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# Stem cell and biomaterials

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**Abstract**

Stem cells are cells that are not yet differentiated, can divide asymmetrically, differentiate into different cell types, and perform functional tissue repair. They are recognized as major cellular candidates for the regeneration of damaged tissues. Biomaterials and biomaterial scaffolds are essential in tissue engineering applications using stem cells. Recently, studies examining stem cell biomaterial interactions in different aspects have attracted attention. This review presents current information about the general properties of stem cells and biomaterials, stem cell-biomaterial interactions, three-dimensional (3D) tissue scaffolds used in stem cell studies, and 3D bioprinting.

**Keywords:** stem cells, biomaterials, biomaterial stem cell interaction, 3D tissue scaffold

## 1. Introduction

Stem cells, found in the niches of various healthy tissues, have the potential to self-renew and differentiate after trauma, disease or ageing (1). Stem cells (SC) make an indispensable contribution to tissue morphogenesis, repair and the homeostatic cell cycle in the body. Due to these properties, they are recognized as major cellular candidates for the regeneration of injured, aged or diseased tissues (2). The capacity for self-renewal and the potential to generate many different types of cells form the basis for stem cells to benefit the field of regenerative medicine (3). SC therapies are gradually being recognized as a critical building block in tissue regeneration, offering treatments for various diseases. However, many challenges, such as low cell retention and engraftment and poor long-term maintenance of SC function, limit the successful use of SC translation in clinical practice (4).

The biomaterial was once described as a nonviable material used in a medical device intended to interact with biological systems. It was later revised as a material designed to interface with biological systems to evaluate, treat, augment or modify any tissue, organ or function of the body (5). Biomaterials have benefited patients with increased longevity and improved quality of life (6). They are synthetic or natural materials used to replace, improve or interact with a biological system (7). Extensive efforts have been made to mimic in vivo microenvironments to direct and control stem cells into specific cell types required for regenerative medicine (8).

## 2. Stem Cells

Stem cells are defined as cells that can divide asymmetrically, renew themselves and differentiate into mature cells (9). Many types of stem cells can be isolated from embryonic or adult tissues with potencies ranging from pluripotent to unipotent, depending on the type of SC (10). Totipotent stem cells can divide and differentiate into cells of the whole organism. Totipotency has the highest differentiation potential and allows cells to form both embryonic and extra-embryonic structures. The zygote formed after a sperm fertilizes an egg is totipotent (11). SC can be multipotent, as in the blood sample, or unipotent, as in the testicles (12).

In general, stem cells can be characterized as embryonic and adult stem cells.

Embryonic stem cells (ESC) are pluripotent stem cells isolated from the inner cell mass within the blastocyst. They can differentiate into all three germ layers. They express pluripotent markers such as Sox2, Oct4 and Nanog. Despite the differentiation potential of these cells, they have some disadvantages, such as ethical problems arising from the destruction of the human embryo and the formation of teratomas when transplanted directly as undifferentiated cells (13). Adult stem cells have been identified in a wide range of adult tissues, including the brain, heart, lungs, kidney, and spleen. SC in adult tissues produces differentiated cells suitable for that tissue. Somatic stem cells in adult tissues can be reprogrammed into a pluripotent state in vitro. These resulting cells are called induced pluripotent stem (iPS) cells (12). The most famous adult stem cell subgroup is mesenchymal stem cells (MSC), which can efficiently differentiate into all cell types derived from the mesoderm. These cells can be relatively easily isolated from bone

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marrow, adipose tissue, and umbilical cord blood (14). MSC are a source of precursor cells that can be replicated in vitro and used for tissue regeneration for different clinical applications (15).

