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Mini review

# The role of bone morphogenetic proteins in myeloma cell survival

Toril Holien [a,*], Anders Sundan [a,b,1]

[a] KG Jebsen Center for Myeloma Research, Department of Cancer Research and Molecular Medicine, NTNU, Faculty of Medicine, Norwegian University of Science and Technology, Postbox 8905, 7491 Trondheim, Norway
[b] Centre of Molecular Inflammation Research, Department of Cancer Research and Molecular Medicine, NTNU, Faculty of Medicine, Norwegian University of Science and Technology, Postbox 8905, 7491 Trondheim, Norway

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ABSTRACT

Multiple myeloma is characterized by slowly growing clones of malignant plasma cells in the bone marrow. The malignant state is frequently accompanied by osteolytic bone disease due to a disturbed balance between osteoblasts and osteoclasts. Bone morphogenetic proteins (BMPs) are present in the bone marrow and are important for several aspects of myeloma pathogenesis including growth and survival of tumor cells, bone homeostasis, and anemia. Among cancer cells, myeloma cells are particularly sensitive to growth inhibition and apoptosis induced by BMPs and therefore represent good models to study BMP receptor usage and signaling. Our review highlights and discusses the current knowledge on BMP signaling in myeloma.



## 1. Introduction

### 1.1. General introduction

The BMP family of ligands has been shown to play a role in a multitude of processes throughout the body, in particular in cellular lineage commitment, morphogenesis and patterning, differentiation, proliferation, cellular maintenance and survival [1–3]. Also in multiple myeloma, BMP signaling has been proposed to influence important processes such as growth control, bone homeostasis, iron metabolism and angiogenesis. However, BMP signaling is highly dependent on cell type and context. Multiple myeloma is characterized by the presence of slowly growing, malignant plasma cells in the bone marrow [4]. Dependent on receptor expression, many BMPs potently induce growth arrest or apoptosis in myeloma cells, making them unique among cancer cells. Myeloma cells are therefore particularly interesting tools to study BMP receptor use and signaling. Moreover, a hallmark of myeloma is severe osteoporotic or osteolytic bone disease and the BMPs are known as potent mediators of bone formation. Thus, BMPs have the potential not only to suppress survival of myeloma cells but also to restore bone in these patients. This review focuses on the roles of BMPs, their related ligands and receptors in regulation of myeloma cell growth.

### 1.2. An introduction to bone morphogenetic proteins

Bone morphogenetic proteins (BMPs) constitute the largest subgroup of the transforming growth factor (TGF)-β family of ligands that also include growth and differentiation factors (GDFs), activins and nodal. The bone inducing activity of BMP was discovered in the 1960s and the first proteins of the family were characterized in the late 1980s [5,6]. Further studies have revealed multiple functions for BMPs, such as involvement in embryogenesis, hematopoiesis and neurogenesis (reviewed by Bragdon et al.) [2], as well as both tumor promoting and growth inhibiting effects in various cancers [3]. The signal is usually transduced through the (small) mothers against dpp (decapentaplegic) homolog (SMAD) pathway that is unique for the TGF-β family [7]. The pleiotropic effects of BMP suggest the need for tight control of its activities. This is achieved by multiple regulatory mechanisms, including regulation of ligand activity, availability of ligand, particularly regulated by highly specific antagonists, expression of receptors, decoy receptors, co-receptors and the inhibitory (I)-SMADs, SMAD6 and SMAD7 [2].

### 1.3. BMP signal transduction

BMPs and other TGF-β family members signal by binding as active homo-, or sometimes, heterodimers to their respective

*Abbreviations:* BMP, bone morphogenetic protein; TGF, transforming growth factor; GDF, growth and differentiation factor; SMAD, (small) mothers against dpp (decapentaplegic) homolog; ALK, activin receptor-like kinase; BMSC, bone marrow stromal cells.

* Corresponding author. Tel.: +47 72825267; fax: +47 72825736.
*E-mail addresses:* toril.holien@ntnu.no (T. Holien), anders.sundan@ntnu.no (A. Sundan).
[1] Tel.: +47 72825339; fax: +47 72825736.

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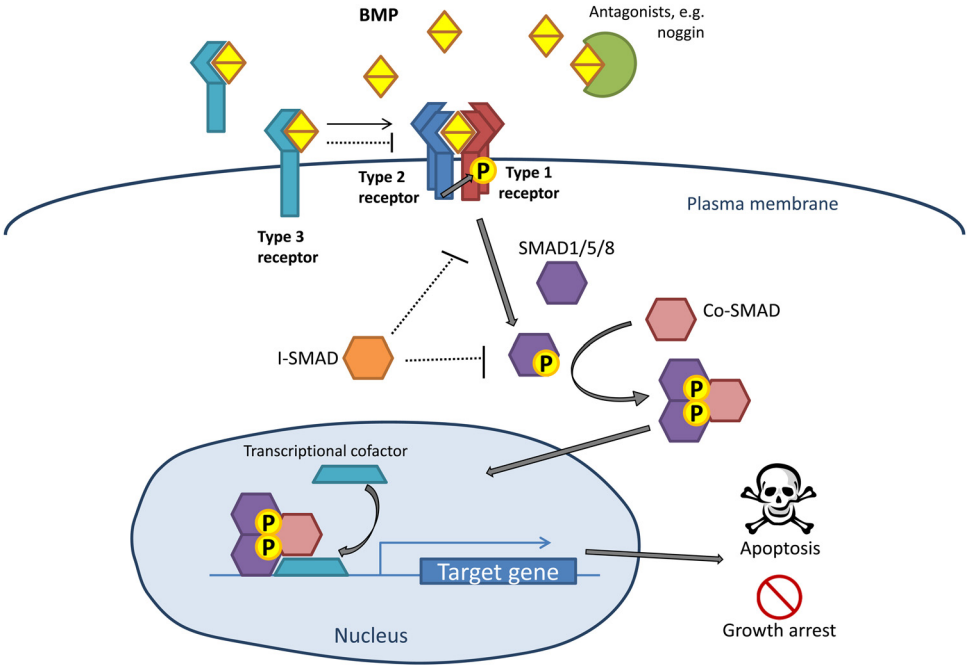


