REVIEW ARTICLE

A Developmental Biology of Endochondral Ossification Critical Size Defect Bone

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ABSTRACT

Bone is a highly dynamic tissue that constantly remodels throughout life. Bone damage caused by surgical procedures or trauma can be repaired using a variety of mechanisms that vary depending on the level of immobilization, the degree of trauma, and the ongoing biological processes. This is related to the process of endochondral and intramembranous ossification that will occur to regenerate fractured bone. During human development, most of the human skeleton is formed through endochondral ossification. The majority of craniofacial bone is formed through intramembranous ossification. It is known that endochondral ossification occurs during the development of the mandibular column, skull base, and temporal bone. Although endochondral ossification is limited to the previously mentioned regions of the craniofacial skeleton, it is the original pathway in the growth of the human face and skull. Furthermore, trauma to the craniofacial bone heals similarly to that of the long bone skeleton. Endochondral ossification may be found in the healing of craniofacial fractures depending on the type and location of the defect as well as the mechanical environment. Many aspects of the healing cascade, such as bone molecules, cells, and events, have been identified, but complex interactions and processes remain unknown. This review examines endochondral ossification avenues, the current state-of-the-art in critical size defect reconstruction, challenges in implementing current knowledge, and the future. give insight into the future of translational research from the bench to the bedside.

Keywords: trauma, buiological process, endochondral ossification, craniofacial, human health

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INTRODUCTION

Defects in the alveolar bone caused by tooth extraction, resulting in a horizontal defect larger than the vertical defect seen on radiographs. The defect occurs for 6-12 months in the healing period, if the condition is not treated, the alveolar bone will lose its volume by 40%-60% of the ridge volume gradually over a period of 3 years. These dimensional changes occur during the first three months and can last for up to five years, with an additional 11% occurring over the next five years. (1,2,3) A critical size defect (CSD) is a short defect that cannot be bridged spontaneously, resulting in non-union. Although there are numerous bone reconstruction techniques, each has its own set of indications and limitations. Methods that have been established include distraction osteogenesis or bone graft, which includes autologous bone graft, bone marrow aspiration, allografts, and bone substitution or growth factor. (4,5)

In the surface of damage, bone has its own repair mechanism. The phases of inflammation, repair, and remodeling all play important roles in post-traumatic bone repair. These repair phases can be efficient in general, but 10% of bone regeneration due to fracture or trauma has delayed or failed bone union(6,7). Bone healing, however, can occur through two repair patterns. First, intraosseous osteoblasts and osteoclasts mediate direct contact repair, also known as primary ossification. Primary ossification occurs at the fracture site, resulting in rigid stability and a 0.1 mm space between bones. This flaw can be discovered following minor trauma, open reduction, and internal fixation of fractures like mandibular ramus fractures (8,9). The second type of ossification is secondary ossification, which is usually mediated by the endoperiosteal layer and/or marrow tissue. Callus formation occurs during the healing of displaced fractures without surgical intervention and treatment with mandibulomaxillary fixation.(9,10).

Intramembranous ossification

Intramembranous ossification refers to the formation of bone tissue directly on top of mesenchymal tissue (rather than on cartilage as in endochondral ossification). This happens during fracture healing and the early stages of skull formation. This procedure is also responsible for jaw and collarbone shaping (11). Mesenchymal stem cells (MSCs) in bone fracture mesenchyme or medullary cavity initiate intramembranous bone repair. A few MSCs replicate and form a cell cluster (12). Once formed, the MSC within it ceases to replicate. MSCs undergo morphological changes as they mature into osteoprogenitor cells, with the cell body becoming larger and rounder and the long and thin cell processes disappearing. Golgi apparatus and endoplasmic reticulum expansion. To become osteoblasts, osteoprogenitor cells undergo a morphological process that causes their shape to become more columnar. The number of Golgi apparatus and endoplasmic reticulum is increasing. Type-I collagen is found in the extracellular matrix produced by osteoblasts (osteoids). The osteoid's osteoblasts fuse to form an osteocyte. Mineralization occurs, producing bone tissue and spicules. Osteoid secretion causes spicules to grow in size and join together to form trabeculae. The trabeculae become interconnected as the spicules continue to grow, resulting in the formation of woven bone (11). The initial trabecular tissue is also referred to as primary spongiosa. The periosteum then forms around the trabeculae. Periosteal osteogenic cells promote appositional growth and bone formation. Finally, lamellar bone replaces woven bone (13,14,15).

