). These subunits can be chemically and genetically tailored to generate distinct cages best designed for a specific biomedical application (Bhattacharya et al. 2014; Uchida et al. 2007; Chen et al. 2012). The most common protein cage applications involve DNA assays, biomineralization, immunoassay, sequestration, and the delivery of drugs and nucleic acids (Bhattacharya et al. 2014). Huard et al. developed the reverse metal-templated interface redesign (rMeTIR) method which converts a natural protein–protein interface into one that selectively responds to a metal ion (Harrison and Arosio 1996).

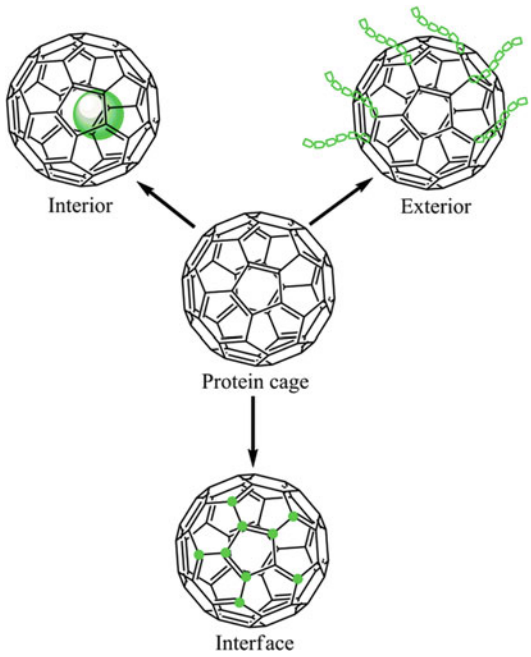

Fig. 1.2 Schematic representation of interfaces in a protein cage available for chemical or genetic modification

They employed this method to the self-assembly of ferritin protein cage bound by divalent copper metal. In this case, copper acts as a structural template for ferritin assembly like RNA sequences that serve as the template for viral capsid formation (Bhattacharya et al. 2014). This process helps to mimic the structure, stability and modifications of isolated ferritin occurring under physiological conditions (Bhattacharya et al. 2014). The most common protein cage applications involve DNA assays, biomineralization, immunoassay, sequestration, and the delivery of drugs and nucleic acids (Bhattacharya et al. 2014). Huard et al. developed the reverse metal-templated interface redesign (rMeTIR) method which converts a natural protein–protein interface into one that selectively responds to a metal ion (Harrison and Arosio 1996). They employed this method to the self-assembly of ferritin protein cage bound by divalent copper metal. In this case, copper acts as a structural template for ferritin assembly like RNA sequences that serve as the template for viral capsid formation (Bhattacharya et al. 2014). This process helps to mimic the structure, stability and modifications of isolated ferritin occurring under physiological conditions (Bhattacharya et al. 2014).

1.2.1.1 Application of Protein Cage Towards Nanomedicine

Protein-based nanomedicine systems are attractive for drug delivery because of their biocompatibility, biodegradability and low toxicity (Bhattacharya et al. 2014; Suchi et al. 2009). The subunits of the same protein or a mixture of proteins self-assemble and form cage-like structures. Drugs can be loaded into the void within the protein cage and then selectively delivered to target cells (Bhattacharya et al. 2014). Cage sizes are consistent and facilitate the loading of comparatively even amounts of drugs (Tang et al. 2011; MaHam et al. 2009). Ferritin- or apoferritin-based protein cages are naturally derived, physiologically stable and used as biocompatible drug delivery systems. The removal of iron atoms from ferritin forms apoferritin (Mazur et al. 1950; Nakamura and Konno 1954). At pH 2, the 24 subunits of ferritin/

apoferritin can dissociate and when the pH of the solution is gradually increased, it restructures into an integral shell structure at neutral and basic pH (Aime et al. 2002). The dissociation–reassembly characteristics of ferritin/apoferritin facilitates the encapsulation of small drugs and biomarkers (Turyanska et al. 2009; Zhang et al. 2011a, b. c). Maeda et al. reported apoferritin as a tumor-targeted drug delivery system. The difference in pHs of the tumor cells and pH-responsive property of apoferritin make it a promising carrier to load and deliver drugs to cancer cells. They loaded daunomycin—a drug normally used to treat acute myeloid leukaemia and acute lymphocytic leukaemia diseases—into apoferritin (Maeda et al. 1999). Fan et al. demonstrated that magnetoferritin nanoparticles could be employed to target and visualize tumour tissues without any targeting ligands or contrast agents (Fan et al. 2012). For this purpose, they incorporated iron oxide nanoparticles into human heavy-chain ferritin (HFn) protein shells, which can bind target tumour cells (Maeda et al. 1999). The iron oxide core catalyses the oxidation of peroxidase in the presence of hydrogen peroxide to yield a colour reaction which is used to visualize tumour tissues (Bhattacharya et al. 2014; Maeda et al. 1999). They studied 474 clinical samples from patients with nine types of cancers and proved that the magnetoferritin nanoparticles can discriminate cancerous cells from normal cells with a sensitivity of 98% and specificity of 95% (Bhattacharya et al. 2014; Maeda et al. 1999). Zhen et al. reported that RGD-modified ferritin is an efficient carrier of doxorubicin for tumor-targeted delivery (Zhen et al. 2013). They loaded doxorubicin onto RGD-modified apoferritin nanocages with high efficiency (up to 73.49 wt %) after being pre-complexed with Cu(II) (Zhen et al. 2013). The doxorubicin-loaded ferritin nanocages exhibited longer circulation half-life, higher tumor uptake, improved tumor growth inhibition, and less cardiotoxicity than free doxorubicin on U87MG subcutaneous tumor models (Zhen et al. 2013). Lin et al. described several multifunctional ferritin nanocages with defined control of their composition (Lin et al. 2011). They performed *in vitro* and *in vivo* studies to assess their possible suitability as multi-modal imaging probes. An excellent tumour targeting efficiency was observed and attributed to the EPR effect and biovector-mediated targeting (Lin et al. 2011).

1.2.1.2 Protein Cage Nanomaterials for DNA Assays and Immunoassays

Protein cages also act as templates to prepare monodispersed nanoparticles for protein assays. In these methods, the protein cage has diverse roles: (1) it offers a precise environment and conditions for the development of highly monodispersed nanoparticles, (2) it inhibits aggregation of the designed nanoparticles, and (3) in several cases, it prompts a mineralization reaction (Bode et al. 2011; Scuderi et al. 1986). For example, the Liu group developed different marker-loaded apoferritin nanoparticle labels for highly sensitive electrochemical immunoassays of protein biomarkers and DNA assays (Liu and Lin 2007; Liu et al. 2006a, b). Apoferritin-templated synthesis of cadmium phosphate nanoparticle labels for electrochemical immunoassay of tumour necrosis factor-α (TNF-α) protein biomarker was performed by Liu et al., where sharp cadmium signals were observed with low concentrations of TNF-α (i.e., from 0.01 to 10 ng/mL) (Scuderi et al. 1986 (Bhattacharya et al. 2014). The response achieved with a TNF-α target concentration of 10 pg/mL specifies a detection limit of about 2 pg/mL. The low detection is equivalent to the values acquired by means of a common immunological assay, like the enzyme-linked immunosorbent assay (40 pg/mL) (Bhattacharya et al. 2014). Jaaskelainen et al. developed a method of fabricating modified nanoparticles using human ferritin as a labelling agent for a bioaffinity assay (Sharma et al. 2017). A single chain antibody Fv fragment (scFv) was employed as the binding substrate and Eu^{3+} ions as the label. They claimed that the synthesized nanoparticles rapidly bound antigens, and that the process is inexpensive and ecologically sustainable, thus making the system highly beneficial, specifically in large-scale applications (Bhattacharya et al. 2014).

