MINIREVIEW

# Bone Morphogenetic Proteins and Their Receptors in the Eye

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**The human genome encodes at least 42 different members of the transforming growth factor-β superfamily of growth factors. Bone morphogenetic proteins (BMPs) are the largest subfamily of proteins within the transforming growth factor-β superfamily and are involved in numerous cellular functions including development, morphogenesis, cell proliferation, apoptosis, and extracellular matrix synthesis. This article first reviews BMPs and BMP receptors, BMP signaling pathways, and mechanisms controlling BMP signaling. Second, we review BMP and BMP receptor expression during embryonic ocular development/differentiation and in adult ocular tissues. Lastly, future research directions with respect to BMP, BMP receptors, and ocular tissues are suggested.** Exp Biol Med 232:979–992, 2007

**Key words:** bone morphogenetic proteins; bone morphogenetic protein receptors; bone morphogenetic protein signaling; ocular tissues

## Introduction

Bone morphogenetic proteins (BMPs) are secreted proteins that constitute the largest subfamily within the transforming growth factor-β (TGF-β) superfamily of growth factors. The TGF-β superfamily also includes TGF-β1 through TGF-β3, activins/inhibins, nodal, myostatin, and anti-Mullerian hormone (1). BMPs were originally identified as osteoinductive growth factors that promoted bone and cartilage formation. However, BMPs are expressed in a number of other tissues and are involved in development, morphogenesis, cell proliferation, and apoptosis. It is becoming clear that BMPs have multiple functions in the body, and it has recently been suggested that this subfamily of growth factors should more accurately be referred to as "*body* morphogenetic proteins" (2). A number of BMPs have been implicated in the pathophysiology of several diseases, including cancer, osteoporosis, kidney diseases, pulmonary hypertension, arthritis, and cerebrovascular disease (3).

Numerous reports have demonstrated BMP expression and function in adult and embryonic ocular tissues. However, no review article has attempted to summarize this body of literature. In this article, we first introduce BMPs and BMP signaling and then discuss various cellular mechanisms that control/modify BMP signaling. We then review the body of literature that demonstrates the role of BMPs in embryonic development and differentiation of ocular tissues. This section is followed by a discussion of the role(s) of BMPs in adult ocular tissues. The review article concludes with a discussion of future directions that would aid our understanding of the role of BMPs in ocular tissues.

## BMPs

Members of the BMP subfamily of growth factors can be classified into several subclasses based on structural similarities (4). For example, BMP-2 and BMP-4 have 80% amino acid homology and constitute class 1. Members of class 2 consist of BMP-5, BMP-6, and BMP-7 and have 78% amino acid homology. Class 3 consists of BMP-3

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because its amino acid structure is significantly different from that of the other BMPs. It should be noted that BMP-1 has been erroneously included as a member of the BMP subfamily. BMP-1 is actually a protease that cleaves procollagen and has no homology to other BMPs (5). In addition, BMP nomenclature has been diverse. In an attempt to help the reader, alternative names for BMPs are included in Table 1.

BMPs primarily exist as homodimers. The BMPs are synthesized as precursor proteins that contain a hydrophobic secretory sequence and propeptide sequence. The mature BMP is located at the carboxy-terminal region of the precursor molecule, and mature proteins are derived from proteolytic cleavage of this carboxy-terminal region (6). Unlike TGF-β growth factors, BMP proforms do not form latent complexes with their mature counterparts. Cleavage of the variable-length prosegment occurs prior to secretion. As processing proceeds, specific proteolytic enzymes cleave the dimerized proprotein at an RXXR site. This results in the generation of the biologically active dimeric mature protein. Cho *et al.* (7) reported that BMP-4 is proteolytically activated by furin and/or proconvertase-6 (PC-6).

A distinguishing structural feature of members of the TGF-β superfamily, including BMPs, is the presence of seven conserved cysteines. Six of the conserved cysteines are involved in the formation of intrachain disulfide bonds that permit folding of the molecule into a unique three-dimensional structure called a cystine knot (8, 9). The seventh cysteine residue makes a single interchain disulfide bridge between the two subunits. This results in the formation of a covalently linked dimer, which is critical for biological activity (10–12). Each mature BMP molecule may be either a disulfide-linked *homodimer* consisting of two similar BMPs (e.g., BMP-4/BMP-4) or a disulfide-linked *heterodimer* consisting of two different BMPs (e.g., BMP-2/BMP-4). The existence of homodimers and/or heterodimers may allow for variability of BMP interactions with receptors leading to activation of different signaling pathways and cell functions.

