Driving Vasularization: The Key to Bone Repair

(Organized by the ORS Women’s Leadership Forum)

Organizer:
Sophie Verrier, PhD

Speakers:
Theodore Miclau, MD
Sabine Fuchs, PhD
Louis Gerstenfeld, PhD
Driving Vascularization: The Key to Bone Repair

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Bone repair is a complex mechanism that involves many well-orchestrated events. It is widely accepted that blood vessels and blood flow brings oxygen and nutrients, but cells and specific molecular factors are also crucial in this processes. Impaired vascularization often occurs following trauma as well as or in specific health conditions (e.g. diabetes), can compromise the course of bone repair leading to delayed healing, mal union or non-union which results in an increase in patient burden and related healthcare costs. Ensuring an adequate blood supply for bone healing still constitutes a clinical challenge and is therefore a clinical therapeutic target.

This workshop will first give insight into the clinical problems associated with poor or no vascularization, and the current clinical methods used to improve vascularization. In addition, this workshop will explore the latest knowledge about the key cellular players and the role of VEGF in driving vascularization during bone repair. Finally, we will discuss the cutting edge strategies to drive neo-vascularization

In addition, this workshop will facilitate an exchange of knowledge and stimulate discussion between renowned keynote speakers, scientists and clinicians at all career levels with an interest in bone healing.

Speakers:

Prof. Theodore Miclau, MD, Dpt. of Orthopaedic Surgery, University of California, San Francisco, US
"Vascularization and Bone Healing: Limits and Solutions From a Clinician Perspective"

Prof. Sabine Fuchs, PhD, Experimental Trauma Surgery, University Medical Center Schleswig Holstein, Kiel, Germany
"The role of angiogenesis in bone repair and its implication on tissue engineering approaches"

Prof. Louis C Gerstenfeld, PhD, Boston University School of Medicine, Orthopedic Surgery, Boston, US
"Role of Vascular Endothelial Growth Factor Receptor (VEGFR) Signaling In Both Intramembranous and Endochondral Bone Formation"
Vascularization and Bone Healing: Limits and Solutions from a Clinician Perspective

Theodore Miclau, MD
Department of Orthopaedic Surgery, University of California, San Francisco
UCSF/ZSFG Orthopaedic Trauma Institute, San Francisco, USA

Fractures affect 15 of every 1,000 people worldwide, occurring at rate of approximately 15 million fractures per year in the US and representing an enormous societal burden secondary to direct and indirect recovery costs. Impaired healing, estimated at 10-15% of all fractures, further exacerbates the economic burden of fracture-related conditions, particularly when the fracture progresses to a nonunion. Clinical evidence suggests that compromised vascularity is a leading cause of impaired healing, which is consistent with experimental work showing that new blood vessel formation is critical in the repair process. Nearly half of patients who have a fracture and accompanying vascular injuries experience impaired bone healing. Patients with vascular-related comorbidities, such as diabetes, smoking, and aging, also have notably lower rates of healing.

While clinical work clearly shows the importance of the blood supply during healing, the specific roles that the vasculature plays are unknown. The blood supply serves several critical functions during fracture repair, including the delivery of nutrients to the damaged tissue, transportation of cells, and provision of oxygen and nutrients that are necessary to the site of injury for cell survival, and enabling the migration inflammatory and other systemically-recruited cell types. The vasculature may also provide important signals that help regulate the overall fracture repair process. While surgeons have created minimally-invasive procedures to preserve the blood supply, which have improved rates of healing and decreased rates of complications, more targeted therapies to enhance new blood vessel formation would likely further enhance the therapeutic options to stimulate bone repair. This presentation will review the clinical problem, demonstrate the effectiveness of existing surgical approaches to maintain the blood supply, and frame the discussion of future approaches.

References:


The role of angiogenesis in bone repair and its implication on tissue engineering approaches

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The vascularization process is of central importance for bone repair and involves much more aspects then the supply of oxygen and nutrients. On the cellular and molecular level guiding the processes vascularization are to a large extend controlled by the interaction of endothelial cells and bone forming cells, as well as circulating cells via paracrine factors, extracellular matrix components and direct cell communication mechanisms. Interactions of endothelial cells and osteogenic cells have a direct impact on the formation of new blood vessels but also on the differentiation and maturation of bone forming cells. On the other hand circulating inflammatory cells and circulating pre-osteoclasts of myeloid origin enter the site of bone repair via the bloodstream and the differentiation is guided by the interaction of these cells with endothelial cells or bone forming cells, respectively. Accordingly, a better understanding of these cellular and molecular processes might also result in new therapeutical approaches to improve vascularization and bone healing in general. On the other hand, the inhibition of angiogenesis provides a mean to counteract tumor growth in osteosarcoma for instance.

