Chapter 64
BMP Signaling in Regenerative Medicine

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ABSTRACT

More than 40 years after the discovery of Bone Morphogenetic Proteins (BMPs) as bone inducers, a whole protein family of growth factors connected to a wide variety of functions in embryonic development, homeostasis, and regeneration has been characterized. Today, BMP2 and BMP7 are already used in the clinic to promote vertebral fusions and restoration of non-union fractures. Besides describing present clinical applications, the authors review ongoing trials highlighting the future possibilities of BMPs in medicine. Apparently, the physiological roles of BMPs have expanded their range from bone growth induction and connective tissue regeneration to cancer diagnosis/treatment and cardiovascular disease prevention.

INTRODUCTION

The matrix bone has fascinated scientists throughout centuries beginning with Hippocrates who initially theorized the capacity of endogenous substances for medicinal purposes. Even though earlier studies in the field of bone regeneration are known, Dr. Marshall Raymond Urist, an orthopedic surgeon, made the landmark discovery in 1965. Urist described his elusive observation with the following words: "Wandering histiocytes, foreign body giant cells, and inflammatory connective-tissue cells are stimulated by degradation products of dead matrix to grow in and repopulate the area of an implant of decalcified bone" (Urist, 1965). From this discovery, that new bone is formed upon applying a demineralized bone extract in a rabbit muscle he concluded that a certain agent

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within this crude protein mix has to be responsible for such an ectopic bone growth. He named this substance Bone Morphogenetic Protein, generally known as BMP.

Over the past five decades, cloning and purification of BMPs as well as the mechanisms of BMP signal transduction have been extensively studied and reviewed (Chen, Zhao, & Mundy, 2004; Wang, et al., 1990; Wozney, et al., 1988). To date, BMPs are well characterized and known as multi-functional growth factors belonging to the transforming growth factor ß (TGFß) superfamily. The superfamily of TGFß ligands is a phylogenetically conserved group of signaling molecules that comprises over 30 members in mammals including TGFβs, Activins, Inhibins, Bone Morphogenetic Proteins (BMPs), Growth and Differentiation Factors (GDFs), Myostatin, Leftys, and Müllerian-Inhibiting Substance (MIS) (Figure 1) (Wu & Hill, 2009).

In this chapter, we will start by introducing BMPs in a general manner covering synthesis,

Figure 1. Phylogenetic tree of the human TGF-ß superfamily. Phylogenetic tree derived from protein alignments of preproproteins of the members of the TGF-ß superfamily.