

The interplay of transcriptional and post-transcriptional regulation of migration of mesenchymal stem cells during early stages of bone fracture healing

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Abstract. – Bone fractures are a medical condition where the continuity of the bone is broken due to a fall or accident. The fracture may also be the result of medical conditions such as osteoporosis, cancers of bone or osteogenesis imperfect. During the bone fracture healing process, the mesenchymal stem cells (undifferentiated connective tissue cells) are recruited from local and systemic sources. The modulation of mesenchymal cell migration to the fractured site is the desired goal. Still, there are many processes that are still required to be studied and analyzed. We aimed to consolidate and review the available information on this topic.

Key Words:

Bone fracture, Bone fracture healing, Mesenchymal stem cells.

Introduction

The processes happening in skeletal bones during embryonic and childhood stages of a human life are called bone modeling. During adulthood, the bones undergo a constant repair process, called bone remodeling. Bone remodeling can be intensified by an active lifestyle (regular physical exercise). Remodeling is also a crucial part of bone healing after a bone fracture. Fracture healing relies on timely recruitment and differentiation of mesenchymal stem cells into bone cells. The regulating processes are very complex, and they involve transcriptional and post-trans-

criptional determinants, as well as their interplay factors.

In a country like China having a large population, bone fractures are very common. It was estimated that there were 3.21 cases per 1000 people in 2014¹. The occurrence of bone fracture incidents is almost double in the older age populations¹. From the studies carried out earlier, it has been reported that men have higher incidences of bone fracture from their childhood until their retirement age¹. Whereas, the women population has higher incidences of bone fractures during the pre-retirement age in comparison to their male counterpart¹. The reasons for the bone fractures in women at later ages are due to osteoporosis². Similar trends were also reported from studies carried out in other countries as well³. Also, based on a study carried out in UK, it was estimated that the prevalence of lifetime fractures are over 50% in middle-aged men and 40% in women older than 75 years of age⁴. Due to the prevalence of bone fractures in adulthood, with trends toward higher prevalence at an older age, facilitation of bone repair and healing is attracting substantial attention. In this perspective, a modulation of mesenchymal cell migration to the fractured site is the desired goal. Some progresses have been made but there are still many not clarified issues. Considering that there is a great interest in the study of bone fracture and their healing process, the current review highlights how the interplay of transcriptional and post-transcriptional regu-

lation of recruitment of mesenchymal stem cells can be used to achieve an expedited bone fracture healing process. This review papers specifically focuses on the early events following bone fracture. Understandably, these events have a great impact on how fracture healing will envelop. Thus, a great hope is associated with modulation of mesenchymal stem cells to achieve faster and more complete fracture healing.

Bone Modeling in Embryonic and Childhood Stage

There is a considerable growth of bones from the embryonic stage up to the age of 25 years. Bone formation of most skeleton bones occurs in the fetal stage through differentiation of mesenchymal stem cells, which are undifferentiated connective tissue cells into cartilage cells called chondrocytes. These cells formed the cartilage tissue, and the process is called chondrogenesis (Figure 1). The cartilage bones are replaced by the bone tissues over a period of time, as illustrated in Figure 1. Most skeletal bones are formed by endochondral ossification (also called endochondral osteogenesis). Formation of skull and some skeletal bones involves the process known as intramembranous ossification, which skips the formation of the cartilage.

As mentioned earlier, cartilage is mostly formed during the embryonic stages of development. For simplification, cartilage can be seen as a template for future bone growth process. Cartilage is not vascularized and for the cells formation it receives nutrients by the process of diffusion. Between 6th to 8th weeks of embryonic development, the mesenchymal stem cells and the embryonic precursors of connective tissue cells start differentiating into chondrocytes. Eventual-