1.2.1.3 Synthetic Dendrimers as Alternative Protein Cages

Dendrimers are unimolecular, three-dimensional, highly branched monodispersed macromolecules (Sharma et al. 2017). The term 'dendrimer' initiated from the Greek word 'dendrons' which means tree or branches, and the word 'meros' means parts (Sharma et al. 2017; Tomalia et al. 1990). The availability of various exterior functional groups and tunable surface engineering empower the modifications of the dendrimer for gene and drug delivery. The distinctive properties of dendrimers (e.g., monodispersity, flexible surface functionality and internal holes), make them model gene and drug delivery carriers. The important properties of dendrimers which aids their use in drug delivery include rapid uptake by cells, presence of large numbers of different functional groups (e.g., hydroxyl, amine, and carboxylic acid), and their capability to conjugate comparatively higher-molecular-weight drugs at a higher percentage (Sharma et al. 2017). Among various dendrimers, poly(amido amine) (PAMAM) dendrimers are especially promising and have a topology similar to biomacromolecules, mimicking globular proteins (Bhattacharya et al. 2014). Dendrimers are more robust for biomedical applications than proteins, because: (1) globular proteins are vulnerable to denaturation by pH, temperature, and light due to their bent structures containing linear polypeptides units, (2) the interiors of protein are heavily packed and their surfaces are more heterogeneous. While, the globular character of dendrimers is covalently linked and their homogeneous surfaces with precise interiors give a structural reliability for specific biological functions (Bhattacharya et al. 2014). Dendrimer-encapsulated gold nanoparticles as carriers of thiolated anti-cancer drugs were reported by Wang et al., where dendrimer-encapsulated drugs exhibited significantly lower cytotoxicity compared with free anti-cancer drugs (Wang et al. 2013a, b, c, d). Dendrimer-encapsulated gold nanoparticles have been used to covalently immobilize a monoclonal electrochemical carcinoembryonic antigen for highly responsive immune-sensing (Jeong et al. 2013). Dendrimer-encapsulated Pt nanoparticles have also been employed as protein mimics that displayed similar catalytic action to catalase, an enzyme which removes excessive reactive oxygen species (ROS) in normal cells (Wang et al. 2013a, b, c, d). The generation 9 PAMAM dendrimers also provide distinctive benefits to fabricate artificial enzymes (Bhattacharya et al. 2014). Both dendrimers and protein cages have also been utilized as magnetic resonance imaging (MRI) contrast materials with high relaxivity of water protons (Helms and Meijer 2006; Aime et al. 2002).

1.2.2 Medical Applications of Graphene-Based Biomaterials

Graphene is a single-layer two-dimensional structured nanomaterial (Yang et al. 2013a, b). Recently, graphene-based materials received profound interest in physical, chemical and biomedical fields (Fig. 1.3) because of their distinctive physicochemical properties (e.g., high surface area (2630 m2/g) (Zhu et al. 2010), strong mechanical strength (~1100 GPa) (An et al. 2011), outstanding electrical conductivity (1738 siemens/m) (Weiss et al. 2012), consummate thermal conductivity (5000 W/m/K) (Balandin et al. 2008), and ease of modification (Georgakilas

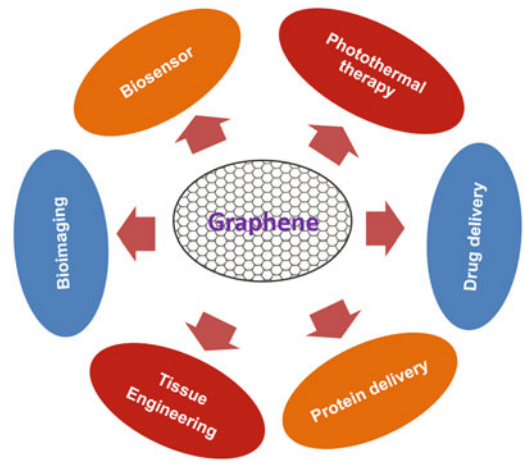

Fig. 1.3 Schematic representation of potential biomedical applications of graphene

et al. 2012; Huang et al. 2012). Graphene-based materials exhibit excellent electrochemical and optical properties, with the ability to adsorb several aromatic biomolecules via π– π stacking interaction and/or electrostatic interaction, which make them excellent candidates for bio-sensing and drug delivery (Yang et al. 2013a, b).

1.2.2.1 Graphene-Based Biosensors for Biomolecule Detection

Graphene-based materials have been used to build several biosensors which work through optical and electrochemical signalling mechanisms (Liu et al. 2012). The powerful electrochemical properties of graphene create a favorable electrode substrate to improve biomolecule detection (Yang et al. 2013a, b). Zhou et al. designed graphene-based electrodes to detect H_2O_2, which exhibited higher rate of electron transfer than graphite-based and bare electrodes. The result suggest that these materials can be used as highly sensitive electrochemical sensors (Zhou et al. 2009). It has also been noted that N-doped graphene (N-graphene) shows enhanced electrocatalytic activity toward H_2O_2 reduction compared with graphene (Shao et al. 2010). The H_2O_2 release from living cells was also detected by N-graphene (Wu et al. 2012). Numerous graphene-based glucose biosensors have been developed and may be useful for the diagnosis and treatment of diabetes. Thermally split graphene was used to design a glucose oxidase-graphene chitosan nanocomposite modified electrode by Kang et al., where the electrode showed a broader linear range of glucose sensitivity and a detection limit of 0.02 mM (Kang et al. 2009). Shan et al. developed a graphene-based glucose biosensor on the modified electrode through electrostatic interaction with poly(vinyl pyrrolidone)-protected graphene and negatively charged glucose oxidase (Shan et al. 2009). Wang et al. showed that nitrogen doped-graphene displayed high sensitivity and selectivity for glucose biosensing (Wang et al. 2010a, b). The high sensitivity of graphene-based materials towards glucose suggests that graphene is a potentially promising material for biosensors (Yang et al. 2013a, b).

Graphene-based materials have been used to detect dopamine, a monoamine neurotransmitter and hormone usually dispersed in the central nervous system of mammals (Yang et al. 2013a, b). Changes in dopamine concentrations are connected with human health issue, and fast and sensitive detection of dopamine is sometimes critical. Wang et al. reported a graphene-based electrode for selective determination of dopamine (Wang et al. 2009). Because of the presence of phenyl ring, dopamine adsorbs on the electrode surface via the pi–pi stacking interaction with graphene (Wang et al. 2009).

