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Popular Article

Use of stem cells for healing of bone and cartilage defects

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Stem cells for bone tissue engineering

Stem cells have emerged as a cornerstone in the realm of bone tissue engineering, revolutionizing the field with their remarkable potential to address bone defects and enhance regenerative medicine strategies. The remarkable potential of these adaptable cells, encompassing embryonic stem cells (ESCs), mesenchymal stem cells derived from bone marrow (BM-MSCs), mesenchymal stem cells sourced from umbilical cord blood (UCB-MSCs), stem cells originating from adipose tissue (ADSCs), stem cells derived from muscle tissue (MDSCs), and dental pulp stem cells (DPSCs), lies in their distinctive capacity to undergo differentiation into osteogenic lineages-the essential components in the intricate process of bone formation. By inducing the controlled differentiation of these stem cells into osteoblasts, the bone-forming cells essential for bone growth and repair, researchers are unlocking new avenues to construct functional, biocompatible bone substitutes and advanced therapies that have the potential to transform the landscape of bone tissue engineering and orthopaedic medicine.

In regenerative medicine, stem cells/progenitor cells should have the following important characteristics: (i) availability in large amounts, (ii) multiple differentiation, (iii) painless isolation methods, (iv) use in autologous or allogeneic transplant, (v) agreement with Good Manufacturing Practice guidelines (GMP) (Trohatou and Roubelakis, 2017).The repair and functional reconstruction of bone damage ultimately depends on cells, where stem cells

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have been shown to play a key role in this process. The application of these stem cells to bone tissue engineering requires inducing in vitro differentiation of these cells into bone forming cells, osteoblasts. Stem-cell based therapy strategies are promising approaches for the treatment of bone defects. However, extensive cell expansion steps, low rate of cell survival and uncontrolled differentiation of the stem cells transplanted into the body currently remain as the key challenges in advancing stem cell therapeutics. An alternative strategy is to use specifically designed bone scaffolds to recruit endogenous stem cells upon implantation and to stimulate new bone formation and remodelling. Stem cells recruitment based on scaffold features for bone tissue engineering relies on development of scaffolds that can effectively mobilize and recruit of endogenous stem cells to implantation site. Among these, mesenchymal stem cells (MSCs) stand out as exceptionally promising bone progenitor cells, attributed to their robust proliferation capacity, remarkable multi-lineage differentiation potential, and minimal immunogenicity. MSCs are considered to be a more appropriate cell source for bone tissue engineering (Shang *et al*., 2020).

Bone structure

Bone is a rigid and highly dynamic tissue that supports and protects several organs in the body. Moreover, bone tissue provides the environment for red and white blood cell production, plays an important role in mineral homeostasis, such as calcium and phosphorus, and gives a solid base for skeletal muscles (Meguid *et al*., 2018). There are two discernible types of bone tissue: dense cortical or compact bone, constituting 80% of bone mass, and the remaining portion is trabecular bone. Cortical bone forms the tough outer layer, while the structure of trabecular bone is designed to enhance load distribution. Both cortical and trabecular bones undergo bone remodeling, a vital lifelong process crucial for maintaining bone mass balance and mineral equilibrium (Tolar *et al*., 2004).

Furthermore, bone tissue can be categorized into two distinct phases: (i) the bone matrix and (ii) an organic phase encompassing cellular elements like osteoblasts, osteoclasts, and osteocytes. Bone metabolism and regeneration, integral to the dynamic nature of bone, involve on-going remodelling and self-regeneration processes that persist throughout adulthood.

Bone metabolism and regeneration

Bone, an exceptionally dynamic tissue within the body, continuously undergoes remodeling and self-regeneration throughout adulthood. Moreover, this intricate organ performs a multitude of essential roles, including hematopoiesis, meticulous regulation and storage of essential minerals, safeguarding vital life-sustaining organs, and enabling

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locomotion, among other functions (Shang *et al*., 2020). Bone tissue undergoes a life-dominant process known as bone remodelling, which significantly contributes to maintaining balance in bone mass and mineral homeostasis. During bone remodelling, osteoclasts, arising from hematopoietic stem cells, dismantle aged or impaired bone. Subsequently, osteoblasts, derived from mesenchymal stem cells, are mobilized to the impacted area to restore the bone removed by osteoclasts. Conversely, osteocytes, originating from osteoblasts, enter a state of inactivity when encased in the bone matrix.