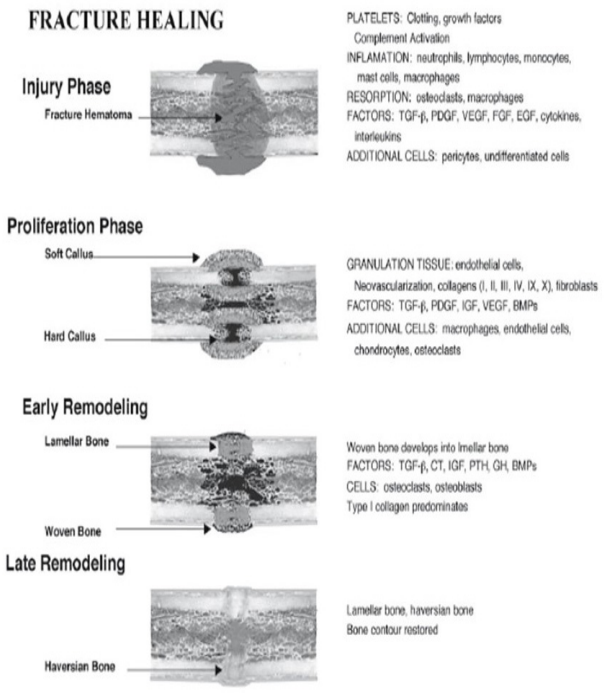

Fig.1 : Secondary ossification process (20)

According to Runyan and Gabrick, a study using a rabbit mandibular fracture model revealed that in the absence of rigid mandibular fixation, fracture healing had several histologic similarities to long bone fractures (16). Over the next two weeks, this callus is gradually replaced with trabecular bone and completely bridged with the new neovascular tract and the Haversian system (17,18,19). Paccione and coworkers, In a rat mandibular fracture model, the presence of islands of rudimentary cartilage matrix formation, vascular growth, osteoblast activation, mineralization, and lamellar bone formation resembled secondary ossification or endochondral ossification.

The healing process is divided into secondary ossification stages. Secondary ossification involves the formation of bone via both direct and indirect endochondral and intramembranous pathways, as well as the progression of inflammation, callus formation, and remodeling. The goal of this intricate process is to gradually increase the mechanical stability of the fracture site by gradually replacing fragile tissue with more stable tissue, eventually reaching a point where further vascular enlargement and mineralization are possible. (21,22). The endochondral pathway is a logical approach to craniomaxillofacial regeneration. This mimics both natural repair mechanisms and bone development processes (9).

Inflammation

Fracture healing starts with an early anabolic phase in which inflammation increases the volume of local tissue. A hematoma forms at the fracture site, acting as a temporary scaffold for the differentiation of host cells into fibrous tissue, cartilage, and bone. Hematoma formation is the first stage of remodeling, followed by acute inflammation (23). Bone fractures disrupt local vascularity within bone tissue, as well as on the endosteal and periosteal surfaces, bone marrow, and surrounding soft tissue. Hematoma formation occurs as a result of the activation of the coagulation cascade of plasma and platelets exposed to the extravascular environment. Neutrophils are the first inflammatory cells to arrive at the fracture site within the first 24 hours. Neutrophils are involved in the second wave of inflammatory cell infiltration to the fracture site, namely monocytes/macrophages that reside in the periosteum and endosteum and then participate in the regulation of fracture healing by secreting inflammatory and chemotactic mediators (21). The second wave of inflammatory cells to infiltrate the fracture site is monocytes/macrophages, which live in the periosteum and endosteum and then control fracture healing. Neutrophils are also involved in this process (24). Among the inflammatory and chemotactic mediators secreted by macrophages are tumor necrosis factor alpha (TNF-), CCL2, transforming growth factor beta (TFG-), bone morphogenetic proteins (BMP), IL-1, IL-6, IL-17F, and IL-23 (25). These mediators activate fibroblasts, mesenchymal stem cells (MSCs), and osteoprogenitor cells from the surrounding niche (21,

25).

Osteoprogenitor cells are stimulated to proliferate, differentiate, and produce extracellular matrix by platelets and macrophages. Events crucial to chondro-osteogenesis, such as chemotaxis, proliferation, and differentiation of mesenchymal and osteoprogenitor cells, as well as extracellular matrix ossification, are regulated by the TGF-superfamily, which also includes BMPs, PDGF, FGF, and IGF. Because of this, initially fractured days to weeks after the fracture, the hematoma and initial inflammatory reaction that followed vanish, to be replaced by granulation tissue rich in mesenchymal cells and entrenched in an unorganized extracellular collagen matrix. Mechanical stressors such as strain or hydrostatic stress also have a significant impact on the healing of bone fractures in addition to these cytokinetic variables (26).

Formation of soft callus

Local vascular disruption and reactive contraction of arterioles, hypoxic fracture sites, particularly close to the fracture gap. Particularly in the more concentrated regions of the fracture fissure, low levels of oxygen, direct differentiation via the chondrogenic route in conjunction with the amount of micromotion, a variety of other microenvironmental cues, and macrophage cues. After a few weeks, chondrocytes produce cartilage that bridges the space between the damaged bone's ends. This cartilage tissue, often referred to as the soft callus, works with the surrounding fibrotic tissue to initially stabilize the fracture mechanically and act as a scaffold for the development of endochondral bone. Associated cells and osteoprogenitor cells in the periosteum develop into osteoblasts, which systematically arrange bone, while new bone development occurs via the intramembranous route concurrently with the development of the soft callus in an area with increased mechanical stability and blood flow. Last but not least, the outside of the soft callus is covered with braided bone, providing mechanical support and indicating the start of mineralization (21). With a progressive healing, endothelium and skeletal cells work together to fill the space between the broken pieces of bone, forming a soft callus in the process. Soft callus then develops into hard callus (25).

