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Review Article

Hylonome

The potential role of muscle in bone repair

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Abstract

Bone repair is a complex phenomenon involving many cell types and signaling factors. Substantial evidence exists to suggest that stem cells originating from local osseous tissues, particularly the periosteum, can contribute to bone repair. However, there are situations where injury or post-surgical management can deplete the amount of, and/or access to these crucial progenitors. The fact that bone repair can still occur in these circumstances implicitly reflects the existence of compensatory secondary systems. One potential alternate source of osteoprogenitors is muscle, which is closely associated with bone and typically suffers trauma during an orthopedic insult. While muscle access is known to be beneficial to bone repair, this is conventionally credited to its high vascularity, and thus its contribution to the local blood supply. However, there is emerging evidence to suggest that progenitors from muscle may directly contribute to bone healing. Defining the role of muscle in bone formation and repair has significant clinical implications, particularly where promoting access to this tissue may enhance the repair outcome.

Keywords: Osteoblast, Myoblast, Bone Repair, Osteoprogenitors, Fracture

Introduction

The dry appearance of bone together with its principal role as a structure has historically led physicians to view this tissue as acellular and inert. Indeed, the word "skeleton" is derived from the Greek word meaning "dried up". Quite contrary to its deceiving appearance and its word origin, bone is a biologically dynamic tissue with cells lining both its internal and external surfaces. It is these cells, their secreted growth factors, and their interactions with cells of the surrounding microenvironment that give bone its unique ability to repair itself following a fracture without the formation of a scar.

Bone repair is conventionally viewed as a well-orchestrated progression of biological events involving a series of distinct cellular responses controlled by specific autocrine and paracrine signals[1-3]. However, the reality is that differences in physiological, cellular, and genetic variables, the site and severity of the injury, as well as the approach to orthopaedic management all combine to make each fracture unique. While medical technology and orthopedic management have improved greatly over the past several decades, the precise reason why some patients' fractures do not heal remains unknown.

Much of the focus of modern orthopedic trauma care is on ensuring stability, re-establishing the blood supply, and providing a stimulus so that progenitor cells that reach the injury site are able to form mature osteoblasts. These are aspects that can be largely controlled and are vital for successful bone healing. When augmented, they can lead to improved rates of bone repair. Nevertheless, one factor that is often left out of the equation is the importance of osteoprogenitor cells which, when deficient, may have a detrimental effect on the bone repair outcome.

Fracture stability and repair

One of the primary goals of orthopedic management of fractures is to ensure that a bone injury is not grossly unstable. For long bones, stabilization can be internal (using a plate and intramedullary nail) or external (such as with an external fixator, e.g. an Ilizarov frame). The type of fixation can influence the healing process in accordance with Wolff's law (form follows function)[4-6]. While biomechanics can have a powerful affect on the

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biology of bone healing, biological elements are responsible for sensing and generating responses to mechanical forces. Moreover, by targeting the biological response, the influences of biomechanics can be surmounted. For instance, the bone loss associated with unloading (disuse osteopenia) can be at least partly overcome with pharmaceutical intervention, such as with a bisphosphonate[7-9]. Emerging work has shown that the protein Sclerostin secreted by osteocytes (the primary mechanosensory cell in bone) is a critical negative regulator of bone formation[10]. Sclerostin is responsive to mechanical forces, but again it is possible that anti-Sclerostin therapies will be able to separate biomechanics from the biological response in the context of fracture healing. The interactions between mechanical forces and the downstream biological processes (and particularly how they affect osteocytes and osteoclasts) remain an area of active investigation.

Re-vascularization is essential but not sufficient for fracture repair

Blood supply is commonly viewed in orthopedic literature as one of the key elements that ensure the timely and accurate restoration of the osseous tissue to its pre-injured state. Fracture healing recapitulates the morphogenetic cascades of embryonic development which are strongly believed to be dependent on local angiogenesis[11]. The re-establishment of bone's blood supply and stimulation of the adjacent circulation are seen as early essential components for successful fracture repair. Strong clinical correlation exists between impaired vascular function and development with a failure in fracture repair[12,13]. In addition, animal models where angiogenesis is disrupted via physical interference[14,15], disease such as anemia[16,17], ischemia[18,19], radiation treatment[20,21], or smoking[22] have been shown to delay the fracture repair process.