1.2.2.2 Graphene-Based Bioimaging Materials

Graphene-based materials, specially graphene oxide (GO), have been used for biological imaging due to excellent cellular uptake, biocompatibility, ease of chemical modifications and typical optical properties. To visualize adenosine-5′-triphosphate (ATP) and guanosine-5′-triphosphate (GTP) in living cells, an aptamer-carboxyfluorescein/graphene oxide nanosheet nano-complex was developed (Wang et al. 2013a, b, c, d) and tested in JB6 cells (Wang et al. 2010a, b) and a human breast cancer cell MCF-7 (Wang et al. 2013a, b, c, d), where graphene does not affect the fluorescence property of the complex.

Different, coloured (e.g., blue, green and yellow) graphene quantum dots have been developed by changing the reaction temperature (Yang et al. 2013a, b). Tetsuka et al. and Pan et al. prepared blue fluorescent graphene quantum dots from cutting graphene sheets by a hydrothermal process (Tetsuka et al. 2012; Pan et al. 2010). Zhang et al. fabricated yellow-photoluminescent graphene quantum dots using an electrochemical method (Zhang et al. 2012). Peng et al. prepared graphene quantum dots from carbon fibres using the acid treatment and chemical exfoliation process (Peng et al. 2012). All the prepared quantum dots are associated with high solubility, excellent biocompatibility, and favorable optical properties, and hence can be used directly for intracellular imaging without any surface treatment or modification (Zhang et al. 2012; Peng et al. 2012; Wu et al. 2013; Zhu et al. 2011).

1.2.2.3 Graphene-Based Drug/Gene Delivery Materials

The ultrahigh surface area (2630 m^2/g) and presence of large numbers of SP^2 hybridized carbon make graphene a more suitable and competent drug carrier than other nanomaterials (Yang et al. 2013a, b). For instance, Dai's group reported loading of anticancer drugs SN38 (Liu et al. 2008) and doxorubicin (Sun et al. 2008) onto nano-graphene oxide, which occurred due to physisorption through π-π stacking interaction. Zhang et al. described controlled loading of mixed anticancer drugs (doxorubicin and camptothecin) onto the folic acid-conjugated nano-graphene oxide through π–π stacking and hydrophobic interactions. They used it for the targeted delivery to MCF-7 cells. Results established that folic acid-conjugated nano-graphene oxide loaded with the two anticancer drugs showed very high cytotoxicity against target cells than that of a single drug-loaded graphene conjugate (Zhang et al. 2010).

Graphene-based materials are also used for gene delivery. For example, poly(ethylene imine) (PEI) and graphene oxide (GO) were covalently combined through an amidation process (Zhang et al. 2011a, b, c). The synthesized PEI-GO supported loading of siRNA by electrostatic adsorption and anticancer drug doxorubicin through π–π stacking. The loaded PEI-GO-siRNA and PEI-GO-DOX were transported into Hela cells. Because of the synergistic effect of reducing Bcl-2 protein activity (via Bcl-2-targeted siRNA) and preventing DNA and RNA production (via DOX), the anticancer efficiency was considerably increased (Zhang et al. 2011a, b, c).

1.2.2.4 Graphene-Based Photothermal Therapy Materials

Phototherapy is an approach taken for the treatment of many diseases. This method controls disease by specific light irradiation through two processes: (1) photothermal therapy, and (2) photodynamic therapy (Yang et al. 2013a, b). In case of photothermal therapy, an optical-absorbing agent capable of producing heat under light irradiation is required. Elevated temperatures facilitate the selective death of abnormal cells (Li et al. 2012). Owing to the strong optical adsorption in the near-infrared region, graphene gained significant attention in photothermal therapy. Zhang et al. synthesized DOX-loaded PEGylated nanographene oxide that can transport both the heat and drug to the tumorigenic area to assist chemotherapy as well as photothermal treatment (Zhang et al. 2011a, b, c). Yang et al. fabricated a nanocomposite probe using chemically reduced graphene oxide and iron oxide nanoparticle for tumor bioimaging and photothermal therapy (Yang et al. 2012). Hu et al. developed a nanocomposite of quantum-dot-tagged chemically reduced graphene oxide capable of cell/tumor bright fluorescence bioimaging and use as a photothermal therapy (Hu et al. 2013).

1.2.2.5 Graphene-Based Tissue Engineering Biomaterials

The functionalized graphene, specifically graphene oxide, serves as a complementary carbon nanomaterial to design scaffolds for tissue engineering due to its high mechanical strength, large surface area, and favorable electrical properties (Xie et al. 2013; Shin et al. 2011; Ramón-Azcón et al. 2013; Li et al. 2013; Geim and Novoselov 2007; Park and Ruoff 2009; Gao 2015). Wang et al. described that compared to a crosslinker, a small amount of graphene oxide dramatically improved the mechanical property of their prepared self-healing nanocomposite (Wang et al. 2013a, b, c, d). The effect of graphene on the proliferation of human mesenchymal stem cells (hMSCs) was studied by Nayak et al. and results showed that it did not hamper cell proliferation and specifically enhanced their differentiation into bone cells (Nayak et al. 2011). Shin et al. designed RGD peptide-graphene oxide-PLGA nanofiber mats to be used as scaffolds for vascular tissue engineering (Shin et al. 2017). It was observed that the physicochemical, thermal and mechanical properties of fabricated nanofiber mats are suitable for supporting cell growth and thus may serve as promising scaffolds for vascular tissue engineering (Shin et al. 2017).

1.2.3 Nanogel as an Effective Drug Delivery System

As a member of nano-size particulate materials, nanogels have potentially enormous significance for the drug delivery field. By definition, nanogels are three-dimensional, crosslinked swellable polymeric networks (smaller than 1000 nm) that, without dissolving into aqueous media, have high water-holding capacity (Oh et al. 2008; Soni et al. 2016). Gels with particle size ranges within 200 nm are efficient for targeted drug delivery. While these particles are mainly spherical, recent advances in synthetic approaches permit for the design of nanogels with different shapes (Rolland et al. 2005; Kersey et al. 2012). Nanogels are fabricated using physical or chemical crosslinking methods (Zhang et al. 2016). They possess combined characteristics of gels—a soft material which merges the properties of solids and fluids—and nanoparticles (Soni et al. 2016). Nanogels have the capacity of absorbing large amount of water or biological fluids principally due to its large surface-to-volume ratio and the presence of –OH, –COOH, –CONH–, $–CONH_2$, and $–SO_3H$ group in their polymer chains (Zhang et al. 2016). The biocompatible nature of the nanogels is attributed to the high water content and low surface tension (Zhang et al. 2016).