**BMP Receptors and Signaling Pathways.** *BMP Receptors.* An in-depth review of BMP signaling has recently been published (8). Signaling by BMP ligands involves two types of transmembrane serine/threonine kinase receptors termed type I (BMPR-I) and type II (BMPR-II) (9, 10). Both types of receptors are needed to form a functional complex to initiate downstream signaling events. BMPR-I and BMPR-II are expressed at the cell surface as homeric and heteromeric complexes. The serine/threonine kinase domains of the type II receptor are constitutively active and, upon BMP binding, phosphorylate Gly-Ser domains in the type I receptor (Fig. 1).

BMPs can interact with two distinct type I receptors that are activin receptor–like kinases (ALK). Type I receptors are termed BMPR-IA (ALK-3) and BMPR-IB (ALK-6). These type I receptors are structurally similar to one another. BMP-2 and BMP-4 preferentially bind to BMPR-IA and BMPR-IB, respectively. BMPs can interact with three distinct type II receptors (BMPR-II, ActR-II, and ActR-IIB). However, the majority of BMP signaling utilizes the BMPR-II receptor. The BMPR-II receptor has a long C-terminal tail following the serine/threonine kinase domain (13). Upon binding of BMP ligand to the BMP receptor complex, either the canonical Smad-dependent pathway or the Smad-independent signaling pathway is activated (see below). BMPR-IA, BMPR-IB, and BMPR-II are expressed differentially in various cells, and the pattern of receptor expression can influence cellular responses to BMPs.

Two interesting questions are why are two different BMP type I receptors (e.g., BMPR-IA and BMPR-IB) needed and how are they utilized? Because the specificity of intracellular signals is determined by type I receptors, the differential expression of BMPR-IA and BMPR-IB may be significant in understanding the pleiotrophic effects of BMP action. Gilboa *et al.* (12) showed that the oligomerization pattern of the BMP receptors is quite different from that of receptors used by other members of the TGF-β superfamily. For example, BMP receptor oligomers are present at the cell surface prior to ligand binding, with heteromeric complexes of BMPR-II/BMPR-IA or BMPR-II/BMPR-IB being the most prominent. This subpopulation of preformed heteromeric receptor complexes is unique to the BMP receptors. This finding implies that if such complexes transduce specific ligand-induced signals, the signals should be mediated by conformational changes within the subunits in the complex upon ligand binding. Interestingly, Nohe *et al.* (14) demonstrated that the mode of BMP receptor oligomerization determines which BMP signaling pathway is activated. Prior to ligand binding, a measurable level of BMP receptors is found as *preformed* hetero-oligomeric complexes. However, the majority of the receptors are *recruited* into hetero-oligomeric complexes only after ligand addition. For this latter event to occur, BMP first binds to BMPR-II that then recruits a specific BMPR-I into the signaling complex. They reported that BMP binding to *preformed* receptor complexes activates the Smad signaling pathway, whereas BMP-induced *recruitment* of receptors activates a Smad-independent signaling pathway (Fig. 2). The most likely Smad-independent pathway to be activated *via* recruitment of receptors appears to be the p38 MAPK pathway. The presence of preformed receptor complexes or the recruitment of receptors following BMP binding has not been studied adequately in any ocular cell population.

*Smad-Dependent Signaling.* Upon ligand binding, BMP signaling is conveyed from the cell membrane to the nucleus by the Smad family of proteins/transcription factors (11, 12). An excellent review article on Smad protein/transcription factors has recently been published by Massague *et al.* (15) and should be consulted for a detailed description of the Smad-dependent signaling pathway. The Smad protein/transcription factors are subdivided into three separate classes: receptor Smads (R-Smads), common Smad (Co-Smad4), and inhibitory Smads (I-Smads). In Smad-

**Table 1.** Alternative Names for BMPs

| BMP family member | Alternative title (symbol) |
|---|---|
| BMP-1 | Tolloid, procollagen C–proteinase |
| BMP-2 | BMP2A |
| BMP-3 | Osteogenin |
| BMP-3B | Growth differentiation factor 10 (GDF10), Sumitomo-BIP |
| BMP-4 | BMP2Bp, BMP2B1 |
| BMP-5 | — |
| BMP-6 | VG1-related sequence (VGR1), DVR6 |
| BMP-7 | Osteogenic protein 1 (OP1) |
| BMP-8 | Osteogenic protein 2 (OP2) |
| BMP-8B | Osteogenic protein 3 (OP3), PC8 |
| BMP-9 | Growth differentiation factor 2 (GDF2) |
| BMP-10 | — |
| BMP-11 | Growth differentiation factor 11 (GDF11) |
| BMP-15 | Growth differentiation factor 9B (GDF9B) |