Although many studies support the concept that vascularization is *essential* for bone repair, other studies also exist in the literature that demonstrate re-vascularization to be *insufficient* for bone repair. Evidence from animal studies in mice[23], rabbits[24] as well as clinical studies in fracture patients[25], indicate comparable vascularization between healed bone, delayed unions and non-unions. In addition, while pro-angiogenic factors can augment bone repair, they are incapable of inducing bone *de novo*[26], and do not always result in union. This brings forward the argument that inadequate vascularization alone is no longer a satisfactory explanation for a failure in fracture repair, and that other factors, such as the role of local progenitor cells, may have more impetus.

Pro-osteogenic treatments rely on endogenous osteoprogenitors

A common approach for treating highly problematic orthopedic injuries, such as high-energy open fractures and critical sized bone defects as well as persistent non-unions, is to intervene with an anabolic therapy[7]. Such therapies include bone grafting (autograft and allograft) and recombinant Bone Morphogenetic Proteins (BMPs). The underlying goal of these therapies is to provide

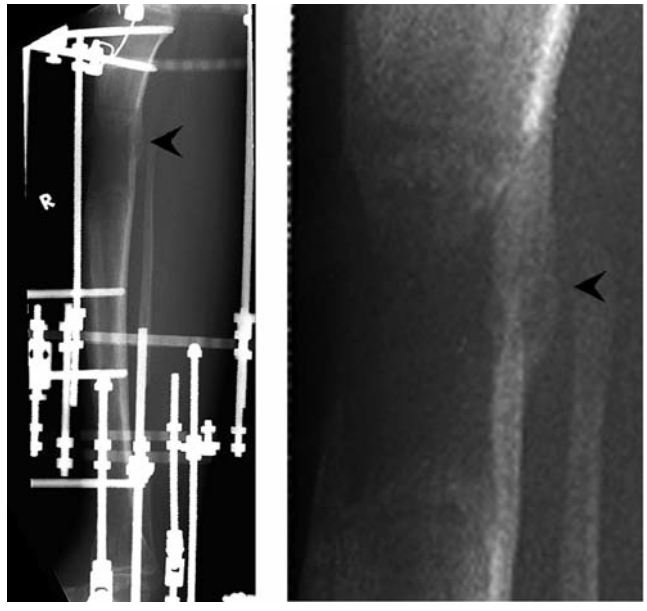

Figure 1. The bone that first forms in response to a fracture is often adjacent to the muscle. A child with a broken tibia in an Ilizarov frame. The bony callus is first seen next to the surrounding muscle (arrow in left panel, and enlarged).

factors that facilitate osteoprogenitors to develop into mature, functional bone forming osteoblasts. While these therapies are effective in the treatment of severe bone injuries[27,28], there exists the underlying assumption that there is a readily available pool of osteoprogenitors for these agents to act upon.

Severe traumatic injury and subsequent orthopedic management can lead to depletion or reduced access to progenitors within the periosteum or the marrow. In high energy fractures, the periosteum can be stripped[29,30], and marrow access can be limited by intramedullary fixation or repeated debridement (washing). While periosteal cells are recognized as highly osteogenic, the role and relative importance of marrow cells in bone healing is still being debated[31-33]. Nevertheless, the fact remains that fractures can go on to unite in situations where periosteal and bone marrow contributors are absent and/or reduced, albeit slowly, suggests that other sources of inducible osteoprogenitors do exist.

Support for the presence of osteoprogenitors within muscle

It has long been hypothesized that muscle contains cells capable of contributing to bone formation. Muscle is one of the most common sites for ectopic bone to form, whether it is the result of physical trauma (*myositis ossificans*) or in the context of genetic disease (*fibrodysplasia ossificans progressiva*)[34]. Moreover, in the context of recalcitrant fracture healing or distraction osteogenesis, any bone that forms is typically seen adjacent to muscle (Figure 1). In addition to these clinical observations, there