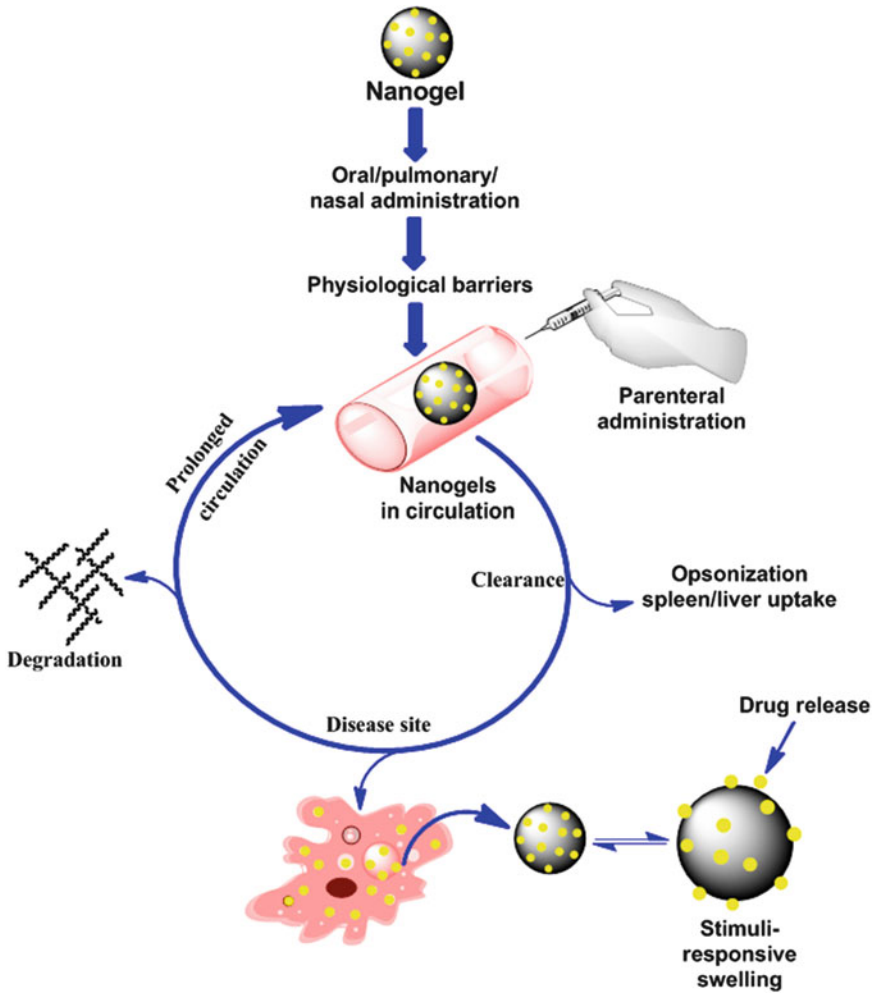

Fig. 1.4 *In vivo* behaviors of nanogel

The porous nature of nanogels contributes to the high loading efficiency of guest molecules and excellent swelling property which makes them suitable for controlled release systems (Fig. 1.4). Their features (e.g., size, charge, porosity, softness, and degradability) can be tuned by changing the chemical composition of the nanogels (Soni et al. 2016). Their flexibility permits for incorporation of different types of guest molecules (e.g., inorganic nanoparticles, proteins, drugs and DNA), without disturbing their gel-like behaviors (Chacko et al. 2012). These multi-functionalities and stabilities are not observed in other categories of nano particulates (Napier and DeSimone 2007) particularly the capacity to incorporate materials with different physical properties within the same carrier. Nanogels prevent the denaturation and degradation of loaded guest molecules (e.g., enzymes, drugs and genetic material), while the structural properties of nanogel macromolecular networks and sustained releases of bioactive molecules enhance the circulation half-lives of small drug molecules, and provide a suitable matrix for combination delivery of therapeutic molecules (Zhang et al. 2016). They can be specifically target sites of interest through conjugation with a targeting ligand or by passive targeting owing to their nano-scale size (Zhang et al. 2016).

1.3 Biomimetic Materials and Tissue Engineering

Tissue engineering is a process designed to repair diseased or damaged tissue by incorporating healthy cells (from the patient or a donor) into scaffold materials which serve as matrices for cell cultivation (Kolos and Ruys 2013). To construct biological tissues, three main components are essential: (1) scaffold materials, (2) cells, and (3) signals (Fig. 1.5). Biocompatibility, 3D-structure, distribution of interconnected pores to encourage vascularization, cell attachment and growth are primary attributes of a promising scaffold material (Kolos and Ruys 2013; Patterson et al. 2010). Scaffolds may be biodegradable or permanent. Biodegradation is

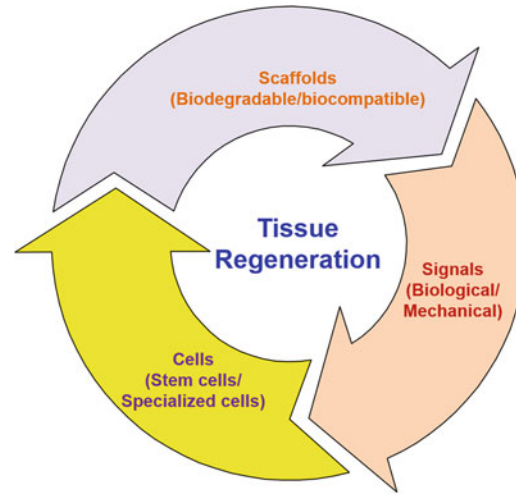

Fig. 1.5 Components for the engineering of tissues

ideal for tissue regeneration where host tissue can substitute the scaffold and that stress can be shifted gradually from the scaffold to the new tissue (Kolos and Ruys 2013). Cell signals can be tuned using differentiation factors or specific receptors (Kolos and Ruys 2013).

Biomimetic materials for tissue engineering mimic the important mechanical features of the organs, tissues and extracellular matrix (e.g., mechanical strength, softness, composition of extracellular matrix), and biological performance (e.g., adhesion, release and delivery of growth factors, and tissue-remodeling behaviors (Patterson et al. 2010). Different types of biomaterials (e.g., naturally occurring molecules, functionalized biomolecules, and synthetic chemical materials) have been used in tissue engineering.

1.3.1 Naturally Occurring Molecules

1.3.1.1 Collagen

Collagen, the most plentiful mammalian protein, is a triple helix primarily made up of glycine, proline and 4-hydroxyproline (Patterson et al. 2010). Collagens can be reconstructed into a fibrillar matrix or gel by changing the temperature or pH, however, reduced mechanical strength of collagen gel is a major concern for *in vivo*

applications (Patterson et al. 2010). Thus, several methods have been applied to improve the mechanical strength of collagen in applications such as hydrogels, hybrid gels, and hybrid scaffolds through chemical or physical combination with other biomaterials (Sheehy et al. 2018; Hatayama et al. 2017).

