 MCB, vol.3, no.4, pp.229-230, 2006

Developmental Paradigms and Cell-Based Approaches for Fracture Repair

R. S. Tuan [1]

Bone fractures are one of the most common insults to the skeleton. Fractures generally repair via a process that involves initial inflammation and hematoma formation, then progressing to the formation of the soft callus then the hard callus, and culminates in remodeling. Bone marrow response, recruitment of progenitor cells, cartilage formation and hypertrophy, vascular ingrowth, endochondral and intramembranous ossification, and coupled osteoclastic bone resorption for remodeling, represent the sequence of biological activities taking place in fracture repair.

This presentation builds on the supposition that embryonic skeletal development offers useful cellular and molecular paradigms for novel approaches to enhance fracture repair. The mechanisms regulating cellular commitment, differentiation, and morphogenesis in the developing embryonic limb will be presented, including cell-cell and cell-matrix interactions, the action of signaling molecules, and mechanisms of pattern formation (**Fig. 1**). The possibility of utilizing and manipulating the pathways identified in skeletal development to accelerate fracture repair will be discussed. To illustrate how knowledge gained from developmental studies may be applied, our recent work on the functional involvement of the signaling molecule, GDF-5 or CDMP-1, in fracture repair will be presented. Loss-of-function mutations in GDF5 result in skeletal malformations that affect the appendicular skeleton in both mouse and human. Analysis of fracture repair in the mouse GDF-5 deficient brachpod mutant showed that the endochondral sequence is abbreviated during repair, resulting in more brittle regenerate bone. These results suggest that a proper cartilage intermediate is critical for proper fracture healing.

Adult stem cells represent another candidate approach to fracture repair. Specifically, adult mesenchymal stem cells display characteristics in their proliferative and differentiation responses that bear similarities to embryonic skeletal progenitor cells, suggesting that similar regulatory pathways operate during developmental and regenerative phases of skeletal tissues. Challenges in using adult stem cells for skeletal fracture repair include their expansion and maintenance, guided and controlled differentiation, and effective introduction into the fracture site. Successful outcome will depend on the adaptation and combination of cellular, molecular, and engineering approaches in a surgically acceptable procedure. Close collaboration among biologists, engineers, and clinicians are critical to bring this to reality.

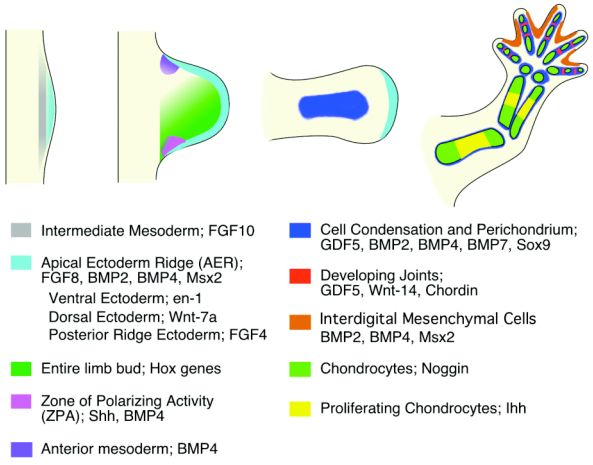

Figure 1 : Expression profiles of developmental and signaling and patterning genes in the embryonic limb.

[1]Cartilage Biology and Orthopaedics Branch, Nationa Institutes of Arthritis, and Musculoskeletal and Skii Diseases, National Institutes of Health, Department o Health and Human Services, Bethesda, Maryland 20892 8022. Email: tuanr@mail.nih.gov

Acknowledgements: Supported by the Intramural Research Program of the National Institute of Arthritis, and Musculoskeletal and Skin Diseases, NIH (Z01 AR 41131).