In this presentation we will highlight the pathways of cellular interaction and show how co-cultures of adult stem cells might be used to study the different mechanisms and pathways of cell interaction which mediate vascularization, bone repair or bone remodeling. In addition, we will discuss tissue engineering approaches using biomaterials to create vascularized tissue equivalents.

The co-cultures we address consist of outgrowth endothelial cells (OEC) appearing as mature endothelial cells in cultures of mononuclear cells from the peripheral blood. These cells form functional blood vessels in co-culture or after co-implantation with osteogenic cells (1-3). Besides OEC, mixed cell populations from the peripheral blood also contain cells named early EPC in accordance with their partly endothelial-like characteristics and their contribution to the neovascularization in vivo (4,5). These populations contain cells with a series of myeloid and M2 macrophage characteristics and are able to enhance the formation of vascular structures (6). These observations are in accordance with the current understanding of M2 macrophages known to be actively involved in endothelial repair. Nevertheless, myeloid precursor cells in principle have the potential to transdifferentiate into osteoclasts but the gene expression and their differentiation is modulated by endothelial as well as bone forming cells (7) thus emphasizing the role these cellular interactions to control cellular differentiation during bone repair.

References


**Visual abstract:**

**The role of angiogenesis in bone repair and its implication on tissue engineering approaches**

Sabine Fuchs, Experimental Trauma Surgery, University Medical Center Schleswig Holstein, Kiel, Germany

The vascularization process is of central importance for bone repair and involves much more aspects then the supply of oxygen and nutrients. Interactions of endothelial cells and osteogenic cells have a direct impact on the formation of new blood vessels but also on the differentiation and maturation of bone forming cells. The use of autologous cell sources, functional materials and the in depth understanding of the cellular cross talk is the basis for the tissue engineering approach to enhance the bone vascularization process.

- **Therapeutical Application**- Vascularization, (Bone, Cartilage and Woundhealing) with autologous cells and scaffolding materials
- **Individualized screening models** based on individual cell types or microtissues
**Role of Vascular Endothelial Growth Factor Receptor (VEGFR) Signaling In Both Intramembranous and Endochondral Bone Formation**

Beth Bragdon, PhD and Louis C Gerstenfeld, PhD

Angiogenesis and VEGFR signaling are critical components of postnatal skeletal tissue formation and healing after injury or surgery. The processes of vascular tissue morphogenesis during distraction osteogenesis (DO) will be presented to highlight the separate processes of arteriogenesis and angiogenesis that take place during DO (1). A review of prior studies will show how inhibition of angiogenesis through blockade of VEGFR1 and 2 signaling during DO both inhibits vascular tissue formation and intramembranous bone formation (2). During the progression of fracture repair which is primarily through endochondral bone formation, angiogenesis occurs early. There is increasing vessel density peaking around day 7 post fracture with angiogenic factors being expressed during cartilage formation and the resorption phase of repair (3,4). While prior studies have shown that angiogenesis and VEGF signaling play a functional role in promoting cartilage resorption by osteoclasts and vessel formation accompanied by bone replacement of the cartilage, no studies to date have examined if VEGFR signaling effects chondrocyte differentiation and development during endochondral bone formation. In order to more definitively characterize the relationship between angiogenesis and chondrocyte development and differentiation, a model of ectopic bone formation was used. Human demineralized bone matrix (DBM) was implanted in immune-deficient mice (rag null (B6,129S7-Rag1<sup>tm1/MOM</sup>/J)) to induce ectopic bone. Inhibition of angiogenesis with either a small molecule (TNP-470) or a targeted biological (Vascular Endothelial Growth Factor Receptor type 2 [VEGFR2] blocking antibody) was shown to prevent ectopic bone formation by 83% and 77%, respectively. Most striking was that the progression of chondrogenesis was halted during very early phases of chondrocyte differentiation between condensation and prehypertrophy (TNP-470) or the proliferative phase (VEGFR2 blockade) prior to hypertrophy, while osteoclast recruitment and resorption were almost completely inhibited. These latter results demonstrate VEGFR signaling and angiogenesis plays a developmental role in much earlier phases of chondrogenesis and endochondral bone formation than suggested by prior findings. In summary the results that are presented here suggest that VEGFR signaling carries out essential roles in vascular, osteogenic and chondrogenic cell differentiation and development.

**References**