1.3.1.2 Glycosaminoglycans

Glycosaminoglycans (GAG) are long unbranched polysaccharides which can amplify the biomechanical and biochemical functions of ECM (Patterson et al. 2010). Most GAGs, with the exception of hyaluronic acid, are components of proteoglycans; hyaluronic acid does not remain covalently attached to a protein core, but rather is entangled within the extracellular space (Patterson et al. 2010). The anionic polymer supplies mechanical strength to the ECM by absorbing water, whereas, the GAG unit influences tissue organization through cell-surface receptor interactions (Toole 2004).

The natural source of hyaluronic acid is rooster comb, however, it can also be produced using *Streptococcus* bacterium. It forms a gel by absorbing large amounts of water, and due to its high molecular weight, loses its shapes very slowly. Through the carboxyl and hydroxyl functional groups of hyaluronic acid, several types of gels and scaffolds with tunable mechanical properties have been developed and applied to tissue engineering (Kutlusoy et al. 2017; Walimbe et al. 2017; Entekhabi et al. 2016; Chen et al. 2017; Fan et al. 2015).

1.3.1.3 Self-Assembling Polypeptides

Like proteins, peptides self-assemble and may form nanofibrillar gels through non-covalent intermolecular interactions (Branco and Schneider 2009). Numerous nanofibrillar gels and scaffolds were developed through self-assembly of peptides and used to deliver growth factors and impact the 3-D organization of cells (Zhang et al. 1995; Gelain et al. 2007; Schneider et al. 2008; Segers et al. 2007; Hsieh et al. 2006). These gels have been designed to form specific cell interactions, depending the availability of specific biofunctional ligands (Branco and Schneider 2009). To increase cell:tissue interactions, a laminin-derived peptide Ile-Lys-Val-Ala-Val-based scaffold was designed by Silva et al., where the encapsulated neural progenitor cells were perceived to differentiate into neurons (Silva et al. 2004).

An alternative polypeptide capable of forming hydrogels from Val-Pro-Gly-X-Gly penta-units (X is amino acid other than proline) is elastin-like-polypeptides. They are soluble in aqueous media, but become insoluble and aggregate at a critical temperature (Chilkoti et al. 2006). Elastin-like-polypeptides stimulate the preparation and preservation of cartilaginous matrix from captured chondrocytes and stem cells (Betre et al. 2006), while, for cell attachment, elastin-like-polypeptides have also been reformed with ECM ligands (Liu et al. 2004).

1.3.1.4 Synthetic Hydrogel Materials Mimicking Biological Functionality

Synthetic analogues of biomaterials may offer several advantages for tissue engineering, however, in some cases, viability may be affected by reaction or physiological conditions (Patterson et al. 2010). Importantly, the use of completely synthetic materials may reduce purification issues. One of the emerging materials which open a new door for tissue engineering is polymeric hydrogels which may be fully synthetic or modified biopolymers. Appropriate swelling characteristics are important to mimic the viscoelastic properties of natural ECM (Patterson et al. 2010). Cell-responsive hydrogels for use in tissue engineering can be prepared by using polysaccharides (e.g., alginate, starch, cellulose, chitosan, chitin, pectins, agar, dextran, gellan, pullulan, xanthan) (Bacakova et al. 2014) and synthetic polymers incorporating cell-responsive peptide domains (e.g., poly(ethylene glycol) (PEG), poly(hydroxyethyl methacrylate), poly (vinyl alcohol) (Patterson et al. 2010). Peptide-conjugated polymers may offer ECM-derived bimolecular signals (Patterson et al. 2010). RGD is an example of a peptide where conformation also has a great effect on cell adhesion. For example, the incorporation of cyclic RGD into photo-

crosslinked PEG-diacrylate hydrogels demonstrated improved endothelial cell adhesion compared with hydrogels containing linear peptides (Zhu et al. 2009).

Degradability is another crucial factor for the design and development of cell responsive biomaterials (Patterson et al. 2010). The degradation behaviour of the general hydrogel can be prompted by the incorporation of hydrolytically degradable moieties (e.g., poly(glycolic acid), poly(lactic acid), alginate, or hyaluronate) (Patterson et al. 2010). *In vivo*, ECM molecules are degraded enzymatically by cell-secreted proteases. Thus, cell-mediated control of degradation can be designed into synthetic hydrogels by combining protease substrates (Patterson et al. 2010). Again, degradation of photo-crosslinked PEG-caprolactone gels take place in the presence of lipase (Patterson et al. 2010). Furthermore, bio-functionalization will also afford signals essential to stimulate cell behaviours (Patterson et al. 2010). For these purposes, researchers are using single or multiple growth factors to recapitulate natural processes (Patterson et al. 2010).

1.4 Biomimetic Materials and Stem Cells

1.4.1 The Potential Roles of Stem Cells in Biomimetic Scaffold Formation

Stem cells have been renowned for their cell therapy potential because of their potential to self-renew via cell division and differentiation into diverse specialized cell types (Liao et al. 2008). The regeneration of diseased and damaged tissues using cell therapy is receiving significant interest because it may potentially extended human organ functionality, and lead to longer and healthier lives (Vunjak-Novakovic and Scadden 2011; Nassar et al. 2017). Recently, due to the lack of matching donor organs, tissues which are away from repair, or missing owing to surgical resection or inborn abnormalities are being substituted by transplantation (Vunjak-Novakovic and Scadden 2011). Current advances in stem cell biology and tissue engineering are allowing tissue engineers to instruct multipotent stem cells to differentiate into a proper phenotype at the right time and location to assist well-designed tissue structures (Vunjak-Novakovic and Scadden 2011). A proper combination of biology and engineering is required for creating biomimetic atmospheres appropriate for the development and regeneration of tissue *in vivo*. The presence of bioactive molecules capable of supplying chemical, physical and spatial signals in the scaffolds is indispensable to mimic natural tissue growth (Vunjak-Novakovic and Scadden 2011). In addition to that flexibility of stem cells, one vital characteristic for multiple-tissue engineering applications is the most promising source for this purpose.

Generally, stem cells are one of two types, (1) pluripotent stem cells, containing embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), and (2) multipotent adult stem cells (Fig. 1.6) (Lee et al. 2018). Shinya Yamanaka's group first discovered induced pluripotent stem cells (iPSCs) using the nuclear reprogramming of unipotent adult somatic cells (Takahashi and Yamanaka 2006; Rashid and Alexander 2013). These are a distinct group of stem cells, which retain pluripotency and the capacity for self-renewal (Takahashi and Yamanaka 2006; Rashid and Alexander 2013). Like embryonic stem cells, induced pluripotent stem cells are known for their ability to grow indefinitely in culture without the losing pluripotency and ability to differentiate into different somatic cells. Multipotent adult stem cells are seen in many tissues and organs (e.g., bone marrow, skin, and within the central nervous system) (Caplan 2007). Human mesenchymal stem cells (hMSCs) are a type of multipotent stem cells found in muscles, fats, and bone marrow) (Caplan 2007). The hMSCs of bone marrow are capable of differentiating into different tissue lineages, like osteoblasts (i.e., bone cells), adipocytes (i.e., fat cells), and chondrocytes (i.e., cartilage cells) (Pittenger et al.