Adult stem/progenitor stem cells reside in a specialized microenvironment called the stem cell niche, which houses a large number of cells such as fibroblasts, endothelial cells, and/or stromal components. The stem cell niche, a highly dynamic microenvironment housing stem cells, is usually composed of different cells (e.g., stem cells, immune regulatory macrophages and T cells), soluble secreted factors (e.g. growth factors, chemokines, hormones and androgens) (16). Niche and its components tightly regulate the behavior and function of stem cells through direct interactions and/or signaling cues from soluble factors (17). Traditionally, stem cell differentiation has been regulated through soluble signals such as growth factors. While these signals are important, factors from niche or extracellular matrix (ECM) molecules also contribute to stem cell activity and fate.

Understanding the microenvironment factors that influence stem cell fate, such as mechanical properties, topography, and specific ECM ligands, is essential for designing advanced biomaterials (18).

The development and regeneration of tissues is largely the result of stem cell function. In order to achieve this goal, stem cells can self-renew by symmetrical cell division (19). Self-renewal is the result of cell division, which takes place in the niche where stem cells are located. Stem cell division can occur as asymmetric division or symmetric division. Asymmetric division forms a progenitor cell and a daughter cell, which remain stem cells. In a symmetrical division, two new stem cells are formed (20). SC can increase in number by dividing symmetrically and renewing themselves asymmetrically to form a differentiated generation (9).

Cancer stem cells (CSCs) are defined by their potential for self-renewal, differentiation and tumorigenicity. They are considered responsible for drug resistance and relapse (21). CSCs are associated with the metastatic nature of cancer and the recurrence of cancer after treatment (22). New biomaterials have been widely evaluated as in vitro platforms for their ability to mimic the cancer microenvironment. Biomanufacturing methods and models designed with biomaterials offer opportunities to investigate signaling pathways and related phenomena that control cancer progression and drug response (21).

## 3. Biomaterials

Biomaterials are synthetic or natural materials that are used to replace, improve, or interact with a biological system. Various types of biomaterials are used for medical purposes, such as drug delivery, stents, and implants (7). Biomaterials are compounds that interact with biological systems, thereby affecting the growth and health of cells around them. Biomaterials have been used for targeted differentiation to generate a variety of cell types (3). Biomaterials with tunable biophysical and biochemical properties to maintain and enhance stem cell function, conjugated growth factors, and tissue-derived ECM are vehicles for the survival and differentiation of transplanted cells. Studies have shown that, with the increased effects of engraftment and differentiation, engineered materials transplanted with stem cells can facilitate functional recovery and structural integrity, such as angiogenesis and electromechanical enhancement, providing a suitable niche for tissue regeneration (4).

The biocompatibility of biomaterials is important. Biocompatibility is defined as the ability of a material to perform desired functions relative to a medical therapy without any risk of injury, toxicity, or rejection, to induce an appropriate host response in a given application, and to interact with living systems (6). Biomaterials are often designed to have favorable biochemical and biophysical properties, including molecular compatibility, high porosity, and favorable mechanical strength that mimic the microenvironment of the natural ECM (23). Biomaterials preserve the properties of stem cells, such as self-renewal, proliferation and differentiation. In some cases, they can induce the microenvironment of stem cells by mimicking the natural ECM (13).

Compared with the traditional cell-type-specific biomaterial, new stem cell-interacting biomaterials are designed to meet the needs of various cell types due to the presence of bioactive cues. Such studies aim to identify materials that can regulate cell function and find the appropriate biomaterial-stem cell combination for the human body (23). In an in vitro cell and tissue culture, biomaterials are designed to provide chemical, mechanical, and physical cues that activate several molecular signaling pathways, thereby determining the fate of the cell (7).

Next-generation biomaterials are intended to be used as scaffolds to mimic native ECM and provide a 3D environment to sustain body adhesion, migration, proliferation and differentiation (24). 3D bioprinting is a digital model-based technology for printing all kinds of materials layer by layer to create objects with complex structures. Biomimetic scaffolds, biomaterials, cells and other bioactive molecules can be created accurately and efficiently by using them as units. By creating a personalized bionic 3D scaffold to simulate the diverse tissue microenvironment, proliferation and differentiation of stem cells can be induced (25). The biomaterial will transmit specific signals to the cells, especially depending on their composition and structure. Therefore, biomaterials' topography, chemistry, and physical properties are critical parameters for guiding cell fate (20). Numerous studies have shown that the simple addition of biophysical factors to biocompatible biomaterials without any chemical factors can significantly affect stem cell

behavior and differentiation into desired cell lines (16).

