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Editorial

Engineering Bone Niche Signals to Control Stem Cell Fate for Bone Tissue Regeneration

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Tissue engineering, also referred as regenerative medicine, is the regeneration and remodelling of tissue in vivo to repair, replace, or enhance organ function, as well as to engineer and grow functional tissue substitutes in vitro for implantation in vivo as biological substitutes for damaged or diseased tissues and organs. Over the last decades, scientists have paid significant attention to tissue engineering approaches and explore their potential application for bone repair and regeneration. As a result, the knowledge of bone tissue engineering has been rapidly growing and the number of articles with the search term of "bone tissue engineering" in PubMed increased from 272 in 1999 to 1709 in 2014. Mesenchymal stem cells (MSCs) is one of cornerstones in the concept of bone tissue engineering to serve as a promising cell source due to their innate functionalities, including multiple differentiation capability, immuno-modulatory and trophic functionalities. However, it would be of great importance to get deep understanding of the signalling pathways controlling the commitment of MSCs into osteogenic lineage, by which we are able to recreate these signalling pathways for MSC-based bone tissue engineering.

Bone tissue has a hierarchical structure characterized with a mineral phase (hydroxyapatite nanocrystals), an organic phase (composed of 90% collagen type I and other noncollagenous proteins), a cellular phase (osteoblasts, osteoclasts and osteocytes), and a soluble factor phase (growth factors and /or cytokines) entrapped therein [1]. These components provide a specific and balanced signalling network in bone tissue microenvironment, contributing to the innate bone metabolic and anabolic activities and maintaining the structure and functions of the bone. A great deal of effort, therefore, has been made to mimic the bone tissue microenvironmental components for controlling the commitment of MSCs into osteogenic lineage for bone tissue regeneration.

First, by mimicking bone extracellular matrix **(**ECM) chemical and/or physical characteristics such as architecture, topography and mechanical properties, it has been demonstrated that the bone ECM-mimicking substrata (biomaterials) are able to prime the fate of the cellular phenotype into osteogenic lineage, and they allow the attachment, proliferation, and extracellular matrix formation of bone-related cells on their surface, as well as actively induce new bone formation via the recruitment of and interaction with osteoprogenitor cells [2]. To mimic the bone nanostructure to engineering bone-related biomaterials, one typical strategy is to incorporate nanocrystals into or in-situ generate nanostructures on the biomaterials, which have been shown to be effective in regulating various cellular functions including cell adhesion, proliferation and differentiation [3-5]. Second, mimicking the signals provided by bone cellular phase has also been shown as a feasible approach to control stem cell fate into osteogenic lineage. Osteoblasts is one main cell type in bone cellular phase, and their function and phenotype vary depending on their developmental stage, and the active osteoblasts (in early stage) are cuboidal in shape, mononuclear, and able to secrete collagen type I and glycoproteins, cytokines, and growth factors into a region of unmineralized matrix. Osteoblasts thus provide complex but bone specific signals for bone remodelling process via communicating with other cells such as MSCs. Different co-culture models have been employed to co-culture osteoblasts and MSCs, and it has been showed that osteoblasts are able to direct MSCs into osteogenic differentiation via either direct cell-cell contact or through a paracrine manner [3,5,6]. Third, the cytokines and/or growth factors within bone microenvironment play a key role as well in the bone remodelling process, and mimicking their signals has been proven to be very successful in steering MSCs into bone lineage. The best-known growth factor is bone morphogenetic protein-2 (BMP-2), with an essential role in promoting bone formation both *in vitro* and *in vivo* [7-9]. Recently, inflammatory factors, transiently expressed by macrophages upon tissue injury, have increasingly been appreciated for their role in tissue repair and regeneration [10-12]. For example, short-term tumour necrosis factor-alpha exposure mimicking the scenario upon bone fracture is able to promote the proliferation, migration and osteogenic differentiation of adipose tissue-derived stem cells [10].

As discussed above, we have been successfully mimicking some signals within bone microenvironments to confer stem cells fate into osteogenic lineage differentiation, however, in order to better control MSCs into bone lineage differentiation for an effective clinical application, we have to shed light on how the different signalling pathways orientated from bone tissue

components interact each other to form a bone tissue-specific signalling network, as it is no doubt that each signalling pathway plays different roles in different signalling networks and has different effects on cell behaviours. This is best exemplified by BMP-2 signalling which plays a key role in different tissues such as bone, cartilage, muscle, and neuro, but how BMP-2 signalling can differently decide stem cells fate by interaction with other signals remains to be identified.

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