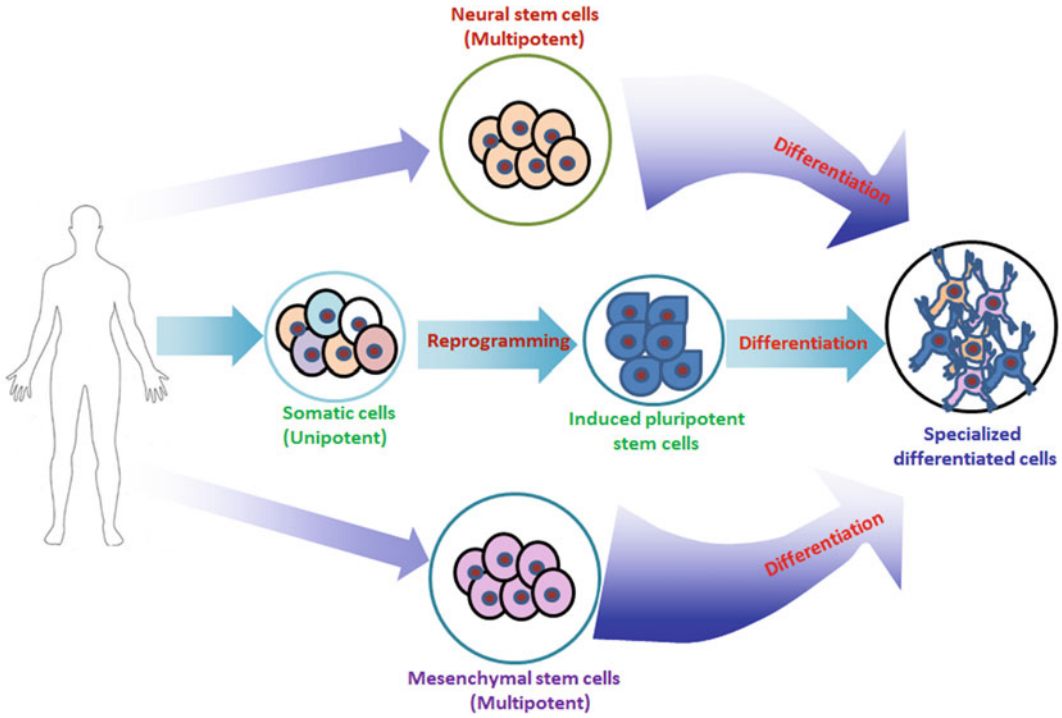

Fig. 1.6 Classification and processing of stem cells

1999). These hMSC-associated abilities support their potential as striking alternatives for musculoskeletal tissue regeneration.

1.4.1.1 Stem Cells Fate

For practical tissue engineering and regenerative medicine, morphological and physiological similarity is required between *in vivo* condition and converted stem cells and tissues. The reformations of these cells depend on various factors (e.g., cell-ECM interaction, concentration of growth factors, topography, elasticity, stiffness, and porosity of the ECM) (Lee et al. 2018). Generally, cell-secreted molecules (e.g., proteoglycans, collagen and elastin) in ECM have important roles for stem cell activities (Lee et al. 2018).

1.4.1.2 Polymeric Materials Impacting Stem Cell Fates

To reduce challenges associated with *in vivo* physiological cellular microenvironments and to control stem cell fate, advanced research is focusing on in the field of biomaterials science and engineering (e.g., manipulation of biomaterial's composition, stiffness, surface topography, and porosity) (Lee et al. 2018). In this regard, polymeric hydrogels have been employed to mimic the physiological microenvironments of stem cells (Hoffman 2012) due to the available of compatible space for cellular adhesion, proliferation and its mechanical properties (Hoffman 2012). Hydrogels made from natural products (e.g., collagen, silk protein, hyaluronic acid, cellulose or chitosan) have been extensively used to arrange stem cells and improve embryonic body differentiation (Lee et al. 2018). Besides, synthetic polymers [e.g., poly(ethylene glycol), poly(lactic acid), and poly(lactic-co-glycolic acid)] have been used for the *in vitro* and *in vivo* stimulation of stem cell differentiation by incorporating bioactive signals (Lee et al. 2018).

1.4.1.3 Nanomaterials for Stem Cells Fate

As nanotechnology and material sciences progress, various nanomaterials (eg, 0-D nanoparticles, 1-D nanotubes, 2-D nanosheets, and 3-D nanofoams) have been developed to mimic natural cellular environments to optimize stem cell control (Lee et al. 2018). Nano-architectured scaffolds have been designed to improve cellular attachment and enhance the modification of overall cellular shapes and alignments (Lee et al. 2018). Moreover, nanomaterials should ideally play an important role leading to improved mechanical properties and electrical conductivity of the scaffolds (Lee et al. 2018). Typically, 0-D nanoparticles are used to design differently patterned topographies to mimic natural ECMs and to enhance cellular attachment for cell-ECM interactions (Hou et al. 2013). By controlling surface charges and hydrophobicity of nanoparticles, they can be used in protein targeting and binding, which will be beneficial for stem cell applications (Lee et al. 2018). Again, the uses of 1-D carbon nanotubes and 2-D graphene nanosheets, and graphene oxide are broadly used for the improvement of properties of synthetic tissue engineering scaffolds because of their excellent electrical conductivity and strong mechanical strengths, and particularly accelerating stem cell proliferation and differentiation ability of carbon nanotubes (Lee et al. 2018).

1.5 3-D Bioprinting Materials

In spite of advances in tissue engineering, demand for substitute fabrication methods to build up complex tissues and organs is increasing due to limited controlling power of conventional techniques including porogen-leaching, electrospinning, and injection molding on scaffold architectures, composition, pore shape, size, and distribution (Ji and Guvendiren 2017; Murphy and Atala 2014; Groen et al. 2016; Shafiee and Atala 2016). 3D bioprinting provides immense prospective to construct highly multifaceted designs with precise control of structures, mechanics, and biological characteristics (Ji and Guvendiren 2017). Owing to diverse advantages (e.g., computer-supported patient-specific design, controlled manufacture, superior structural complexity, and high-efficiency), 3-D printing is a striking technology to make scaffolds, devices, and tissue models for biomedical applications (Ji and Guvendiren 2017; Guvendiren et al. 2016). 3D bioprinting processes involve fabrication of scaffolds or devices in a layer-by-layer approach using living cells into a tissue construct with or without a carrier (Cui et al. 2017; Shafiee and Atala 2016). The biomaterial used for cellular bioprinting is called bioink. Cell-loaded hydrogels, decellulerized ECM-based solutions, and cell suspensions are the most commonly used bioinks (Ji and Guvendiren 2017; Chen et al. 2016; Gu et al. 2016).