ly, the cartilage becomes bigger in size because of chondrocyte hypertrophy (Figure 2) and sufficient mineralization. The nutrients will no longer reach the chondrocytes in certain parts of the cartilage. So, the chondrocytes will undergo apoptosis and will die, leading to a pore formation in those parts of the cartilage. Blood capillaries will penetrate those areas (Figure 2) and subsequently the blood supply will provide both the nutrients and bone precursor cells from outside of the bone. The latter bone precursor cells are called osteoblasts (Figure 2) and their function is to generate the bone matrix (Figure 2), which later replaces the cartilage. Importantly, both chondrocytes and osteoblasts differentiate from the same progenitor cells (Figure 1). The bone tissue replaces most of the cartilage by the time fetuses are delivered. The only remaining cartilage is at the joint surface and at two distal ends of the bone. The extension of the bone length (i.e., bone growth) occurs by replacing the cartilage areas that remain within the bone after birth. During bone growth and until early adulthood, the sequence of events described above repeats itself. Chondrocytes will grow and matrix will be mineralized leading to a lack of the nutrients chondrocyte death, pore formation and blood capillaries' penetration. With the subsequent invasion of osteoblasts, bone tissue will be formed. In addition, to increase their lengths, the bones also increase in circumference due to formation of bone tissue on the outer surfaces.

The extracellular signals driving bone modeling are Transforming Growth Factor (TGF) β , Bone Morphogenic Proteins (BMP), Fibroblast Growth Factors (FGF), Growth Hormone (GH), Insulin-like Growth Factors (IGF), Parathyroid Hormone (PTH), Glucocorticoid Hormone (GC), Osteoprotegerin (OPG), Vitamin D₃ and some others factors.

Undifferentiated mesenchymal stem cells

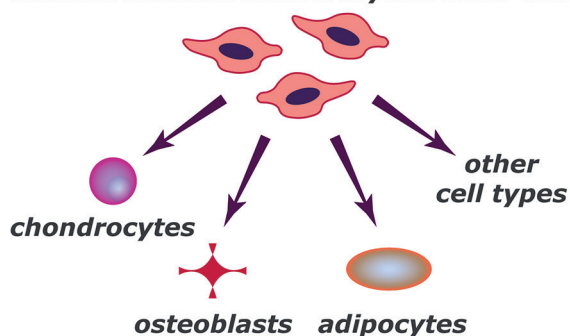


Figure 1. Schematics of mesenchymal stem cell differentiation.

Bone Remodeling During Adulthood

In the adulthood, bones do not have an active growth and the process slows down. Bone modeling is substituted by bone remodeling, which is a constant process of bone tissue resorption and renewal. The resorption is mainly executed by the cells called osteoclasts, whereas bone renewal is the function of the aforementioned osteoblasts. Unlike bone modeling during the period of active bone growth, which occurs at localized areas of the bone, bone remodeling occurs simultaneously at multiple areas of the bone. Another difference is the scale of either process, since bone remodeling occurs at a smaller scale.

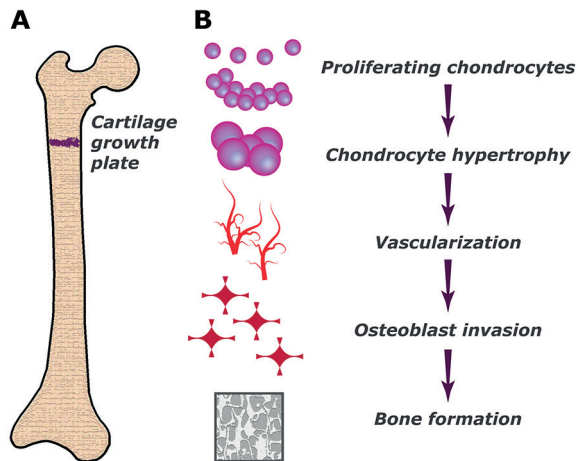


Figure 2. Major events during bone formation.

Despite these differences, there are also similarities between the modeling and remodeling. In particular, bone modeling and remodeling largely overlap in their inducers and intracellular signaling pathways. Bone remodeling is controlled by TGF- β , BMPs, FGFs, IGFs, PTH, GC, OPG, the sex hormone estrogen, and Vitamin D₃. In addition, the remodeling is negatively regulated by factors controlling osteoclasts, such as inflammatory cytokines.

Notably, the mesenchymal stem cells are essential to the process of bone renewal process⁵. Their abundance is estimated as a very small percentage of bone marrow cells⁶. This is not surprising, given the slow turnover of bone tissue⁷. Concomitantly, the scale of involvement of mesenchymal stem cell is expected to be much less than during active bone growth (described above) or bone fracture healing.