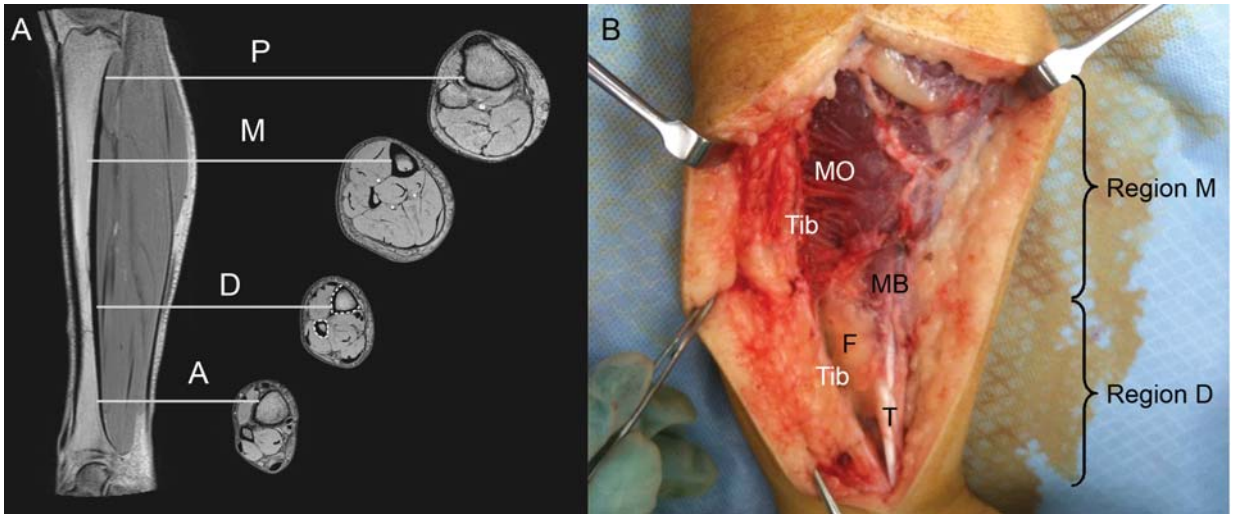

Figure 2. The fracture outcome may be dependent on the fracture location. **A.** A magnetic resonance image (MRI) of a tibia from a healthy adult. The proximal tibia (P) can be seen to contain cortical bone (dark regions) with trabecular bone embedded in the lighter elements of the marrow. There is also minimal posterior muscle coverage. We believe cells from the endosteum provide the major contribution to repair at this location. In the tibial mid-shaft (M), the marrow consists mainly of fatty tissue. However, there is excellent muscle coverage with various muscle groups attached to the bone surface at their origins. Direct attachment of muscle at this level means the bone and muscle are not likely to be separately compartmentalized when a fracture occurs. The muscle may act as a "*secondary periosteum*" in this area. In contrast, in the distal third of the tibia (D), the marrow remains fatty, and in addition, there is no direct bone-muscle tissue attachment. The muscles present are running over the bone in completely separate compartments (denoted by the white lines). In the bone near the ankle (A), there are again trabecular bone and marrow elements, as in the proximal tibia (P). **B.** Surgical photo illustrating the tissue attachment to the tibial mid-shaft (M) and the distal tibia (D). In region M, the muscle origin (MO) is directly from tibial bone (Tib), separated by a thin periosteum and attached by Sharpey's fibers. In most cases, displaced fractures at this location will also cause injury to the muscle, resulting in fracture and muscle hematomas that are in continuity. Fractures at this region usually have a superior prognosis. In contrast, muscles in Region D do not attach directly to the tibia, but are separated by fat (F) and a fascial layer to facilitate exclusion of the muscle belly (MB) as it condenses and becomes tendonous (T). The muscle and bone tissues are separately compartmentalized in this area and remain so after a fracture. We believe this anatomical arrangement results in the paucity of cells that can contribute to repair, leading to the poor prognosis for fractures at this location.

is a growing quantity of research data that suggests myogenic (muscle) progenitors can be "reprogrammed" to form bone.

Many of the original studies examining the osteogenic potential of BMPs have reported its effects in the context of muscle[35]. In culture, clonal myoblastic cell lines and primary muscle cells readily down-regulate muscle genes and up-regulate bone markers in response to BMPs[36-39]. Furthermore, several groups have reported that myogenic cells have a superior osteogenic response to BMPs compared to other cell types[40-42]. Numerous studies have gone on to isolate progenitor cells from muscle for the purposes of bone tissue engineering. These approaches often utilize *ex vivo* gene therapy approaches where the forced expression of osteogenic BMPs in cultured myoblasts can lead to new bone formation after their subsequent implantation into experimental animals[43,44]. Even without pro-osteogenic gene expression, labeled implanted myoblasts have been shown to incorporate into a bone defect model[45]. Nonetheless, no study has yet shown directly nor conclusively a contribution by endogenous myogenic cells to bone repair. Our group has recently presented for the first time that muscle cells can contribute to bone formation and highly participate in fracture repair (manuscript in preparation)[46].