Embryonic stem cell and osteogenic differentiation

Having boundless self-renewal capability, these cells have the potential to give rise to diverse cell lineages. Such attributes render ESCs highly valuable as a cellular resource in the realms of tissue engineering and regenerative medicine. The controlled differentiation of ESCs along specific lineages can be achieved through meticulous cultivation conditions and strategic manipulation of the microenvironment. Notably, a significant focus has recently been directed towards steering ESC differentiation into the osteogenic lineage. In light of thorough investigations into the *in vitro* osteogenic differentiation of ESCs, contemporary studies in bone tissue engineering have unveiled the promising utilization of ESCs in facilitating bone tissue regeneration. This promising potential is realized through the synergistic integration of ESCs with 3D polymeric scaffolds and well-suited culture systems. Lineage specific differentiation of ESCs can be directed under specific culture conditions and by manipulating the microenvironment.

Mesenchymal origin cells participation in bone remodelling

Bone remodeling is an ongoing life-long mechanism involving the removal of mature bone tissue from the skeletal structure through resorption, followed by its renewal through ossification or bone formation. This intricate process contributes to the preservation of stable bone mass throughout adulthood, as well as during periods of rapid skeletal development and growth (Raisz, 2005). Throughout these processes, the exact regulation of bone structural integrity is orchestrated by distinct cell types. The osteoblast, derived from mesenchymal origins, guides bone formation; the osteoclast, originating from hematopoietic lineage, governs bone resorption; and during the concluding stage of bone remodeling, the osteocyte, emerging from osteoblast lineage, plays a pivotal role (Chen et al., 2017). The MSCs serve as the progenitors of osteoblasts while also assuming the role of regulators for osteoclasts (Raisz, 2005). MSCs unequivocally play a significant role in the context of bone metabolism under diseased conditions, either through direct or indirect mechanisms, as they function as

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progenitors for both osteoblasts and osteoclasts. When there are bone defects or fractures, the inherent MSCs can migrate to the damaged site and play an active role in rebuilding bone tissue. In clinical settings, the molecules secreted by MSCs may guide various mature cells to undergo differentiation. This process of differentiation takes place under specific conditions, such as the presence of a particular medium composition and/or properties of biomaterials.

Presently, the potential implications for maintaining skeletal balance have led to MSCs garnering widespread attention across the globe, as researchers strive to unveil the underlying causes of bone disorders (Zhou et al., 2014). MSCs originating from inflammatory microenvironments exhibit a detectable reduction in their capacity for bone regeneration, underscoring their involvement in compromised bone healing facilitated by autologous MSCs (Chen et al., 2017). When bones encounter injuries, such as trauma or infection, pro-inflammatory signals are triggered. Similar to how these processes unfold in other tissues and organ systems; the innate immune system orchestrates responses that influence local repair and the healing of bone. Ensuring the restoration of tissue integrity amidst ongoing immune activity is crucial to mitigate potential harm and facilitate the resolution of inflammation (Shang et al., 2021). Preserving tissue integrity both during and following an active immune response holds utmost importance in mitigating pathological outcomes and fostering the resolution of inflammation. Notably, the interaction between stem cells and immune cells in the context of wound healing and inflammation traces its origins back to ancient times (Shang et al., 2020). Diverse subtypes of innate lymphoid cells can assume specific roles in guiding the process of regeneration and the differentiation of stem cells, depending on the prevailing context (Von moltke et al., 2016). Tissue-engineering strategies combining biomaterials/scaffolds, MSCs and growth factors are used in order to improve bone repair in fractures greater than 50 mm (Decambron et al., 2017).

