A Spine Surgeon’s Perspective: Orthobiologics: Osteoinductive / Osteoporomotive Growth Factors
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1) Introduction
a) ICBG is the “gold standard” for difficult healing situations
   i) Osteoconduction- scaffold
   ii) Osteogenesis- live cells
   iii) Morbidity may be up to 20% of patients
b) Osteoinductive bone graft alternatives are experiencing increasing popularity
   i) Osteoinductive means it is capable of inducing bone de novo in ectopic location
   ii) Bone graft extenders or enhancers
   iii) Bone graft substitutes
   iv) Osteopromotive category – helpful when bone is already forming, but not capable of ectopic bone formation from scratch

2) Peptide Signaling Molecules
   These peptide growth factors stimulate the activity of osteoprogenitor cells and osteoblasts and may enhance osteogenesis. They cannot induce bone formation from undifferentiated cells.
   a) Fibroblast Growth Factor (FGF)
      i) Expressed during fracture repair
      ii) FGF-2 can accelerate fracture repair in NH primates (baboons)
      iii) Phase III clinical trials for tibial fractures underway
   b) Vascular Endothelial Growth Factor (VEGF)
      i) Ability to induce angiogenesis
      ii) Necessary for bone healing, but not sufficient to be osteoinductive
      iii) Can enhance bone healing and can enhance suboptimal doses of BMP
   c) Platelet Derived Growth Factor (PDGF)
      i) Several different isoforms
      ii) Not osteoinductive
      iii) Helpful for diabetic wound healing
      iv) Possibly helpful for diabetic fracture repair
      v) Inhibitory for spine fusion when combined with autograft or DBM
      vi) Can inhibit BMP activity in cell cultures
      vii) May require optimal concentration and pulsed rather than constant release
   d) Prostaglandin Agonists
      i) PGE2 increases bone mass administered systemically or locally
      ii) An agonist to prostaglandin receptor EP2 enhanced healing of canine long bone segmental defects

3) Bone Morphogenetic Proteins
   i) Timeline
      (1) 1965 – Urist – Autoinduction principle (DBM)
      (2) 1988 - Rosen, Wozney et al cloned BMP cDNAs
      (3) 2001 - rhBMP-7 (OP-1) approved for spine fusion in Australia, then Europe, later for long bone nonunions
      (4) 2002 - rhBMP-2/ACS (InFuse) PMA approved by FDA for Interbody Spine Fusion
(5) 2003 - rhBMP-7 (OP-1) HDE approved by FDA for long bone nonunion and eventually posterolateral spine fusion nonunion
(6) 2005 - rhBMP-2 (InFuse) PMA approved by FDA for open tibia fractures
(7) 2007 - rhBMP-2 (InFuse) PMA approved by FDA for dental applications

ii) Mechanism of Action
(1) BMPs are chemotactic for MSCs
(2) BMP homo/hetero dimers bind to cell surface receptors (serine threonine kinase) resulting in phosphorylation of Smad 1/5 which binds to Smad4 and translocates into the nucleus where it can bind to specific DNA sequences in promoters of osteoblastic genes.
(3) Inhibitory Smads can block this process
(4) Smurf1 can result in ubiquitin-mediated proteosomal degradation of Smads
(5) Much crosstalk with other pathways that may affect cellular responsiveness to BMPs – poorly understood.
(6) Osteoinductive BMPs can induce bone and bone marrow formation de novo in an ectopic location.

iii) Are all BMPs created equal? NO
(1) Most osteogenic BMPs are BMP-2, BMP-6, BMP-9
(2) Somewhat less osteogenic BMPs are BMP-4, BMP-7
(3) Data based on in vitro effects on pluripotent cells, immature OB, mature OB as well as in vivo ectopic bone formation with each BMP delivered by AdV vector in thigh muscle of athymic rat
(4) Different BMPs can have different distant organ effects
(a) rhBMP-7 has positive effects on kidney (was considered as a potential treatment for acute renal failure)
(b) rhBMP-6 has been examined for osteoporotic bone enhancement

4) Summary of Outstanding Issues with BMPs
a) Are there differences between BMPs?
b) Will difficult patients (revisions, diabetes, smokers, steroids) require higher doses of BMPs?
c) Are there safety issues (antibodies)? – probably not clinically relevant
d) Beware of Off-Label (Physician-Directed) use – increased possibility of local side effects
e) Local Side Effects with rBMPs?
   i) Ectopic Bone (PLIF, TLIF)
   ii) Seroma, Edema (ACDF, PLIF, TLIF, PLF)
   iii) Transient Local Resorption (ALIF, PLIF, TLIF) near cancellous bone
   iv) Transient Radiculopathy (TLIF, PLIF)
v) Can be minimized by avoiding hyperconcentration of BMP solution on carrier, switching carriers with unknown release kinetics, avoiding overstuffing BMP/carrier into fixed defect/device volumes
f) Carrier plays an important role in success and dose of BMP needed
g) Segmental Defect is tougher than routine fracture. Posterolateral spine fusion is tougher than interbody fusion – must validate BMP dose and carrier in specific healing environment
h) Rhesus monkey is most predictive pre-clinical model of clinical behavior of BMP+ carrier
i) Less than 100% successful bone induction suggests:
   i) Inferior BMP
   ii) Inadequate dose
   iii) Inadequate carrier

References:

8:06 – 8:11 am

Orthobiologics: Foot and Ankle Surgeon’s Perspective
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REFERENCES

FOOT & ANKLE BONE MORPHOGENETIC PROTEIN

Background: The purpose of this study was to evaluate the effect of rhBMP-2 on bone healing in patients who undergo high-risk ankle & hindfoot fusions. Materials & Methods: Patients who underwent high-risk, elective ankle and hindfoot fusions treated with rhBMP-2 augmentation were reviewed for