Bone Remodeling in the Aging Bone

The aging bone exhibits a changing pattern of bone remodeling and in fact, resorption starts prevailing over bone formation. Especially after menopause in women, this imbalance becomes more exaggerated. The mechanism of bone loss in men has been researched less extensively, so correspondingly less information is available on this subject. It is clear, though, that multiple mechanisms can contribute to altered osteogenesis in advanced age. In particular, secondary hyperparathyroidism, declining levels of sex hormones (especially, estrogen in women), low levels of vitamin D₃ and related changes in calcium metabolism, sedentary life style, and lack of physical exercise, contribute to diminished bone

mass. Thereby, bones become weaker and more brittle with increasing age. There can be associated changes in bone mineral density, which is clinically defined as osteoporosis. There is still ongoing debate in the literature whether osteoporosis is a disease or a physiological condition associated with the aging bone. Regardless whether osteoporosis is a pathological or physiological condition, its higher prevalence in older adults is relevant. This is because osteoporosis predisposes to bone fractures.

Given the fact that the world population is rapidly aging, morphological and cellular changes of bone and the remodeling associated with old age are quite pertinent. Furthermore, fractures of large skeletal bones in the elderly (such as hip fractures) are highly prevalent and the complications are very high for the bone modeling and to study the bone growth processes.

Bone Remodeling as Part of Bone Fracture Healing

Some bone fractures can heal as a primary bone fracture healing process. Specifically, when bone fracture is rigidly stabilized (with or without direct annealing of the fractured ends), the healing may occur in two types, respectively called gap healing and contract healing. While some differences exist between the two, bone remodeling is a very prominent part of both.

In contrast, most bone fractures heal through a secondary bone fracture healing. This process mimics the bone modeling during embryonic development. Secondary healing takes place when the fractured site is not immobilized rigidly, permitting micro-movements between the opposing ends of the bone. The healing begins with the initial response to the injury, which is the so-called inflammation stage of secondary healing. It is, essentially, associated with hematoma formation and inflammatory response, both occurring within minutes and hours after the fracture. The cytokine release at the injured site leads to recruitment of mesenchymal stem cells. As in the embryonic stage of bone development, there is formation of the cartilage. This stage of bone healing is called a reparative stage; it usually occurs in the first couple of weeks after the fracture. Anatomically, this process is first characterized by formation of a soft bony callus. The reparative stage later comprises formation of a hard bony callus (6-12 weeks post-fracture). This is followed by revascularization and neo-angiogenesis, which are associated with the osteoclast recruitment. Eventually,

during the latter steps, normal bone remodeling and establishment of bone marrow ensue. The later phase is the remodeling phase of secondary bone fracture healing and it can take up to several years to complete.

Recruitment and Differentiation of Mesenchymal Stem Cells Pertinent to Bone Fracture Healing

Proper and timely recruitment and differentiation of mesenchymal stem cells are essential to fracture healing. This process is set forth by the local inflammatory response. In particular, the cytokines of the acute inflammatory response (Interleukin [IL]-1, IL-6, and Tumor Necrosis Factor [TNF]- α) are upregulated at the injured site⁸⁻¹¹. Production and kinetics of these cytokines are, in most cases, properly balanced out to initiate the injury-repairing processes. Any disbalance in production or kinetics of these cytokines will negatively affect the bone fracture healing, such as seen with overproduction of TNF- α and abnormal healing in diabetes mellitus¹². Interestingly, kinetics of several cytokines, foremost TNF- α , features two up-regulation peaks^{13,14}. It is assumed that each of these peaks sets in motion different molecular processes¹³. The first peak occurrence is early (hours and days after injury) and is associated with migration and differentiation of mesenchymal stem cells¹⁵⁻¹⁷, whereas the second peak coincides with bone remodeling¹⁵. IL-1 is also expressed biphasically^{14,18}, and its functions are similar to those of TNF- α . In contrast, IL-6 is produced during the initial inflammatory response and is required for osteoclast differentiation¹⁹. The initial peak of cytokine overexpression is followed by production of the factors stimulating bone tissue repair, such as TGF- β , BMPs, and FGFs²⁰. Apparently, the hematoma formed on the site of bone fracture is necessary to stimulate the bone fracture healing^{21,22}. Other cells, such as macrophages, are also needed for proper healing of the fracture²³. Macrophage contribution is complex. This contribution ranges from production of inflammatory cytokines (such as TNF- α ²⁴), which are required for initial phases of bone repair, to later remodeling processes²⁵. This contribution may depend on the underlying macrophage phenotype, or may differ depending on the macrophage origin (resident vs. recruited)²³. Macrophages, along with structural cells, produce growth factors, which lead to migration of exogenous and differentiation of resident mesenchymal stem cells (osteoprogenitor cells) into osteoblasts.

