

New strategy aims to enhance efficacy and safety of bone repair treatment

January 6 2016

Bone morphogenetic protein-2 (BMP2) is used clinically to promote bone repair. However, the high BMP2 concentrations required to stimulate bone growth in humans may produce life-threatening adverse effects such as cervical swelling in spinal fusion procedures, a problem that prompted an FDA warning in 2008. Now, a team of clinicians and engineers has shown that adding the protein kinase C-binding protein NELL-1 (Nel-like molecule-1) to BMP2 therapy may allow clinicians to achieve better results at lower - and safer - BMP2 doses. Their findings are reported in *The American Journal of Pathology*.

BMP2 is an FDA-approved osteoinductive growth factor used for spinal fusions and treatment of skeletal defects. An important limitation of BMP2 treatment is the formation of abnormal, adipose-filled, poor-quality [bone](#) that extends beyond the proper boundaries of the defect. Adverse effects, such as cervical swelling, ectopic bone formation, osteoclastogenesis, and inconsistent bone formation, may occur at high dosages. Therefore, the practical goals of treatment are to produce good-quality bone (osteogenesis) and to inhibit production of the abnormal adipose cell intruders (adipogenesis).

"In this study, we show both NELL-1 inhibition of BMP2-induced adipogenesis and NELL-1 + BMP2 synergy in bone formation. Overall, NELL-1 together with BMP2 forms bone of better quality than BMP2 alone. The combination treatment of NELL-1 with BMP2 may be particularly valuable in clinical scenarios in which bone regeneration is impaired, such as with steroid treatment or osteoporosis," noted Dr. Chia

Soo, MD, FACS, Vice Chair in Research in the Division of Plastic and Reconstructive Surgery and the Research Director of the Operation Mend of the UCLA School of Medicine.

Investigators evaluated NELL-1 and BMP2 in vitro and in vivo in animals. Using a femoral segmental defect model, in which a section of a rat's femur is surgically removed, the investigators studied bone regrowth 8 weeks after surgery.

Histological analysis of untreated controls showed fibrous tissue growth within the surgical cavity, with no connection formed between the surgically-separated ends of the femoral bone and no evidence of trabecular [bone formation](#) (the connective tissue strands that provide a framework for regeneration). With BMP2 treatment, the fractured ends became connected, but the newly formed bone contained adipose tissue interspersed with sparse [trabecular bone](#), which grew beyond the original margins. In contrast, the combination of NELL-1 + BMP2 produced tightly woven trabecular bone that remained largely within the area of the defect.

Other tests confirmed that adipose cells were evident in the BMP2-treated cavities but not in those administered NELL-1 + BMP2. NELL-1 also inhibited BMP2-stimulated adipogenesis in vitro from progenitor cells of multiple species. The investigators used a variety of advanced techniques to show that NELL-1 + BMP2 significantly increased all markers of [bone growth](#) relative to either treatment alone, including tests performed on human bone marrow stromal cells. The authors suggest that NELL-1 encourages cells early in their development to become osteogenic, rather than adipogenic.

NELL-1 regulation of BMP2-induced osteogenesis and adipogenesis may occur through activation of canonical (β -catenin-dependent) Wnt signaling, explained Aaron W. James, MD, Bone Pathologist in the

Department of Pathology of the UCLA School of Medicine, who added that, in general, increased Wnt signaling steers cells toward osteogenesis rather than adipogenesis. (Wnt signaling via Wnt proteins allows cells to communicate and is thought to play a role in the regulation of mesenchymal stem cell maintenance and differentiation during bone development and maturity.)

"The ability of NELL-1 to activate Wnt signaling suggests potential utility in conditions such as osteoporosis, where the balance between osteogenesis versus adipogenesis and the balance between bone deposition versus resorption is perturbed to favor bone loss," said Dr. Kang Ting, DMD, DMedSc, Professor and Chair in the Division of Growth and Development of the UCLA School of Dentistry, and Professor in UCLA's Departments of Bioengineering and Orthopaedic Surgery. He added that these findings uncover new treatment possibilities for osteoporosis, such as the use of antibodies against endogenous Wnt pathway inhibitors, two of which are currently in Phase 3 clinical trials.

Treatments to promote [bone development](#) may be valuable for those with weakened bones, whether due to osteoporosis, cancer, medications, surgery, or trauma. Recombinant BMP is FDA-approved for use in limited patient populations such as patients with degenerative disc disease needing lumbar spine fusion, stabilized acute open tibial shaft fractures, and inability to undergo a successful autograft. In future work, the investigators hope their findings will enable a reduction of the currently-required clinical dose of BMP2 and, subsequently, result in fewer adverse events.

More information: "Novel Wnt regulator Nel-like molecule-1 antagonizes adipogenesis and augments osteogenesis induced by bone morphogenetic protein-2," by Jia Shen, PhD, Aaron W. James, MD, Xinli Zhang, MD, PhD, Shen Pang, PhD, Janette N. Zara, MD, Greg

Asatrian, BS, Michael Chiang, BDS, Min Lee, PhD, Kevork Khadarian, BS, Alan Nguyen, BS, Kevin S. Lee, BS, Ronald K. Siu, MS, Sotirios Tetradis, DDS, PhD, Kang Ting, DMD, DMedSc, Chia Soo, MD, FACS (DOI: [dx.doi.org/10.1016/j.ajpath.2015.10.011](https://doi.org/10.1016/j.ajpath.2015.10.011)). This article appears online ahead of *The American Journal of Pathology*, Volume 186, Issue 2 (February 2016)

Provided by Elsevier

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