The relevance of these putative osteoprogenitors in muscle is pertinent only if they can have a functional role in bone formation. Indirect evidence from a surgical study in mice suggests that access to muscle may provide benefits to fracture healing beyond a vascular supply. Harry et al. used an open tibial fracture system to model muscle versus fasciocutaneous flaps by physically excluding either the muscle compartment or the opposing subcutaneous border of the tibia using a polymer sheath[47]. It is common clinical practice to place vascular tissue flaps over high grade open fractures to provide tissue coverage for the injured bone, which in turn facilitates repair. In this murine model, muscle exclusion was found to significantly impair healing, both in terms of rate of repair and strength of the healed bone. Notably, the non-united fractures with muscle exclusion were found to be fibrous but vascularized, and the amount of re-vascularization was higher than that of the controls and the muscle-flap group[48]. While it is possible that growth factors and cytokines present in the microenvironment can affect the formation of the bridging callus, the polymer membrane used for muscle exclusion was permeable to these factors. Thus a more likely explanation is that muscle exclusion led to a deficiency in muscle-derived osteoprogenitors that can functionally contribute to bone repair.

Muscle as a "secondary periosteum" for bone repair

The periosteum is undeniably a potent source of osteoprogenitors with an important role in orthopaedic repair. However, the aforementioned evidence would support the concept of adjacent muscle acting as a "*secondary periosteum*" which is able to contribute osteoprogenitors when the periosteum itself is damaged. The relative importance of muscle as a periosteal substitute would depend on the location of the fracture and its proximity to muscle as well as the severity of the damage to the local muscle and periosteum[49].

For instance, we propose that due to the large trabecular bone area in metaphyseal bone, vertebrae and calcaneus, in addition to an ample vascular supply and the significant cellular marrow elements, marrow progenitors are likely to be the primary cellular contributors to injury to these regions. On the other hand, cortical diaphyseal bone lacks both trabecular bone and significant red marrow compartments. Nevertheless, fractures that occur in this locality rarely undergo delayed or non-unions. We believe this lack of viable cells within the marrow is compensated by the donor osteoprogenitor cells arising from the surrounding musculature. In most long bones, the muscle origin is directly from the bone, separated by the periosteum and the fibrous attachment of muscle to bone. In this location the initial impact of a fracture injures both bone and the surrounding muscle and as a result, the fracture and muscle hematoma are contiguous. This complementary relationship between the two tissues provides both the vascular supply and the cellular populations needed for successful repair (Figure 2A).

In contrast, fractures of the distal tibia have a poorer prognosis, possibly due to anatomical disadvantage. The distal tibia lacks major red marrow elements and trabecular bone is limited to the metaphysis. The surrounding tissue consists mostly of tendons, moving freely over the bone in a separate compartment, with a paucity of muscular elements present. There are extensive condensations of fascial coverings over the bone which separates it from the small amount of surrounding muscle. Therefore, an injury to the bone at this level does not necessarily result in a contiguous muscle injury, and usually results in the formation of two distinct hematomas which undergo repair without necessarily sharing the same signaling elements. This lack of available donor cells from both the marrow and the surrounding muscle is posited by us to be responsible for the sparse anabolic response in this area (Figure 2B).

Concluding remarks

The muscle and the bone compartments are often regarded as separate elements. While these concepts are useful in the management of compartment syndromes and in the Enneking system of tumor classification, we believe these concepts require re-evaluation for orthopedic management. Muscle is closely related to bone and contains highly osteo-inducible cellular populations that have been implicated to have roles in bone formation and repair. In addition, myoblasts can be easily manipulated for genetic modification, which is highly appealing and relevant for gene therapy and tissue engineering. The role of endogenous myogenic progenitors in bone repair and maintenance is another rich area for future research. Understanding the role of muscle and its associated cells in bone formation and repair will guide surgical approaches and initiate new therapeutic approaches for the treatment of severe orthopedic injuries utilizing muscle.

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