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Is there a potential need for proangiogenic therapy in posttraumatic musculoskeletal trauma regeneration to improve bony healing?

Soenke Percy Frey
University of Würzburg, Germany

High-energy injuries like open fractures of the lower extremity are devastating injuries associated with soft-tissue damage, bone defects and impaired local perfusion. Initial treatment of this fracture type includes radical soft-tissue and bone debridement, acute shortening to close bone defects and stabilisation with an external fixator. But the trauma itself and the following debridement lead to impaired biological properties which are essential for regeneration. Complications like non unions, infections, osteomyelitis or secondary amputations can arise. From an socioeconomic point of view patients often drop out their former social environment and return late to work.

Fracture healing and muscle regneration are deteriorated. This is aggravated by the fact that the complex process of inflammation, angiogenesis, chondrogenesis, enchondral ossification and bone remodelling is disturbed by the injury. Elevated compartment pressure impairs bone and soft-tissue perfusion, which improves when the limb is shortened about 10%. One treatment option for restoring the original length is a distraction procedure, normally using a second osteotomy near the metaphyseal region. Alternatively, distraction osteogenesis at the fracture site can gain bone regeneration in a shorter period of time without the necessity for further operations.

Microvascularisation and microcirculation are crucial for fracture repair and bone regeneration. Soft-tissue trauma and elevated compartment pressure are two of the main reasons for regional hypoxia. Also, initial fracture haematoma, eliminated by surgery, consists of a variety of phyisiological growth factors important for angio- and vasculogenesis and fracture repair, which are then missing at the fracture site. Previously, we demonstrated that acute soft-tissue trauma significantly compromises callus formation in a rabbit tibia after primary acute limb shortening and secondary distraction. In animals with soft-tissue trauma and elevated compartment pressure, normalised mechanical values of the newly reconstructed tibia and average normalised callus diameters were smaller than in animals without soft-tissue trauma.

There is a close relationship between maintaining blood supply and muscle regeneration, indicating revascularization plays an important role in the success of muscle regeneration. In models of revascularization, endothelial cells and capillary pericytes undergo degeneration and subsequently new capillaries begin to develop along the existing capillary basement membrane. The new capillaries sprout out from peripheral surviving capillaries toward the center of the injured area. Taken together, these observations suggest the newly developed capillaries would help to provide the injured area with oxygen and substrates and therefore aid in the regenerative process. Angiogenesis is highly regulated by factors such as vascular endothelial growth factor (VEGF) and cysteine-rich protein 61 (CYR61, CCN1). As a mitogenic factor, VEGF acts on endothelial cells and plays a crucial role in vasculo- and angiogenesis. Several studies suggest increased VEGF-A expression after acute exercise or electrical stimulation. CYR61 which is an extracellular-matrix-associated angiogenic regulator supporting cell adhesion, stimulating endothelial cell migration and enhancing growth-factor-induced cell proliferation in culture. Direct proliferative action of CYR61 was described on mesenchymal stem cells, osteobasts and endothelial cells, with evidence of angiogenic activity, including in rabbit ischemic hindlimbs like VEGF. As a proangiogenic regulator, it is transcriptionally induced under hypoxia, a condition that favours blood-vessel growth by inducing several angiogenic factors, including vascular endothelial growth factor (VEGF), through the action of hypoxia inducible factor-1a (HIF-1a). Furthermore, CCN proteins can also modulate activities of several growth factors and cytokines, including transforming growth factor beta (TGF-a), tumour necrosis factor alpha (TNF-a), VEGF, bone morphologic proteins (BMPs) and Wnt proteins, and it may thereby regulate a broad array of biological processes. (Frey et al. CORR 2012, Frey et al. Int Orthop 2012)

The purpose of this study was to investigate the influence of locally applied proagniogenic growht factors (2 test groups: VEGF & CRY61) on bony regeneration after musculoskeletal trauma. We investigated the effect of these growth factors on regeneration of traumatized bone after acute soft-tissue trauma and following a limb-shortening distraction procedure in a