

Commentary

Commentary: Important considerations on bone morphogenetic protein-2 and neuroinflammation

Michael H. Heggeness, MD, PhD*

Baylor College of Medicine, 6620 Main St, Houston, TX 77030, USA

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COMMENTARY ON: Dmitriev AE, Lehman RA Jr., Symes AJ. Bone morphogenetic protein-2 and spinal arthrodesis: the basic science perspective on protein interaction with the nervous system. *Spine J* 2011;11:500–5 (in this issue).

The growth factor recombinant human bone morphogenetic protein (rhBMP-2) came into very widespread clinical use before the very complex biologic activities of the molecule were well understood. Indeed, the complex biological actions of BMP-2 are still not completely established and remain under active study. As the Dmitriev et al. [1] review article describes, the interaction of BMP-2 with neurological tissue is an important issue.

At this point of time, the fact that BMP-2 induces inflammation is indisputable. We also know that along with this potent inflammatory process, BMP-2 stimulates the local formation of brown fat (with the production of heat and water via uncoupled mitochondrial activity) and ultimately leads to cartilage formation, neovascularization, and bone formation [2–4]. Very recent work has strongly suggested that there is a direct action of BMP-2 on peripheral nerves in a process that includes the direct induction of neuroinflammation. It further appears that this neuroinflammation may be basic to the process of BMP-2-induced bone formation [5]. This recent work, well summarized in the review by Salisbury et al. [5], demonstrates that the “release of BMP-2, such as during the induction of Heterotopic Ossification in soft tissue, initiates

neurogenic inflammation within the local environment.” This process appears to involve the participation of mast cells.

The frequent occurrence of new and “paradoxical” symptoms of leg pain, radiculitis, and sciatica in patients where BMP-2 had been applied near the spine may possibly be related to the direct interaction of BMP-2 with peripheral nerves or nerve roots within the surgical field. The Dmitriev et al. group also indicate that some of this effect may be because of direct effect on the dorsal root ganglia. Although these are currently early findings, the clinical complication involving apparent neurological effects (such as neuropathic pain, radiculitis, retrograde ejaculation, and so on) may be explained by these diverse mechanisms.

In the future, the clinical use of recombinant BMP-2 may need to be carefully considered with attention to the protection of nerve roots, their dorsal root ganglia, large nerves, and autonomic plexuses from the local area of rhBMP-2 application. For now, it is important to understand that the BMP-2 interaction with neurologic tissues is complex, involves a potent inflammatory response, and that the downstream effects are not yet well understood.

References

- [1] Dmitriev AE, Lehman RA, Symes AJ. Bone morphogenetic protein-2 and spinal arthrodesis: the basic science perspective on protein interaction with the nervous system. *Spine J* 2011;11:500–5.
- [2] Olmstead-Davis E, Gannon FH, Ozen M, et al. Hypoxic adipocytes pattern early heterotopic bone formation. *Am J Pathol* 2007;170:620–32.
- [3] Dilling CF, Wada AM, Lazard ZW, et al. Vessel formation is induced prior to the appearance of cartilage in BMP-2-mediated heterotopic ossification. *J Bone Miner Res* 2010;25:1147–56.
- [4] Shafer J, Davis AR, Gannon FH, et al. Oxygen tension directs chondrogenic differentiation of myelo-monocytic progenitors during endochondral bone formation. *Tissue Eng* 2007;13:2011–9.
- [5] Salisbury E, Sonnet C, Heggeness M, et al. Heterotopic ossification has some nerve. *Crit Rev Eukaryot Gene Expr* 2010;20:313–24.

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* Corresponding author. Baylor College of Medicine, 6620 Main St, Houston, TX 77030, USA. Tel.: (713) 986-5730; fax: (713) 986-5731.

E-mail address: heggeness@bcm.edu (M.H. Heggeness)