### 3.1. Natural and Synthetic Biomaterials

Biomaterials must provide informative microenvironments that allow stem cells to interpret biomaterial instructions and change their fate accordingly. Biomaterials for modulating stem cell differentiation can be broadly categorized as natural and synthetic polymers (5). Natural biomaterials have been used for a long time because of their superior biocompatibility, biodegradability, low toxicity and low allergenicity. It turns into degradation products that are less cytotoxic and more easily metabolized by host tissues (26). Natural biomaterials contain a structure similar to biological tissue, where they can serve as reparative materials for tissue regeneration (24). Natural biomaterials are materials that can support stem cell proliferation and act as a natural base for regulating the behavior of implanted cells or even the differentiation of stem cells into the target tissue (13). Protein-based biomaterials such as collagen, fibrin, elastin, and silk-based material scaffolds are known to be suitable for tissue engineering applications such as stem cell differentiation, transplantation and wound repair. Hyaluronan, also known as hyaluronic acid, has been used as natural polysaccharide-based biomaterials for stem cell cultures in the field of tissue engineering and regeneration (24). They have similar mechanical and adhesive properties as natural ECM. It has some disadvantages such as short degradation time, difficult purification and quality control. Natural biomaterials can regulate the proliferation and differentiation of implanted stem cells into the target tissue (13). Despite their superior biocompatibility, natural biomaterials face poor mechanical strength due to rapid degradation once implanted. Time is needed for the newly formed tissue to become fully functional. Therefore, rapid degradation should be avoided. To improve their mechanical integrity, natural biomaterials are often combined with synthetic ones to produce hybrid or composite biomaterials that achieve the advantages of both categories (17).

Synthetic materials are attractive due to their more adjustable mechanical properties and ease of manufacture on a large scale (26). Synthetic materials have the advantages of controllable degradation, mechanical properties, and controllable composition of materials. However, synthetic materials often lack cell adhesion sites and cell recognition signals (24). Synthetic biomaterials can be obtained from Food and Drug Administration (FDA)-approved polymers with excellent biodegradable and biocompatible properties, such as poly (lactic acid) (PLA), polylactide caprolactone (PCL), polyglycolide (PGA) (17). Adapting synthetic materials is accomplished by adding biochemical modifications, modulating the material's mechanical properties, and/or determining the microscale structure and topography. The presentation of growth factors and morphogens is a complementary approach to giving additional biochemical functionality to synthetic material (27).

## 4. Biomaterial Stem Cell Interaction

Research has shown how biomaterial/structure cues in the form of biomaterial chemistry, material hardness, surface topography, porosity, and degradation properties play an important role in controlling cellular events in vitro and in vivo (28). Biomaterial selection alone can affect the behavior of stem cells (27). Poly-lactic-co-glycolic acid (PLGA) and self-gelling alginate are used to generate neuronal stem cells, astrocytes, adipocytes, osteoblasts, cardiomyocytes and chondrocytes (3). Chemical and biological modifications can directly affect SC behavior by changing substrate properties, surface interactions, scaffold degradation rate, microenvironment architecture, and ultimately manipulating signal transduction pathways in SC (29). It has been stated that microenvironment factors such as ECM proteins, growth factors (GF), stiffness and topography play a critical role in guiding stem cell behavior and fate (1).

Naturally derived ECM components such as fibrillar proteins or glycosaminoglycans (GAGs) offer an attractive starting point for biomaterials to guide the differentiation of stem cells. Most of these components are found in the natural stem cell niche and contain bioactive motifs and cell binding domains of stem cells that can promote cell survival and proliferation (27).

