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Tribute to Dr. Marshall Urist

Musculoskeletal Growth Factors

Editorial Comment

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Growth factors are triggering and/or signaling molecules that regulate not only growth but also musculoskeletal repair and regeneration. Bone morphogenetic proteins (BMPs), which regulate cellular proliferation, differentiation and extracellular matrix production, were first described by Dr. Marshall Urist in 1965 [22], and are the most well-known and researched of the musculoskeletal growth factors. They also function in apoptosis [13] and reshaping the extracellular matrix. The membrane receptors and intracellular signaling mechanisms of these growth factors are well-defined [2]. Not only osteoblasts and chondrocytes but also osteoclasts [19] contain these membrane receptors, which indicates growth factors have a key role in the homeostasis of the musculoskeletal system. The externally administered local therapeutic quantity and duration that is required to trigger and/or control the event is, however, substantially higher than that of the endogenous dose. Responsive cells are essential at the administration site to have an optimal healing effect. BMP producing and marketing sources indicate that injecting or implanting these growth factors attracts stem cells. The mechanism of how BMPs work at atrophic nonunions where such cells are lacking needs further investigation. Recent preclinical and clinical studies including those published in this symposium will give insight into these mechanisms.

There are several published clinical studies [9, 14] with small sample size and a lack of control groups. In most of these studies the growth factor was combined with autografts or allografts. Are we willing to replace autografts and allografts with BMPs? Studies reporting complications of autografts and allografts suggest the answer is yes. BMPs may replace autografts when safety, efficacy and reliability studies are completed. Outcomes of other clinical studies [4, 7, 12] indicate BMP reduces blood loss between 43 to 336 ml and decreased operation time for 9 to 15 minutes. Although these findings are statistically significant, their clinical importance is open to discussion. The mechanism by which BMPs might reduce infection and improve disability, quality of life and pain scores needs to be explained. Do BMPs have complications? The answer is yes again. Increased numbers of inflammatory cells in sheep [6], increased serum antibody levels against BMPs, generalized edema, bone overgrowth and heterotopic ossification have recently been reported [20]. We must be aware of the side effects of musculoskeletal growth factors to use them safely. Indications of BMPs are expanding [1], however, clinical results on difficult healing fractures such as those of the scaphoid [3] and talus are infrequent. It is obvious that growth factors will find their deserved place in tissue engineering strategies in the near future [2]. Cells, carriers and growth factors are essential elements of this emerging technology. Appropriate carriers [16, 21] of BMPs are still a focus of research. Today, nonviral delivery of the gene of the growth factor into the repair site is the preferred method as highlighted in this symposium.

The cost [5] of musculoskeletal growth factors is another issue that requires further study. Conventional augmentation materials cannot be replaced by BMP in scoliosis surgeries where a single level of fusion will cost 3000 to 5000 USD and yet only 3 mg/ml is recommended to be used per case. The industry somehow needs to decrease the production and marketing costs of these mediators.

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Currently BMPs are reportedly effective in (1) anterior and posterior spinal fusion; (2) enhancing fracture fixation; and (3) segmental bone defect healing [17]. They should be used in skeletally mature patients in combination with a fixation device. Their use is contraindicated in patients with tumors, active infections or pregnancy. The use of BMPs in children and young adults should be approached with caution since their effects on growing tissues is unclear. One study published in this symposium focuses on this issue.

The predictive, personalized, preventive and participatory role [10] of musculoskeletal growth factors in the future will likely develop as an essential element of tissue engineering. However, mechanical stability, a crucial requirement of bone healing, may not be achieved immediately. Combining bone stimulating growth factors with angiogenic factors [11, 18], parathyroid hormone [15] and mesenchymal stem cells [8, 11] is promising. The need to combine musculoskeletal growth factors with others, however, emphasizes the lack of independence of these mediators. The role of musculoskeletal growth factors in fresh fractures, preexisting medical comorbidities such as diabetes and vascular diseases, multiple trauma, infection, osteoporosis and osteoarthritis are current areas of research. Some of these issues are covered in this symposium. A better understanding of receptor expression at the fracture site, endogenous BMP production and non-viral delivery of these mediators will enhance our knowledge.

The "Tribute to Dr. Marshal Urist: Musculoskeletal Growth Factors" Symposium was proposed by Dr. Richard Brand. I thank him for inviting me to be the guest editor for this symposium. As orthopaedic surgeons, we need to conduct more well-designed, focused and randomized controlled clinical studies on the indications and outcomes of musculoskeletal growth factors.