Formation of hard callus

In soft callus hypertrophy, chondrocytes undergo apoptosis, create calcium-based mediators, and induce vascular expansion, ultimately releasing the extracellular matrix of partially calcified cartilage. This process resembles a growth function. The development of construction of braided bone on the cartilage scaffold and the transformation of osteoprogenitor cells into osteoblasts are accompanied by vascular expansion into the fracture gap and a corresponding increase in blood flow to the fracture site. The creation of firm calluses is the term used to describe this stage of fracture healing. In the end, the osteoclasts destroy the immature woven bone and the matrix, starting a remodeling process that eventually rebuilds the characteristics of the Haversian system and the osteon structure depending on the mechanical forces acting on the bone (21).

Remodeling phase

Following these procedures, over the course of several months, coordinated osteoblast and osteoclast activity starts the bone remodeling phase. Lamellar bone is created while callus tissue is reabsorbed. Woven bone is replaced by lamellar bone during the osteonal remodeling phase of bone remodeling. After the fracture has fused with the woven bone, remodeling takes place. Then, by osteonal remodeling and surface erosion, lamellar bone gradually replaces the woven bone. This procedure continues until the bone fully regains its previous architecture, including the restoration of the medullary canal, which can take anywhere between several months and many years (25).

A well-vascularized granulation tissue is produced throughout the angiogenesis-driven renewal of the barrier membrane and the osteogenic cells migration from the border to the center. The blood clot first organizes, then grows vascularly and deposits braided bone, then forms lamellar bone, and lastly remodels to resemble bone development. Regeneration of mineralized bone is also slowed when the expansion of bone marrow into bone breakdown is impeded or delayed. Large defects, however, only have a central zone of loose, disorganized connective tissue where bone formation occurs, necessitating the use of extra bone graft material that serves as both a source of bone grafting and a scaffold for osteoconduction. Chemicals that are osteogenic and osteoinductive for the development of flat bones (4,27) The VEGF pathway related with the creation of endochondral bone, in which BMP induces the synthesis of VEGF by osteoblasts and osteoblast-like cells, has also been discovered. Both of these pathways are involved in the early phases of the healing process. Growth factors must also be controlled by inhibitor molecules, and a variety of BMP antagonists are released into the extracellular compartment (noggin, sclerostatin, follistatin). Receptor inhibitors of a number of TGF-superfamily members that have been linked to pseudo-receptors known as BAMBI are additional inhibitory mechanisms (BMP and membrane-bound activin inhibitors, and intracellular inhibitors with activation of I-Smads, among other mechanisms) (28).

DISCUSSION

Along with the intramembranous pathway, endochondral bone formation is a naturally occurring process for the development and repair of bone fractures in the craniofacial region. For bone regeneration techniques in maxillofacial applications, the endochondral ossification pathway is a potential choice. It is well known that

tiny motions between implanted material and bone stop new bone from growing and instead cause fibrous tissue to form. For the initial tissue entering the pore to generate direct or appositional bone by differentiating into bone. If the region is sufficiently vascularized and the local inflammatory reaction is mild, bone formation can nevertheless take place in porous materials with little initial movement. Additionally, by stimulating vascular remodeling and boosting the number of big vessels while reducing the number of tiny ones, delayed mechanical stress greatly boosts bone production. Vascular remodeling is a necessary step in the formation of new vascular tissue, this is necessary for the creation of bones (4).

Although most bone in the facial skeleton is formed by intramembranous ossification, mandibular cells have been shown in unstable fractures to be capable of forming bone via endochondral ossification (29). Thus, using endochondral ossification for craniofacial bone tissue engineering would mimic bone healing in the facial skeleton (9).

Bone remodeling is an effort to maintain bone strength, maintain bone mineral homeostasis, and repair bones damaged by an injury. Bone has excellent regeneration capability in addition to this remodeling process. When bone is injured by pro-inflammatory triggers (infection, trauma, etc.), for the purpose of bone regeneration and local healing, the innate immune system controls the same basic processes as other tissues and organ systems (21,30). The biomaterial system is more than just a scaffold, but it may also be a site of drug metabolism, releasing cytokines, growth factors, or other biological stimuli that can direct and accelerate bone regeneration (31).

CONCLUSION

The complex organ of the bone serves a variety of purposes, such as hematopoiesis, mineral control, and storage, vital organ protection, locomotion facilitation, and others. Endochondral ossification strategies can be viewed as a promising approach for reconstruction of critical sized defects. Although clinical success has been limited, these methods have produced big vascularized bone grafts and the restoration of critical-sized bone lesions with extremely promising outcomes. Nonetheless, research in this field is continuing, and additional study will be required in the future to enhance graft vascularization, scale up structures, and bone formation.

CONFLICT OF INTERESTS

The writers have declared that there is no conflict of interest regarding the publication of this paper.

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