Resident mesenchymal stem cells are believed to originate from the bone marrow, periosteum (fibrous membrane that covers the surface of the bone), and surrounding soft tissue. The sources of exogenous mesenchymal stem cells, which are recruited to the fractured bone, are less clear. It is possible that these cells originate from circulating mesenchymal stem cells^{26,27}, the process involving specific chemokines^{26,28}, thereby starting the process of bone tissue regeneration.

Transcriptional and Post-Transcriptional Regulation of Mesenchymal Stem Cell Recruitment

From the facts mentioned above, the specific chemokines attract exogenous mesenchymal cells to the fractured site²⁸. The main chemokine is believed to be Stromal Cell-Derived Factor (SDF)-1 (also known as C-X-C Motif Chemokine 12)²⁶. At least six alternative variants of the transcript of this gene have been described, five of them being listed at the gene database of the National Center for Biotechnology Information (Bethesda, MD, USA). This chemokine is overproduced at the injured site. The receptor for this chemokine is expressed on mesenchymal stem cells and is called the C-X-C Chemokine Receptor (CXCR) 4. This receptor is part of the family of seven-span transmembrane G protein coupled chemokine receptors. Interestingly, inflammatory factors present at the site of bone fracture exhibit a quite complex effect on SDF-1/CXCR4 signaling. For instance, mesenchymal stem cells become more responsive to the migratory stimulus by SDF-1, if primed with TNF- α ²⁸. This further underlines the importance of this cytokine. On the other hand, the binding of SDF-1 and CXCR4 can be interrupted by proteolytic enzymes that are over abundantly available locally due to production by infiltrating inflammatory cells^{29,30}.

Following the binding of SDF-1, CXCR4 triggers downstream signaling, which involves the G (Guanine Nucleotide Binding) heterodimeric protein. The G α_1 subunit of this protein transmits most of the signaling from CXCR4. Thereby, further downstream signaling pathways are activated, namely through mitogen-activated protein kinases (MAPK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT). Another signaling cascade is activated through another subunit of G protein (G β_γ). This signaling cascade, via phospholipase A, changes intracellular levels of calcium ions. Together, these changes increase mobility of mesenchymal stem cells and enable

their migration to the injured site. An additional signaling is provided by the SDF-1 binding to an alternative receptor, CXCR7; this receptor, through proteins called β -arrestins, stimulate MAPK, thereby contributing to phenotypic changes of mesenchymal stem cells.

The changes in gene expression, which are mesenchymal stem cells that undergo when exposed to SDF-1, are poorly documented in the context of bone fracture healing processes. Most of the available literature data on SDF-1/CXCR4 signaling axis were obtained in the context of cancer or cancer stem cells^{31,32}, whereas noncancerous studies on this subject are very rare. Furthermore, there are no publications covering the test of SDF-1/CXCR4 using comprehensive molecular biology techniques (microarrays or next generation sequencing). Therefore, the global changes in gene expression, that are mesenchymal stem cells undergoing prior to migration to the site of the fracture, are not sufficiently understood so far.

Post-transcriptional regulation of gene expression occurs by mechanisms that do not affect transcription of mRNA, but rather modulate protein levels by interfering with transcribed mRNA (such as through chemical modifications of mRNA or by altering its stability). A mechanism involves the process of short noncoding RNAs, called microRNA (miRNA).

There are two relevant investigations^{33,34} on miRNA regulation of SDF-1-induced migration of mesenchymal stem cells. Specifically, miRNA-23a suppresses the production of SDF-1 by binding to the 3'-untranslated region of mRNA³³. This will create negative inhibition migration of mesenchymal stem cells. The other study carried out using the miRNA (miRNA-27b) has also shown suppressing effects on migration of these cells³⁴, through a similar post-transcriptional mechanism³⁴.

Conclusions

There is not much information available on the transcriptional and post-transcriptional changes that mesenchymal stem cells undergo to migrate to the site of the bone fracture. This identifies a substantial knowledge gap. Therefore, further studies with human cells and with experimental animals are required to be carried out to throw light on the processes governing recruitment of these cells during early stages of bone fracture healing.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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