1.5.1 Essential Properties of Bioinks

A model bioink material should contain several key characteristics of biomaterials and functions (e.g., printability, mechanics, shape stability, functionalizability, biocompatibility, bioactivity, cytocompatibility, and degradability) (Ji and Guvendiren 2017). Printability includes two branches: (1) processability of the bioink, and (2) reliability of mechanical strength of the printed 3D construction after printing (Ji and Guvendiren 2017). Viscosity is a vital bioink factor affecting printability and cell-encapsulation efficiency. Highly viscous polymer solutions do not flow easily and thus cannot hold their shapes for a long time after printing. However, for regular printing through direct ink writing method, high pressure is required. Generally, for inkjet or droplet-based bioprinters, the bioink viscosity value is near to 10 mPa·s (Gudapati et al. 2016; Ozbolat et al. 2017), the viscosity of bioinks for extrusion-based direct ink writing bioprinting ranges from 6–30$\times$ 10^7 mPa·s (Ozbolat et al. 2017), and in case of laser-assisted bioprinting, the bioink viscosity ranges from 1–300 mPa·s (Hölzl et al. 2016). The whole

mechanics, (i.e., attainable stiffness), is significant to produce self-supporting structures and to control and direct cellular behaviors (Ji and Guvendiren 2017). Degradation is noteworthy to progressively replacing the construct with their regenerated ECM *in vivo* by cells. Functionalizability is requisite to incorporate biological signals, specifically, bioactivity, to direct cellular behavior (e.g., migration, adhesion and differentiation) (Ji and Guvendiren 2017). Furthermore, biocompatibility, cytocompatibility, and high cell viability are fundamental for the ink materials (Kim et al. 2016; Park et al. 2016; Jung et al. 2017).

1.5.2 Currently Available Bioinks

Cell-loaded hydrogels, decellularized ECM-based solutions, and cell suspensions are regularly used as bioinks for tissue and organ printing (Ji and Guvendiren 2017). Cell-loaded hydrogels are remarkable because of their tunable characteristics and their ability to recapitulate the cellular microenvironment (Ji and Guvendiren 2017). ECM-based bioink/decellulerized tissue inks are attractive because of their intrinsic bioactivity and easiness of making printable bioink (Ji and Guvendiren 2017). Cell suspension inks are used to generate scaffold-free biological constructs using cell aggregates (Ji and Guvendiren 2017).

1.5.2.1 Cell-Loaded Hydrogels

Cell-loaded hydrogels are typically used as bioinks for extrusion-based, droplet-based (inkjet), and laser-based bioprinting methods to construct scaffolds or organs. Generally, these bioinks are natural hydrogels derived from biopolymers (e.g., agarose, chitosan, alginate, hyaluronate, collagen, fibrin, and gelatin). Additionally, synthetic hydrogels (e.g., pluronic (poloxamer) and PEG) are also used. Except agarose and alginate, biopolymer-based hydrogels have inherent bioactivity and exhibit structural similarity to ECM (Ji and Guvendiren 2017). Compared to natural hydrogels, synthetic hydrogels have more advantageous mechanical properties, but they do not endorse cellular function, thus additional functionalization is required to tether bioactive cues into synthetic hydrogels. Sometimes, the mechanical properties and/or bioactivity can also be modified by embedding nanoparticles into bioink formulation (Ribeiro et al. 2015). Crosslinking is one of the best techniques for bioink preparation using polymeric materials. Two types of crosslinking process exist, (1) physical crosslinking, and (2) chemical crosslinking. Physical crosslinking deals with hydrophobic interactions, hydrogen bonding, and ionic interactions. Chemical crosslinking involves formation of covalent bonds through radical polymerization, enzymatic reaction or Michael-type addition reaction. Chemically crosslinked hydrogels are mechanically stronger than physically crosslinked gels, which is mainly significant for the stem cell behavior including differentiation (Ji and Guvendiren 2017). A stable crosslinked gel of acrylated pluronic has been prepared after printing using UV light by Müller et al. (Müller et al. 2015). Two PEG derivatives (e.g., PEG-diacrylate and PEG-methacrylate) are used as proper polymers for extrusion-based, laser-based, droplet-based printing systems (Wüst et al. 2015). Basically, PEG is hydrophilic, but not adhesive to proteins and cells. For this reason, the addition of natural polymers or functionalization with biochemical cues is required to make it suitable for biological application. Hong et al. synthesized 3D printing of tough and biocompatible, cell-laden PEG–alginate–nanoclay hydrogels infused with collagen (Hong et al. 2015). Alginate is also used to prepare bioinks for inkjet and extrusion-based printing process. In case of inkjet printing, calcium chloride is sprayed onto the solution of alginic acid (Boland et al. 2007). For extrusion-based printing, a viscous solution of alginate is first printed and then the printed designs are exposed to $CaCl_2$ solution to make a stable shape after ionic crosslinking (Ji and Guvendiren 2017). Alginate is not cell-adhesive, therefore, natural polymers like gelatin or fibrinogen are incorporated into the matrix to induce cell adhesiveness and biological activity (Lim

et al. 2016; Pan et al. 2016). Among all biopolymers, hyaluronic acid and gelatin have been widely employed for the preparation of functionalized polymers for 3D-bioprinting applications. For instance, methacrylated gelatin are used for the preparation of hydrogels through radical polymerization for 3D-bioprinting (Loessner et al. 2016; Lim et al. 2016]. Hyaluronate-based hydrogels have also been developed and used for 3D-bioprinting technology by many research groups (Highley et al. 2015; Ouyang et al. 2016). Recently, self-assembled peptides (Raphael et al. 2017), and polypeptide–DNA hydrogels (Li et al. 2015) have been used as other promising materials for bioinks fabrication.

1.5.2.2 Cell Suspension Bioinks

Bioprinting of scaffold-free constructs exploits cell aggregates by forming cellular spheroids as bioinks (Jakab et al. 2010; Christensen et al. 2015). This procedure relies on tissue liquidity and fusion, that permit cells self-assembly of cells and fuse owing to cell–cell interactions (Ji and Guvendiren 2017). Organovo Inc. is a typical medical research company that fabricated liver models through extrusion-based printing technique with high density bioinks using parenchymal cells/non-parenchymal cells (Nguyen et al. 2016). Again, by combining bioprinting and microcarrier technology, Tan et al. proliferated cells on poly(D,L-lactic-co-glycolic acid) porous microspheres and then performed printing (Tan et al. 2016).

1.5.2.3 Decellularized ECM-Based Bioinks

This type of bioink is prepared by: (1) tissue decellularization, (2) ECM drying (to generate a powder) and (3) dissolving the powder in a cell friendly buffer solution (Ji and Guvendiren 2017). A carrier polymer could be employed to enhance solubility, viscosity, or to induce post-crosslinking of the bioink (Ji and Guvendiren 2017). Even though this method offers a novel solution for bioink preparation, the decellularization procedure involves numerous steps (e.g., accurate quantification of the DNA and the ECM components), which make it expensive. Using this method, decellularized ECM-based bioinks supported by PCL has been printed to form 3D constructs (Pati et al. 2014). Printing of vitamin B_2-induced decellularized ECM-based covalent crosslink gel has been recently reported by Jang et al. (Jang et al. 2016; Jang et al. 2017).

