

ORS 2020 Annual Meeting

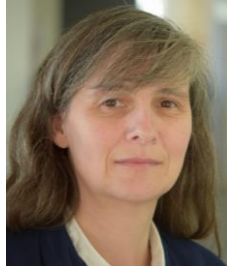
February 8-11, 2020 (Saturday -Tuesday) – Phoenix, Arizona

From Osteoimmunology to Immunotherapy: A progress report

ORS workshop,

Sunday, February 9, 1:30 pm – 3:00 pm

This workshop is focused on the interaction of immune cells and skeletal cells in bone healing, an area of research of great importance to regenerative medicine. Delayed or non-healing in bone is a major clinical problem, with ~ 15% of fracture patients suffering from unsatisfying healing outcomes. Bone healing is a finely tuned sequel of consecutive processes, which can result in fully regenerated and functional bone. Notably, bone healing involves the bone marrow, which harbors key cells of the immune system; in this respect, bone and the immune system are intimately inter-related. The initial inflammatory reaction in bone healing involves the activation and polarization of macrophages which secrete cytokines triggering the migration, proliferation and differentiation of regenerative stem and progenitor cells. There is a growing realization that the inflammatory cells, the types of cytokines they secrete, and the timing of inflammatory cascades are essential in initiating healing processes such as revascularization and matrix formation. Therefore, the specifics of the inflammatory response to fracture are of great interest in bone research. Recently, the essential role of immune cells and their cytokines has been proven in later stages of the bone healing process as well. T cells are important for collagen deposition and thus for the resulting bone quality. The aim of this workshop is to discuss the impact of immune cells on bone healing with a specific focus on the beneficial and unfavorable aspects, which highly depend on the microenvironment of the involved cells that determines their phenotype and signaling. In view of possible future therapeutic approaches, it is essential to understand the immune – bone cell interface. We will review recent advances and some of the key challenges in this exciting research field.



Harvest the interdependency of T cells and bone – towards immune modulation as a new therapy concept

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Regeneration

Tissue healing is a multistage regenerative process involving complex and well-orchestrated steps. These steps are initiated in response to injury and in most cases in response to vessel disruption which in return results in an inflammatory response. At best, these steps lead to scar-free tissue formation. At the onset of healing stationary and attracted macrophages and other immune cells at the fracture site release cytokines in response to the injury, forming a specific cytokine pattern. Consequently the recruitment, proliferation, and differentiation of mesenchymal stromal cells, synthesis of extracellular matrix proteins, angiogenesis, and finally tissue remodeling follows. The strategy of endogenous regeneration in a tissue such as bone is interesting to analyze since it may represent a blueprint of successful tissue formation with bone being one of the few tissues with the capacity to a complete, scar free reconstitution, representing a perfect model system to regeneration in general.

The inflammatory step

The initial immune reaction is essential for the onset of healing. However, different regulatory mechanisms during the inflammatory reaction that initiates healing could well be key processes determining the course of regeneration vs. scar formation. Immune modulation of the early bone healing phase proved to be successful in different settings. The complexity of the immune system and the numerous cell types involved offer several opportunities to address immune modulation during the early healing phase. Inducing the regulatory macrophage phenotype 2 over the inflammatory M1 phenotype is one example, reducing the pro-inflammatory CD8+ T cells during the initial healing phase is another. Finding the optimal solution to stimulate bone healing through an immune modulatory approach is challenging due to the tight interaction of the immune and skeletal system because the aim is to influence one system without consecutively damaging the other.

Immune modulation as a new therapeutic approach

A promising approach to reduce negatively acting pro-inflammatory effector CD8 T cells while simultaneously supporting beneficial regulatory T cells (Tregs) by raising the cyclic adenosine mono phosphate (cAMP) has been tested in vitro, in a pre-clinical proof of concept experiment and will now be advanced towards a clinical trial. Important for this step is the consideration that the immune composition changes with aging and differs individually. Thus a careful stratification of patient will be necessary to yield the best possible results when applying an immune modulatory therapy.



Let's Talk about Crosstalk: MSC-macrophage Communication Early in Bone Healing

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The first stage of bone healing after trauma or other injurious stimulus involves the innate immune system, and the inflammatory cascade. These events are highlighted by a local influx of cells along a chemokine gradient emanating from the injury site. These and other signaling mechanisms in the traumatized bone and surrounding soft tissues are initiated by local cells that are damaged, or otherwise perturbed. Amongst these cells are resident macrophages and regional circulating monocyte/macrophages that are activated by local chemical and mechanical cues and assume a pro-inflammatory phenotype. Other innate immune cells including neutrophils, mast cells, NK cells etc. are recruited to actively participate in events to curtail the inflammatory stimulus, minimize collateral damage, and begin the processes of resolution and repair. If this sequence of events is interfered with or dysregulated, chronic inflammation results, with potential serious adverse consequences that may jeopardize the desired outcome of reconstruction and return to a normal state of homeostasis.

Integral to the healing process is continuous communication amongst different cells of the hematopoietic and mesenchymal lineages. This crosstalk provides real time data of ongoing events at the injury site via the transmission of contextual signals and other cues that alter the metabolic, physiologic, immunologic and functional phenotype of neighboring cells. One major aspect that is relevant to bone is the licensing of MSCs by inflammatory factors from innate immune cells, especially macrophages, and the reciprocal modulation of macrophage inflammatory phenotype by MSCs. Understanding and modulating this important crosstalk may provide opportunities to optimize bone and soft tissue healing and restore normal anatomical function in a more efficient and timely manner.



The Effect of Inflammaging on Bone Fracture Healing

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Bones exhibit a great capacity to regenerate after traumatic injury. However, there are a variety of conditions in which bone healing is delayed clinically and experimentally, such as diabetes, rheumatoid arthritis, smoking, obesity, and aging. While each condition produces a host of problems, a pro-inflammatory environment is common in each of them. However, the impact of this pro-inflammatory environment on healing outcomes is not well known.

As animals age, an increasingly pro-inflammatory environment is produced and this is associated with many age-related co-morbidities. Macrophages are thought to contribute to the age-related increase in inflammation, and macrophages are an essential part of the inflammatory response during bone fracture healing. Initially, monocytes, and other inflammatory cells invade the wound. Monocytes differentiate into macrophages, debride the wound and stimulate the repair process, and then inflammation resolves possibly in response to signals from mesenchymal stem cells. However during aging this process appears disrupted and inflammation does not resolve normally. In part, aged macrophages represent a much more heterogeneous population of cells compared to young animals, and this variation may explain differences observed between young and old animals. Our work has explored these concepts in detail, and we have uncovered a potential mechanism by which mesenchymal stem cells regulate resolution of inflammation. Exploiting these mechanisms may contribute to development of therapies to stimulate fracture healing.