MODULATING INFLAMMATION TO FACILITATE BONE HEALING: FROM THE LABORATORY TO PRECLINICAL ANIMAL MODELS

S.B. Goodman
Departments of Orthopaedic Surgery and Bioengineering, Stanford University, Stanford, CA, USA

Humans and other species respond to injury and adverse stimuli by means of an immediate, pre-programmed, non-specific biological response that is governed by the innate immune system. This patterned reaction maintains tissue homeostasis by mitigating or eradicating potentially injurious stimuli and thereby, preserves and restores the organism’s structural and biological integrity. The initial events of this response involve activation of the processes of acute inflammation, in which a combination of chemical and cellular signalling mechanisms lead to cell recruitment designed to terminate the offending stimulus and limit collateral damage. As the inflammatory reaction recedes and debris is cleared, the stage of tissue repair and regeneration follows suit. If the above sequence of events is altered (i.e. dysregulated), the reconstitution of natural biological architecture, physiology and performance (so called form and function) will be permanently altered. Dysregulated inflammation and repair do not lead to progressive healing of the tissues; rather, the result is persistent chronic inflammation, fibrosis and cell death.

We have employed novel *in vitro* and *in vivo* models to study acute and chronic inflammation and develop potential translational treatments to help repair and restore musculoskeletal tissues, with a focus on bone. The strategy involves modulating the crosstalk between cells of the monocyte-macrophage-foreign body giant cell-osteoclast lineage and the mesenchymal stem cell (MSC)-osteoblast lineage to achieve musculoskeletal tissue repair. Initial short-term inflammation is the foundation for eventual healing of tissues in all organs. By elucidating the interactions between inflammatory cells and mesenchymal based cells to enhance bone healing, one begins to uncover methods and translational strategies that are applicable to all organ systems. We have strived to accomplish these goals by modulating macrophage chemotaxis and polarization, as well as regulating key transcription factors including NFκB and MyD88. We have genetically modified MSCs to overexpress key chemokines, cytokines and growth factors. In one construct, we have created genetically modified MSCs to first sense NFκB activation and then overexpress the anti-inflammatory pro-regenerative cytokine IL-4 “on demand”. We have also formulated a new method of preconditioning or “licensing” MSCs to enhance osteogenesis, and found that like immune cells, MSCs demonstrate an innate immune memory when challenged by the same or another adverse stimulus. We have combined some of these biological constructs with custom scaffolds and delivery devices using *in vitro* and *in vivo* models, including models of critical size bone defects, osteonecrosis, and the inflammatory response to wear particles. It is hoped that these translational interventions will lead to improved healing of musculoskeletal tissues and provide a platform and paradigm for repair of various tissues in different organ systems throughout the body.