The mechanical properties of a scaffold or culture surface can also have a significant impact on the differentiation of the seeded stem cell. By exerting traction forces on a substrate, many mature cell types such as epithelial cells, fibroblasts, muscle cells and neurons sense the stiffness of the substrate and show different morphology and adhesive properties (30). Surface hardness regulates fate. The stiffness of most tissues is several times lower than that of tissue culture plastic or glass and can vary within a given tissue as a function of age or disease. Changes in bulk stiffness of ECM-coated hydrogels elicit differential responses in stem cell populations. Bone differentiation of mesenchymal stem cells is favored by hard substrates, while soft substrates promote adipocyte differentiation. Substrate stiffness also prompts skeletal muscle stem cells to self-renew or differentiate with moderately rigid substrates that mimic normal muscle stiffness that most effectively supports stem cell status (12). The biomaterial stiffness, which restricts stem cell differentiation in various lineages, matches the stiffness of the native tissue microenvironment in which these cells reside. It seems that the differentiation of stem cells from different tissues or species demands quite different stiffness ranges. SC from different sources may respond differently to mechanical stiffness. Several studies have indicated that hard matrix can lead to osteogenic origin by stem cell differentiation, medium stiffness to the myogenic origin, and soft matrix directs stem cells to neuronal cells (8).

Studies have revealed that the size of the topographic

features and the conformations of cavities, folds, pits, pores, symmetries, etc., are also important (30). Biophysical properties of biomaterials, such as porosity, micro/nano-scale surface patterns, architecture, and stiffness/resilience, can influence endogenous stem cells' behavior by changing the local microenvironment through cell-biomaterial interactions after implantation (17). Parameters such as surface topography, surface wettability, and physicochemical properties, including surface charge, strongly influence cell-material interactions (31). The cells were found to perceive micro- and nano-meter topography with uniform chemical properties and align and orient themselves along the grooves. In particular, it has been observed that the groove pattern exerts a dynamic effect in relation to stem cell alignment and elongation (20).

Within vivo regenerative medicine, cell-free biomaterials can be introduced into the body to stimulate and instruct the activity of endogenous adult stem and progenitor cells by changing the niche to increase the body's natural reparative capacities (32). Damaged tissues often also lose deeper layers that contain stem cell niches. In such cases, biomaterials can be useful tools to re-establish the functionality of niches. Artificial niches must contain appropriate 'homing' signals that can attract and localize endogenous stem cells through known cell-cell or cell-matrix adhesive interactions (20).

## 5. 3D Tissue Scaffold

Tissue engineering aims to regenerate damaged tissues by combining cells from the body with highly porous scaffold biomaterials that act as templates for tissue regeneration (33). Stem cells are a good source of cells for tissue engineering with the potential to turn into a large number of desired cell types (8). Growth factors, stem cells, and scaffolds are collectively known as the tissue engineering triad (34). Biomaterials and stem cells coupled with growth factors are imperative to increase the survival rate of stem cells and further facilitate tissue regeneration in vivo (4). The current tissue engineering strategy uses living cells, biomaterials and appropriate biochemical, physical factors and combinations to create tissue-like structures. The ultimate goal is to incorporate these tissue-like structures into the body to repair damage or replace dysfunctional organs (35). Combining stem cells with biomaterial scaffolds offers a promising strategy for the future of biomedicine and regenerative medicine. (36). An ideal scaffold should provide chemical stability or degradability to support cytocompatibility, adhesion, proliferation, stability and mechanical strength, and physical properties suitable for the surrounding tissue (31).

The incomplete differentiation of stem cell populations to the desired target remains an unresolved challenge. Various biomaterials have been designed to mimic the natural ECM action in vitro. Applying biomaterials in a 3D environment can also help create a human-based model that can reduce animal use in research (14). Considering that it once served only as a physical structure, it is now clear that the chemical composition of biomaterial scaffolds can guide, improve and redefine cell behavior (32). Bone marrow-derived mesenchymal stem cells (BMSCs) are considered to be the most commonly studied stem cells in tissue engineering. In recent years, the application of biomaterial scaffolds based on Adipose-derived mesenchymal stem cells (ADMSCs) has become an increasingly hot topic (35).

