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REVIEW

Regulation of Gastric Metaplasia, Dysplasia, and Neoplasia by Bone Morphogenetic Protein Signaling

Andrea Todisco

Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan

SUMMARY

The bone morphogenetic proteins exert important regulatory actions on the homeostasis of the gastric epithelium. Loss of bone morphogenetic protein signaling leads to metaplasia and dysplasia and to enhancement of helicobacter-induced gastric inflammation.

The bone morphogenetic proteins, (BMP)s are regulatory peptides that have significant effects on the growth and differentiation of gastrointestinal tissues. In addition, the BMPs have been shown to exert anti-inflammatory actions in the gut and to negatively regulate the growth of gastric neoplasms. The role of BMP signaling in the regulation of gastric metaplasia, dysplasia and neoplasia has been poorly characterized. Transgenic expression in the mouse stomach of the BMP inhibitor noggin leads to decreased parietal cell number, increased epithelial cell proliferation, and to the emergence of SPEM. Moreover, expression of noggin increases *Helicobacter*-induced inflammation and epithelial cell proliferation, accelerates the development of dysplasia, and it increases the expression of signal transducer and activator of transcription 3 (STAT3) and of activation-induced cytidine deaminase (AID). These findings provide new clues for a better understanding of the pathophysiological mechanisms that regulate gastric inflammation and the development of both dysplastic and neoplastic lesions of the stomach. *(Cell Mol Gastroenterol Hepatol 2017;3:339–347; http://dx.doi.org/10.1016/j.jcmgh.2017.01.014)*

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The bone morphogenetic proteins (BMPs) belong to the transforming growth factor-β (TGF-β) superfamily of regulatory peptides. The BMPs have been shown to play a broad array of biological actions on various cell types such as monocytes, epithelial cells, mesenchymal cells, and neurons.[1] BMP-2, BMP-4, and BMP-7 are among the best-studied members of the BMP family of regulatory peptides. The physiological importance of these BMPs has been underscored by the observation that mouse embryos homozygous for either the BMP-4 or BMP-2 null alleles exhibit embryonic lethality. Similarly, BMP-7 knockout mice die shortly after birth with defects in the morphogenesis of kidneys and eyes.[1] BMP-2, BMP-4, and BMP-7 appear to be significantly expressed in gastrointestinal tissues, where they have been shown to play an important role in the regulation of gastrointestinal growth and differentiation.[2–11]

Bone Morphogenetic Protein Signaling

The BMPs activate several complex signal transduction pathways to exert their biological actions.[1,12–15] In particular, binding of the BMPs to the BMP type I receptor (BMPR-I) leads to the dimerization of BMPR-I with the BMP type II receptor, a molecule that has serine/threonine kinase activity. This event triggers the phosphorylation of both BMPR-I and the regulatory proteins Smad 1, 5, and 8, which are known as R-Smads, which mediate the intracellular actions of the BMPs. On phosphorylation, Smad 1, 5, and 8 associate with Smad 4 in a heterodimeric complex that translocates to the nucleus where it activates the transcription of BMP-regulated genes[1,12] (Figure 1). In contrast to the BMPs, TGF-β peptides signal to the nucleus through the phosphorylation and activation of a different set of regulatory Smad proteins, Smad 2 and 3, which bind Smad 4 to induce gene transcription. The complexity of this system is underscored by the observation that the inhibitory proteins Smad 6 and Smad 7 block the effects of BMP-activated signaling, thus generating a negative feedback loop that controls the level of activation of BMP-mediated signal transduction. Smad 6 and Smad 7 are therefore classified as inhibitory Smads. Although Smad 7 inhibits both TGF-β and BMP-mediated signals, Smad 6 is a relatively specific inhibitor of BMP signaling because it only weakly affects the actions of TGF-β.[16] The actions of the BMPs can be blocked by inhibitory molecules such as noggin, gremlin, and chordin, which are expressed in tissues to modulate the level of BMP signaling.[14] Of these, noggin, a secreted polypeptide present in several mammalian tissues, has been shown to bind to and inhibit the actions of extracellular BMP-2, BMP-4, and to a lesser extent BMP-7.[3,6,17–19] In addition to Smad-dependent

Abbreviations used in this paper: **BMP, bone morphogenetic protein; BMPR-I, BMP type I receptor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-related kinase; IL, interleukin; SPEM, spasmolytic polypeptide expressing metaplasia; TFF2, trefoil factor family 2; TGF, transforming growth factor; TNF, tumor necrosis factor.**

