Wnt Signaling: An Emerging Target for Bone Regeneration

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If we understood how to control the choice between cell self-renewal, proliferation, and differentiation, then theoretically we would have the ability to expand a limited population of adult progenitor cells and then, at will, to induce their timely differentiation to restore the function of a tissue or organ. In terms of skeletal homeostasis and bone repair, the Wnt pathway is among the most attractive targets for such therapeutic intervention. There is now a substantial literature supporting a role of Wnt signaling in skeletogenesis and a growing appreciation for the functions of Wnt in regulating stem cell and skeletal cell behavior.

Wnts are secreted proteins that bind to receptors on the surfaces of stem and osteoprogenitor cells and, once bound, initiate a cascade of intracellular events that eventually lead to the transcription of target genes.[1] Wnt signals perpetuate the self-renewal and proliferation of stem cells,[2] while in osteoprogenitor cells, Wnt signals induce their differentiation.[3] Through these mechanisms, Wnt signaling regulates bone mass.[4] For example, activating mutations (eg, gene mutations that lead to gain-of-Wnt-function) in humans causes high-bone-mass phenotypes such as van Buchem disease,[5] whereas inactivating mutations causes osteopenic diseases such as osteoporosis-pseudoglioma syndrome.[6] These genetic data raise the possibility that modulation of the Wnt pathway is a viable path for improving bone formation in patients.

Early clinical trials support this hypothesis: in phase II trials, elevating Wnt signaling by systemic delivery of antibodies against the Wnt antagonist sclerostin resulted in an increase in bone mineral density in patients with osteoporosis.[7] Enthusiasm for these types of therapies is, however, tempered by serious safety concerns.[8] Lessons learned from the adverse events associated with recombinant human bone morphogenetic protein-2 strongly suggest that introduction of a potent growth or stem cell factor into the human body should be approached with the utmost caution.[9]

Unlike the life-long process of bone remodeling in which imbalances require chronic drug therapy to correct, bone regeneration in response to trauma occurs within a compressed time frame and within a confined location. Although the time scale and body location are different, the molecular and cellular machinery driving bone accrual is the same; consequently, we study how Wnt signaling can be amplified at an injury site to accelerate bone regeneration. This approach enables us to study the effect of Wnt signaling on stem and osteoprogenitor cells within a defined location at a precise time. Studies in this area by our groups and by others provide ample evidence that targeting the Wnt pathway is a feasible strategy for accelerating bone healing. The act of bone injury activates endogenous Wnt signaling, and in the young patient, this endogenous Wnt signal is sufficient to lead to robust bone healing.[3,10] In older animals, this endogenous Wnt signal drops, and with it, a precipitous decline in bone regeneration occurs.[11]

We tested a strategy to augment the body's natural Wnt response to

skeletal damage: Wnt-3a protein is reconstituted in association with a liposomal membrane,[12] an arrangement that mimics the means by which endogenous Wnts are transported between cells.[13] Treating a fracture with this liposomal Wnt-3a results in significantly faster and more robust bone healing, with earlier onset of mineralization and new osteoid deposition than happens normally in young animals.[14] Thus, liposomal Wnt treatment effectively potentiates the endogenous Wnt signal that is initiated by injury and, in doing so, accelerates bone healing.

Given the safety concerns surrounding the use of bone morphogenetic proteins to augment skeletal healing, future methods aimed at enhancing bone regeneration must confine the proliferative effects of these potent agents both spatially and temporally. We recently tested such an approach in which bone graft from aged rabbits was incubated ex vivo with liposomal Wnt-3a. This strategy allowed more precise control over the duration and dose of exposure and also permitted rinsing of the bone graft to remove any protein that had not been internalized by cells of the bone graft. Two interesting findings were reported: First, bone graft material from aged animals undergoes apoptosis immediately upon harvest, which was significantly reduced by incubation with the liposomal Wnt-3a. Second, bone defects treated with the Wnt-3a–activated bone graft from elderly animals behaved similar to bone grafts from juvenile animals, giving rise to significantly more bone than an autograft alone. Together, these data suggest a viable, safe strategy for the treatment of skeletal injuries, especially for individuals with diminished healing potential.[11]

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