The scaffolds act as a synthetic ECM to organize cells in a three-dimensional architecture and deliver stimuli that drive the growth and formation of the desired tissue. Depending on the tissue of interest and the specific application, the required scaffold material and properties differ (37). Regardless of tissue type, biocompatibility, biodegradability, mechanical properties, scaffold architecture, production technology, and biomaterials are important in a scaffold (33).

Various synthetic and naturally derived materials can be used to form hydrogels for their scaffolds. Synthetic materials include poly (ethylene oxide) (PEO), poly (vinyl alcohol) (PVA), poly (acrylic acid) (PAA), poly (propylene fumarate-co-ethylene glycol) (P(PF-co-EG)) and polypeptides. Naturally derived polymers include agarose, alginate, chitosan, collagen, fibrin, gelatin and hyaluronic acid (37).

The tissue structure environment of cells must resemble its native counterpart for cells to maintain their phenotype, establish appropriate cell-cell interactions, and express tissue-specific proteins in conjunction with the ECM (38).

3D cell cluster configurations provide a more natural anatomical environment than single-layer cell cultures (38). The use of 3D culture techniques has become more common in research (10). Among the various techniques available for scaffolding, 3D printing technology is considered a superior technique. 3D printing is a technology that involves the sequential production of the same or different materials through an automated process layer by layer, resulting in the creation of a complete 3D structural object (39). 3D cultures more effectively summarize cell-cell and cell-matrix interactions in vivo, and cells in 3D cultures exhibit many unique and desirable properties. 3D stem cell culture can use a variety of matrices or scaffolds in addition to cells to support complex structures (10).

Organoids are a class of engineered 3D tissues that exhibit similar biological properties to their in vivo counterparts. 3D models, particularly organoids, offer opportunities to design culture systems that bridge the gap between the limitations of two-dimensional (2D) tissue culture and the in vivo organisms of the whole animal or human subjects. The production of tissue-specific organoids is based on the biological principles of organ development, where stem cells are regulated to differentiate and develop into functional tissues and organs (40).

## 6. Stem Cell and 3D Bioprinting

3D bioprinting is a tissue engineering production method that uses the spatial model of combining living cells and other biological materials in a layer-by-layer deposition approach to construct living tissues and organ analogues.

Bio-ink is a combination of inert printing medium seeded with living cells and forms the raw material deposited on the collection substrate. Ideal bio-ink has high mechanical integrity, high stability, insoluble in cell culture medium, non-toxic and non-immunogenic; and should be able to promote cell adhesion (38). 3D bioprinting technology is based on biomaterials, cells and other bioactive molecules as units that can accurately and efficiently form complex bionic functional scaffolds (25). 3D stem cell culture can use a variety of matrices or scaffolds in addition to cells to support complex structures (10)

## 7. Results

An excellent feature is that stem cells are not yet differentiated cells and have the ability to turn into different types of cells. With these features, stem cells have been and will continue to be the subject of scientific research from different aspects. Biomaterials are used in many fields today. Biomaterials play an important role in creating micro-environments to support cells for tissue regeneration. Properties such as biocompatibility, biodegradability, mechanical properties, production technology, the material used, surface topology, roughness, and hardness are important for the functionality of biomaterials. For tissue regeneration, the characteristics of the natural microenvironment of the cells forming the target tissue should also be considered. Tissue scaffolds formed from various biomaterials must be compatible with the targeted tissue properties. Research on stem cell-biomaterial interactions in the stem cell field has shown how important the properties of biomaterials to be used in tissue scaffolds are. Developing technological opportunities have carried stem cell research to different dimensions. Research results with tissue scaffolds to be obtained by 3D bioprinting to mimic the targeted tissue will provide new information about stem cell and tissue regeneration in the future.

## Conflict of interest

None to declare.

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None to declare.

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