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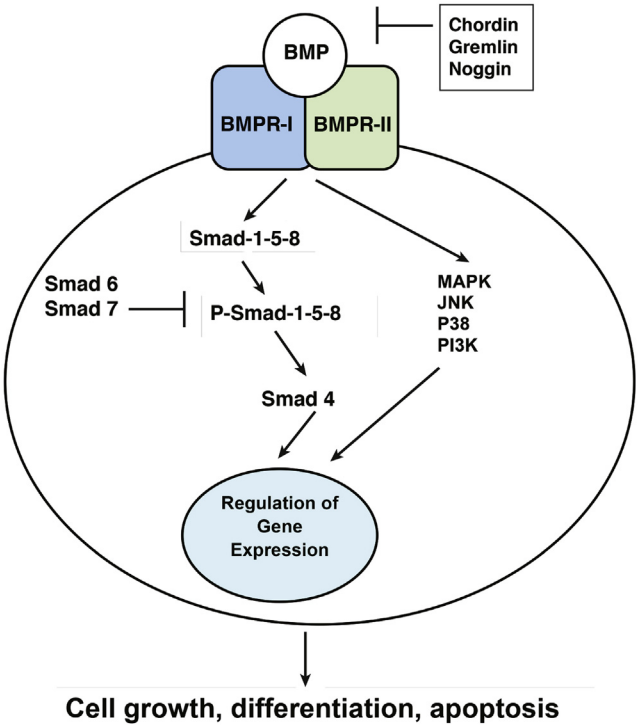

Figure 1. BMP signaling. Binding of BMPs to BMPR-I leads to dimerization of BMPR-I with BMP type II receptor, a molecule that has serine/threonine kinase activity. This event triggers phosphorylation of both BMPR-I and of Smad 1, 5, and 8, proteins known to mediate the intracellular actions of BMPs. On phosphorylation, Smad 1, 5, and 8 associate with Smad 4 in a heterodimeric complex that translocates to the nucleus where it activates the transcription of BMP-regulated genes. BMP signaling is negatively regulated by the inhibitory Smad proteins, Smad 6 and 7, and by secreted BMP inhibitors such as chordin, gremlin, and noggin that bind to BMPs, blocking their ability to activate signal transduction. In addition to Smad-mediated signaling, BMPs can activate in some systems signal transduction cascades that lead to activation of mitogen-activated protein kinase (MAPK), Jun N-terminal kinase (JNK), P38 kinase, and PI3 kinase.

signaling, the BMPs have also been shown to activate in some biological systems the extracellular signal-related kinases (ERKs), PI3 kinase, the P38 kinases, and the C-jun N-terminal kinases.[14]

Localization of Bone Morphogenetic Protein-4 and of Cell Receiving Bone Morphogenetic Protein–generated Signals in the Gastric Mucosa

A series of recently published reports from our laboratory have examined the localization of BMP-4–expressing cells in the gastric mucosa in both the presence and absence of inflammation[20] in genetically engineered mice that express a β-galactosidase marked allele of the BMP-4 gene (BMP-4$^{\beta gal/+}$ mice). X-gal staining of the gastric mucosa of BMP-4$^{\beta gal/+}$ mice indicated that BMP-4 is expressed in mesenchymal cells located both under and between the glands. To analyze the pattern of expression of BMP-4 during inflammation, BMP-4$^{\beta gal/+}$ mice were infected with *Helicobacter felis* for 2 months. *H felis* induced the expression of TNF-α, MIP-2, and interferon-γ mRNAs in these mice, and it led to the development of significant foci of inflammatory infiltrates in the mucosa of the corpus.[20] Moreover, staining of corresponding sections with X-gal demonstrated that BMP-4 is expressed in clusters of cells that appear to be localized in the mesenchymal layers of the mucosa that are adjacent to but not in the inflammatory infiltrates.[20] Localization of cells receiving BMP-generated signals was determined in experiments with transgenic mice that express β-galactosidase under the control of a BMP-responsive element. In this system X-gal positively stained cells could be detected mostly at the level of the isthmus and neck of the glands but not in the mesenchyme in both the absence and presence of inflammation.[20] Similar results were observed when sections of the gastric mucosa of *Helicobacter pylori*–infected mice were stained with antibodies recognizing phosphorylated and active forms of the BMP-4 signal transducing proteins, Smad1, 5, and 8.[20] Thus, studies conducted with 2 different experimental approaches in the presence of 2 types of *Helicobacter* organisms confirmed the notion that BMP-generated signals specifically target cells located in the epithelium but not in the mesenchyme or in the inflammatory infiltrates.

Immunohistochemical analysis of sections of the fundic mucosa of *H felis*–infected BMP-4$^{\beta gal/+}$ mice demonstrated that BMP-4 expression can be predominantly detected in alpha smooth muscle actin–positive cells. No significant BMP-4 expression could be identified in cells expressing macrophage, B, T, dendritic, and neutrophil markers.[20] Thus, myofibroblasts but not immune cells appear to represent the main source of BMP-4 expression in the gastric mucosa.

Bone Morphogenetic Protein Signaling Regulates Gastric Epithelial Homeostasis

The oxyntic mucosa is a complex structure that contains several types of highly specialized cells such as mucus pit, mucus neck, parietal, zymogenic, and endocrine cells. The mechanisms and the factors that regulate the homeostasis of the gastric epithelium have been only partially characterized.[21]

Studies from our laboratory have shown that incubation of cultured parietal cells with BMP-4 leads to stimulation of H^+/K^+-adenosine triphosphatase α-subunit gene expression and to enhancement of secretagogue-stimulated gastric acid production,[22] suggesting that BMP signaling exerts regulatory effects on the physiological function of the gastric parietal cells.

Several reports have shown that the parietal cells play an important role in the process of differentiation and development of other cell lineages in the gastric mucosa. Indeed, studies have shown that loss of mature parietal cells leads