Chapter 1
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 within this crude protein mix has to be responsible for such an ectopic bone growth. He named this

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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, structure, signaling, and regulation. The complexity of these systems already hints towards the importance of BMPs in human diseases, which will be the focus of the following paragraph. By understanding BMPs and also the associated diseases many researchers try to turn the table and utilize BMPs as drugs. We will present current efforts to find BMP treatments for a wide variety of diseases like kidney or liver failure. However, the original field for BMP application is the skeleton and until now only two members of the BMP family are approved for clinical application in bone regeneration, namely BMP2 and BMP7. Their development and role in today's clinical practice, especially in the field of bone regeneration, will be a main focus of this chapter. Finally, we will discuss the current problems of BMP therapy and present possible solutions.

BACKGROUND

BMP Synthesis

BMPs are synthesized as large precursor proteins consisting of an N-terminal signal peptide, a prodomain, and a mature peptide (Eder & Fersht, 1995; Kuhfahl, et al., 2011; Xiao, Xiang, & Shao, 2007). Following N-terminal proteolysis of the signal peptide, the pro- and mature domain remain non-covalently associated and undergo dimerization whereby two monomers are assembled in an antiparallel manner. Prior to receptor binding, the active BMP dimer is derived by intra- or extracellular cleavage within the prodomain at an Arg-X-X-Arg site by members of the Subtilisin-like Proprotein Convertase (SPC) family (Constam & Robertson, 1999; Ploger, et al., 2008).

Structure of BMPs

The general structure of BMP molecules is often compared to a stylized left hand, in which two finger-like ß-sheets form the knuckle region whereas the wrist consists of a four-turn α-helix as well as a variable pre-helix loop (Figure 2). A structural hallmark shared by the majority of BMPs is known as the unique cysteine knot motif, characterized by seven conserved cystein residues. Within this conformation, six cysteines set up three intramolecular disulfide bonds and the seventh cysteine is essential for dimerization by connecting two monomers via a disulfide bond (Miyazono, Kamiya, & Morikawa, 2010; Scheufler, Sebald, & Hulsmeyer, 1999). Interestingly, the latter cysteine is not completely conserved among the BMP family and absent in GDF3, GDF9 and BMP15 (McPherron & Lee, 1993; Rider & Mulloy, 2010).