1.6 Immune Responses of Biomaterials

The immune system is conventionally considered from the standpoint of protecting against bacterial or viral infections (Gardner et al. 2013). The compatibility of biomaterials is important to their structural and genetic functions in biomedical applications (Chung et al. 2017). However, biomaterial implants can also illicit immune responses (Gardner et al. 2013). These immune responses are adjudicated by different molecular cues (e.g., antibodies, cytokines, and cell types, such as macrophages, neutrophils, natural killer cells, neutrophils, T-cells, B-cells, T-cells, and dendritic cells) (Gardner et al. 2013). Normally, these molecular signals direct the production of fibrous capsule around implants, thus protecting the body from these foreign materials (Gardner et al. 2013; Chung et al. 2017).

The effect of the biological scaffolds on the immune system is a crucial feature responsible for the constructive regenerative results. Many mechanisms have been proposed for this response (e.g., the breakdown of ECM can expose multiple secret domains that govern many cell functionalities like invasion, migration, adhesion and differentiation) (Chung et al. 2017). Again, T helper cells coordinate the phenotypic and functional changes of macrophages to regenerative ability (Chung et al. 2017). On the basis of *in vitro* responses to different cytokines, macrophages have two functional phenotypes, M1 (pro-inflammatory) and M2 (pro-healing) (Chung et al. 2017). From the viewpoint of immunomodulatory biomaterials, the ECM renovation process could be an excellent approach to improve regeneration. ECM remodelling is like

tissue homeostasis, and has precise effects on wound healing (Chung et al. 2017). Because of the collagen synthesis and breakdown capacity, and as a part of ECM, fibroblasts are main agents in this process. The interaction between fibroblast and immune cells is related to wound closing and tissue regeneration (Chung et al. 2017). Actually, during the wound repairing process, macrophages favour the anti-inflammatory phenotype, and discharge vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β (Chung et al. 2017). These elements act as intercellular communication signals leading to the proliferation and growth of fibroblast during the wound remodelling process (Chung et al. 2017). Therefore, understanding the crosstalk between fibroblasts and immune cells may empower the design of biomaterials that can control the healing response and regeneration ability (Chung et al. 2017). Synthetic biomaterials have been fabricated in plastics and fabrics, and used for biomedical applications ranging from artificial articulating joints to vascular grafts (Chung et al. 2017). While non-degradable synthetic materials also employed in commercial tissue engineering, synthetic degradable polymers, like polyesters, were used as tissue engineering scaffolds to afford a biocompatible cellular environment which degrades as tissue forms (Chung et al. 2017). However, biological signals including proteins, peptides, small molecules, and carbohydrates could be embedded to improve cell function and tissue development. The biocompatibility of the synthetic implants involved escaping the foreign body response (FBR), fibrotic encapsulation, and toxicity of degradation products (Chung et al. 2017). The FBR was naturally characterized through the arrival and fusion of macrophages around the foreign body to produce giant cells (Chung et al. 2017).

1.7 Intellectual Property (IP) Associated with Biomedical Materials

Inventors and scientists are continuously putting their efforts towards researches in companies and institutions to advance society through innovations in instruments, methods, software, medical devices and biomaterials. Protection of IP is particularly noteworthy in the biomedical industry. Biomaterials used on or in the human body need wide analyses to confirm biocompatibility, and to assess side effects including clinical aspects (Hornick and Rajan 2015). These evaluations increase the costs of R&D for novel advanced products. Innovators think that some yields will be positive, accept endorsement for sales, produce sufficient income to recover research and advance costs for both fruitful and failed products, and make a revenue (Hornick and Rajan 2015). In recent decades, inventors, their attorneys, the courts, and even congress have fought with the patentability of software, as the original patent laws and even recent amendments do not clearly address it (Hornick and Rajan 2015). Likewise, in spite of the prospective to advance science, nanotechnology, 3D bioprinting technology, and tissue engineering raise more queries about what features of these new inventions and advances can be secured by IP, which cannot be protected, and which should not be protected for ethical and public policy motives (Hornick and Rajan 2015).

Implanted biomaterials and medical devices, surgical treatments and methods, engineered tissues and medicinal drugs have been secured by patents, design patents, trademarks, copyrights, and trade secrets (Hornick and Rajan 2015). Implanted devices remain within the machine category, for those patent laws, and design patents are applicable. Although surgical treatments and methods are not protected in some countries but in US, it is under process category of patent laws (Hornick and Rajan 2015). Medicinal drugs have been protected by patents for compositions of substrates, where the patents are approved for the synthetic chemical structures of the drugs (Hornick and Rajan 2015). IP laws are also applicable for all aspects of 3D bioprinting and nanotechnology (e.g., hardware involved for printing, software for the design of tissue structures, and materials with specific compositions used in this system). The most

noticeable forms of IP for 3D bioprinting and nanotechnology are patent and trade secret protection (Hornick and Rajan 2015). Even though copyrights also protect the software of 3D bioprinting and nanotechnology machine (Hornick and Rajan 2015), the issues of engineered tissues and organs still remain to be solved due to humanized used over time.

1.8 Concluding Remarks and Future Perspectives

Development of biomimetic materials is exponentially increasing, especially for their applications in tissue engineering and regenerative medicine, biosensors, drug/protein delivery, stem cell research, 3D bioprinting and so on. These biomaterials have been fabricated by taking inspiration from existing designs and procedures of nature, along with the understanding of the chemistry and mechanisms of cell biology, nature of diseases, mode of actions and mechanism of biomolecules. It is true that till now, numerous biomaterials have been fabricated, have faced several difficulties *in vitro* and/or *in vivo*. Many materials achieved to their best levels but some of them have failed to achieve their best levels. Research is continuously going on in this field to find better options and for progress of the society. However, the inclusive successful development of biomimetic medical materials solely depends on their practical implementation on or in human body. This process is associated with the development of technology, software, device and so on. The modern progress within materials research promotes further investigation into how to best emulate the structures of natural materials in biomimetic materials. The emerging field of biomimetics deals with new technologies created from biologically stimulated engineering at nano- to macro- levels and 3D-bioprinting. Indeed, these technologies revolutionize materials science and engineering, and provide opportunities to develop tissue engineering scaffolds, devices, and tissue models for biomedical applications by embedding several biomimetic features at the molecular, genetic, and nanometer scales.

In conclusion, the developed biomimetic medical materials should be biocompatible and flexible. They should contain cellular and molecular induction and adhesion sites, sufficient mechanical strength, and possess characteristics of biodegradability and tissue remodeling. To be a model biomedical applicable material, effective *in vivo* results are the primary requirements. A combined package of biomaterial, technology, software, and device could offer a systematic approach for medical application. Besides, IP protection is important in the medical industry. Everything that is used on or in the human body needs wide-ranging analysis to confirm biocompatibility, and to evaluate side effects by Food and Drug Administration of each country.

It is expected that in near future, researchers will able to develop more effective and sophisticated biomimetic medical materials for efficient biomedical applications through further improvement of the understandings of biological functions and human anatomy, and using best leverage advanced technologies especially through wide applications of biomimetics such as nanotechnology and 3D-printing.

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