**Fig. 1.** BMP signal transduction. Ligand binding enables the constitutively active type 2 receptor to activate the type 1 receptor. R-Smads are phosphorylated after binding to the activated type 1 receptor. Two activated R-SMADs and one Co-SMAD form a heteromeric complex that translocates to the nucleus where it can regulate transcription of specific target genes. The canonical pathway is regulated at several steps including: regulation of the access to ligand by BMP binding to extracellular BMP antagonists (like noggin, gremlin, follistatin *etc.*), membrane-bound or soluble type 3 receptors that either facilitate or inhibit formation of a ligand/receptor signaling complex, and by inhibitory SMADs-6 and -7 that regulate signaling by different mechanisms. In myeloma cells, activation of R-SMADs leads to downregulation of target genes such as the oncogene c-MYC, concomitantly with induction of growth arrest and/or apoptosis.

serine/threonine kinase receptors. They either bind to a preformed receptor complex, or alternatively, a receptor complex is formed by ligand binding to high-affinity receptors followed by recruitment of receptors with lower affinity. For most BMPs this means initial binding to a type 2 receptor, followed by binding to a type 1 receptor. Upon ligand binding, the constitutively active type 2 receptor phosphorylates the type 1 receptor in the juxtamembrane glycine/serine rich domain (Fig. 1). This activating step enables binding and phosphorylation of receptor activated (R)-SMADs. Which one of the R-SMADs that is activated depends on the type 1 receptor and the composition of the receptor complex. In general, the R-SMADs are divided into two groups: (1) BMP-activated R-SMADs; SMAD1, SMAD5 and SMAD8 that are activated by ALK1, ALK2, ALK3 and ALK6. (2) TGF-β/Activin-activated R-SMADs; SMAD2 and SMAD3 that are activated by ALK4, ALK5 and ALK7. Activated R-SMADs bind the Co-SMAD, which in humans is SMAD4. Trimers consisting of SMAD4 and two R-SMADs translocate to the nucleus to repress or activate expression of SMAD-responsive genes [2].

The ligand-receptor interaction of the BMP/TGF-β family of ligands is highly promiscuous, as evident by the presence of only seven type 1 receptors and five type 2 receptors for over 30 different ligands [3]. Typically, one receptor can bind different ligands, whereas one ligand can activate different sets of receptors. Historically, one has thought that four type 1 receptors of the activin receptor-like kinases (ALK) are involved in BMP signaling. Thus, BMPs are believed to signal through ALK1, ALK2, ALK3, and ALK6, as well as through three type 2 receptors, namely BRII, ActRIIa, and ActRIIb (summarized in Table 1). Now it has become clear that there is another level of complexity in that heteromeric receptor complexes exist that enables ligands to signal to both R-SMAD branches. Thus, TGF-β can activate heteromeric receptor complexes consisting of both ALK5 and ALK1, thereby activating both SMAD2/3 and SMAD1/5/8 [8,9]. Also, BMP-9 has been shown to induce phosphorylation of SMAD2 by signaling through ActRIIa in pulmonary endothelial cells [10]. More recently, it was shown that BMP-2 also could signal through heteromeric complexes consisting of TGFBR2/ALK5/ALK3, leading to SMAD2 phosphorylation, and

**Table 1**
BMP-, activin-, and TGF-β-receptors and their putative ligands in multiple myeloma.

| | Receptor | Alternate names | Myeloma cell expression | Putative ligands |
|---|---|---|---|---|
| Type 1 | ALK1 | ACVRL1 | No | BMP9, BMP10, TGFβ |
| | ALK2 | ACVR1 | Yes | BMP6, BMP7, BMP9, BMP2 |
| | ALK3 | BMPR1A | Yes | BMP2, BMP4, BMP5, BMP6, BMP7, BMP10, BMP12-14 |
| | ALK4 | ACVR1B | Yes | Activin A |
| | ALK5 | TGFBR1 | Yes | TGFβ |
| | ALK6 | BMPR1B | Yes/no | BMP2, BMP4, BMP6, BMP7, BMP10, BMP12-15 |
| | ALK7 | ACVR1C | Yes | Activin A |
| Type 2 | ACTRII | ACVR2A | Yes | BMP2, BMP4, BMP6, BMP7, BMP9, BMP10, BMP-12, BMP14 |
| | ACTRIIB | ACVR2B | Yes | BMP2, BMP6, BMP7, BMP9, BMP10, BMP14 |
| | BMPRII | BMPR2 | Yes | BMP2, BMP4, BMP6, BMP7, BMP9, BMP10, BMP12-15 |
| | TGFBR2 | | Yes/no | TGFβ |
| Type 3 | TGFBR3 | Betaglycan | No | TGFβ |
| | Endoglin | CD105 | Yes/no | BMP9, TGFβ |