References

1. Bagaria V. Bone morphogenic protein: Current state of field and the road ahead. *J Orthopaedics.* 2005;2(4)e3. Available at: http://www.jortho.org/2005/2/4/e2. Accessed August 10, 2009.
2. Bessa PC, Casal M, Reis RL. Bone morphogenetic proteins in tissue engineering: the road from the laboratory to the clinic, part I (basic concepts). *J Tissue Eng Regen Med.* 2008;2:1–13.
3. Bilic R, Simic P, Jelic M, Stern-Padovan R, Dodig D, Pompe van Meerdervoort H, Martinovic S, Ivankovic D, Pecina M, Vukicevic S. Osteogenic protein-1 (BMP-7) accelerates healing of scaphoid non-union with proximal pole sclerosis. *Int Orthop.* 2006;30:128–134.
4. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech.* 2002;15:337–349.
5. Cahill KS, Chi JH, Day A, Claus EB. Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. *JAMA.* 2009;302:58–66.
6. Egermann M, Lill CA, Griesbeck K, Evans CH, Robbins PD, Schneider E, Baltzer AW. Effect of BMP-2 gene transfer on bone healing in sheep. *Gene Therapy.* 2006;13:1290–1299.
7. Friedlaender GE, Perry CR, Cole JD, Cook SD, Cierny G, Muschler GF, Zych GA, Calhoun JH, LaForte AJ, Yin S. Osteogenic protein-1 (Bone Morphogenetic Protein-7) in the treatment of tibial nonunions: A prospective, randomized clinical trial comparing rhOP-1 with fresh bone autograft. *J Bone Joint Surg Am.* 2001;83:S151–S158.
8. Fu TS, Chen WJ, Chen LH, Lin SS, Liu SJ, Ueng SWN. Enhancement of posterolateral lumbar spine fusion using low-dose rhBMP-2 and cultured marrow stromal cells. *J Orthop Res.* 2009;27:380–384.
9. Granjeiro JM, Oliveira RC, Bustos-Valenzuela JC, Sogayar MC, Taga R. Bone morphogenetic proteins: from structure to clinical use. *Braz J Med Biol Res.* 2005;38:1463–1473.
10. Hood L. A doctor's vision of the future of medicine. *Newsweek.* Available at: http://www.newsweek.com/id/204227. Accessed August 10, 2009.
11. Huang YC, Kaigler D, Rice KG, Krebsbach PH, Mooney DJ. Combined angiogenic and osteogenic factor delivery enhances bone marrow stromal dell-driven bone regeneration. *J Bone Mineral Res.* 2005;20:848–857.
12. Jones AL, Bucholz RW, Bosse MJ, Mirza SK, Lyon TR, Webb LX, Pollak AN, Golden JD, Valentin-Opran A (The Bestt-All Study Group). Recombinant human BMP-2 and allograft compared with autogenous bone graft for reconstruction of diaphyseal tibial fractures with cortical defects. *J Bone Joint Surg Am.* 2006;88:1431–1441.
13. Li X, Cao X. BMP Signaling and skeletogenesis. *Ann N Y Acad Sci.* 2006;1068:26–40.
14. McKay WF, Peckham SM, Badura JM. A comprehensive clinical review of recombinant human bone morphogenetic protein-2 (INFUSE® Bone Graft). *Int Orthop.* 2007;31:729–734.
15. Morgan EF, Mason ZD, Bishop G, Davis AD, Wigner NA, Gerstenfeld LC, Einhorn TA. Combined effects of recombinant human BMP-7 (rhBMP-7) and parathyroid hormone (1–34) in metaphyseal bone healing. *Bone.* 2008;43:1031–1038.
16. Nie H, Ho ML, Wang CK, Wang CH, Fu YC. BMP-2 plasmid loaded PLGA/HAp composite scaffolds for treatment of bone defects in nude mice. *Biomaterials.* 2009;30:892–901.
17. NIH. Clinical Trials.gov Web site. Available at: www.clinicaltrials.gov. Accessed August 10, 2009.
18. Patel ZS, Young S, Tabata Y, Jansen JA, Wong MEK, Mikos AG. Dual delivery of an angiogenic and an osteogenic growth factor for bone regeneration in a critical size defect model. *Bone.* 2008;43:931–940.
19. Pederson L, Ruan M, Westendorf JJ, Khosla S, Oursler MJ. Regulation of bone formation by osteoclasts involves Wnt/BMP signaling and the chemokine sphingosine-1-phosphate. *PNAS.* 2009;105:20764–20769.
20. Perri B, Cooper M, Lauryssen C, Anand N. Adverse swelling associated with use of rhBMP-2 in anterior cervical discectomy and fusion: a case study. *Spine J.* 2007;7:235–239.
21. Seeherman H, Wozney JM. Delivery of bone morphogenetic proteins for orthopedic tissue regeneration. *Cytokine Growth Factor Rev.* 2005;16:329–345.
22. Urist MR. Bone formation by autoinduction. *Science.* 1965;150:893–899.