Bone marrow-derived mesenchymal stem cell and osteogenic differentiation

To date, bone marrow stem cells are the most frequently used cell source for bone tissue engineering. Within the marrow reside MSCs, instrumental in the regeneration of various mesenchymal tissues, including bone, cartilage, muscle, ligaments, tendons, adipose, and stroma. (Caplan, 2005). Extensive research into the in vitro osteogenic differentiation of BM-MSCs for the fabrication of tissue engineered bone tissue-like structures using various 3D supporting matrices as well as efficient 3D culture systems such as bioreactors has been conducted. Under proper culture conditions containing certain exogenous factors, BM-MSCs can be directed towards osteogenic differentiation. The BM-MSCs have been harvested from

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the patient's own bone marrow, expanded in vitro, and then induced to differentiate towards osteogenic cell lineage followed by mineralized bone formation on three-dimensional HA ceramics. These tissue-engineered bone constructs can be then implanted back into the original patients, demonstrating bone healing potential without any side effects due to tissue rejection (Morishita *et al* 2006). To date, extensive research into the in vitro osteogenic differentiation of BM-MSCs for the fabrication of tissueengineered bone tissue-like structures using various 3D supporting matrices as well as efficient 3D culture systems such as bioreactors has been conducted.

Umbilical cord blood-derived mesenchymal stem cells and osteogenic differentiation

The UBC-derived MSCs have been reported to be functionally similar to BM-MSCs, and the multilineage differentiation capacity of UCB-MSCs into different connective tissue-forming cells such as adipocytes, osteoblasts and endothelial cells has also been reported (Kestendjieva *et al* 2008). The osteogenic induction of UCB-MSCs is similar to the culture conditions for osteogenic differentiation of BM-MSCs. A great deal of research has focused on the interaction of UCB-MSCs and biomaterials, and isolated UCB-MSCs have been loaded onto suitable biomaterials-based 3D scaffolds. Composite constructs formed by combining these elements have been implanted into animal models lacking immune response or into models simulating bone defects to assess their ability to generate bone tissue in vivo.

Adipose tissue-derived stem cells and osteogenic differentiation

Adipose tissue has been one of the most interesting subjects for research since the existence of multipotent stem cells within this tissue was reported in 1964 (Rodbell 1964). Adipose derived stem cells (ADSCs) are now considered to be a promising autologus cell source in tissue engineering and regenerative medicine strategies, mainly due to its wide availability and easy access (Seong *et al*., 2010). The isolated ADSCs display a multipotent differentiation capacity to differentiate into various cell types such as osteoblasts, chondrocytes, adipocytes, neural cells, endothelial cells and cardiomyocytes depending on specific culture conditions (Bunnell *et al* 2008). Recently, ADSCs have been used by many researchers for bone tissue engineering applications, and a great deal of research has demonstrated that ADSCs show good adhesion, proliferation activity and homogenous bone-like tissue formation on various biocompatible 3D scaffolds.

Underlying mechanism to control osteogenic differentiation

The process of bone development involves four distinct phases: (i) migration of mesenchymal cells with osteogenic potential to the site of future skeletogenesis, (ii)

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mesenchymal – epithelial interactions (iii) condensation (or aggregation) of mesenchymal cells and (iv) differentiation into the osteogenic lineage (Heng *et al*., 2004).

Future challenges

To date, there have been several successful approaches to direct osteogenic differentiation of ESCs, BM-MSCs, UCBMSCs & ADSCs as well as success in the fabrication of bone-like tissue using 3D supporting matrixes and culture systems. A more efficient method of isolation and osteogenic differentiation that can generate large numbers of stem cells and osteogenic cell lineages upon differentiation needs to be developed. The development of feasible and reproducible methods for isolation, expansion, and differentiation, the development of suitable 3D biomaterials and 3D culture systems would constitute an important step towards making stem cell-based bone tissue engineering a reality for patients.

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