dependent BMP signaling, binding of BMP to constitutively active BMPR-II causes phosphorylation of the Gly-Ser domain of BMPR-I. Subsequently, activated BMPR-I docks with and phosphorylates R-Smads. In BMP signaling the R-Smads are R-Smad1, R-Smad5, and R-Smad8, while in TGF-β signaling R-Smad2 and R-Smad3 are utilized (15). Phosphorylated R-Smads subsequently assemble with and form heteromeric complexes with Co-Smad4. Co-Smad4 is a common partner for all R-Smads (14, 16, 17). The heteromeric complex consisting of R-Smad1, R-Smad5, R-Smad8, and Co-Smad4 protein then translocates into the nucleus to regulate transcription of specific target genes (Fig. 1). While R-Smad1, R-Smad5, and R-Smad8 are structurally similar, there appear to be functional differences. For example, BMP-6 and BMP-7 can activate both R-Smad1 and R-Smad5 but have no effect on R-Smad8, whereas BMP-2 can activate all three BMPR-Smad proteins (18). I-Smad6 and I-Smad7 are inhibitory Smads that block Smad-receptor interactions and can also block Smad-Smad interactions, thus downregulating BMP signaling. These will be discussed in detail later in the review article.

Smad proteins consist of two globular regions connected *via* a linker region (15). The globular regions are composed of Mad homology domains (MH1 and MH2) consisting of conserved N-terminal and C-terminal regions on both R-Smads and Co-Smad4. The linker region contains binding sites for Smurf ubiquitin ligases, MAP kinase phosphorylation sites, and, in the case of Co-Smad4, a nuclear export signal site. While the MH2 domain is highly conserved in all Smad proteins, the MH1 domain is conserved only in the R-Smads and Co-Smad4. MH1 domains are involved in binding to specific DNA sequences. The MH2 domains appear to have several functions: (i) interaction with type I receptors, (ii) oligomer formation with other Smad proteins, (iii) activation of transcription, (iv) interaction with cytoplasmic retention proteins, and (v) interaction with nucleoporins of the nuclear pore complex (11, 15).

Recently, it has been shown that in the absence of BMP/TGF-β ligands, R-Smads and Co-Smad4 shuttle constantly between the cytoplasm and nucleus (15). Receptor-mediated phosphorylation of R-Smads allows accumulation of R-Smads in the nucleus and recognition by Co-Smad4. The accumulation of R-Smads in the nucleus following receptor-mediated phosphorylation is a result of decreased affinity of R-Smads for cytoplasmic anchors and an increased affinity of R-Smads for nuclear factors (15). Dephosphorylation of R-Smads stimulates a return to the cytoplasm where they are subsequently available for another round of receptor-mediated phosphorylation followed by nuclear translocation. Until recently, the phosphatases involved in R-Smad dephosphorylation were unknown. Knockaert *et al.* (19) identified a family of small C-terminal domain phosphatases termed SCPs (SCP-1–SCP-3) that selectively dephosphorylated Smad1 in mammalian cells. In addition, they utilized RNAi depletion of SCP-1 and SCP-2 to extend the duration of Smad1 activation and strengthen the gene response to exogenous BMP. Thus, SCPs appeared capable of reversing receptor-mediated phosphorylation of Smad1.

*Smad-Independent Signaling.* Smad-independent signaling pathways have been reported to include ERK, JNK, and p38 MAPK (16) and are collectively called the "noncanonical" BMP signaling pathways.

The mitogen-activated protein kinases (MAPK) are a family of serine/threonine kinases that transduce signals from the cell membrane to the nucleus in response to a wide range of stimuli (17). Upon stimulation, MAPKs phosphorylate specific substrates at serine and/or threonine residues. Conventional MAPKs comprise three families: (i) the extracellular signal-regulated kinase (ERK) family, (ii) the c-Jun NH2-terminal kinase (JNK) family, and (iii) the p38 family (20). The p38 MAPK cascade regulates a variety of cellular responses. The p38 MAPK is relatively inactive in the nonphosphorylated state and becomes rapidly activated by phosphorylation of two Thr-Gly-Try motifs. Functional events attributed to p38 MAPK activation are varied and complicated and include cell-cycle arrest, apoptosis, cell survival, cytokine production, regulation of RNA splicing, cell growth, and cell differentiation (20).

BMP signaling through p38 MAPK has recently been reported. Iwasaki *et al.* (21) demonstrated that activation of the p38 MAPK pathway is necessary for BMP-2–induced neuronal differentiation of PC-12 cells. In addition, they reported that activation of p38 MAPK was sustained for 4 hours. Iwasaki *et al.* (21) and Kimura *et al.* (22) also demonstrated that BMP-2 activated TGF-β–activated kinase (TAK1) and subsequently phosphorylated p38 MAPK. BMP-2 dose-dependently induced apoptosis in mouse MH60 cells. Cells that expressed I-Smad6 (an inhibitory Smad) were resistant to apoptosis. Tazoe *et al.* (23) reported the involvement of p38 MAPK in BMP-4–induced

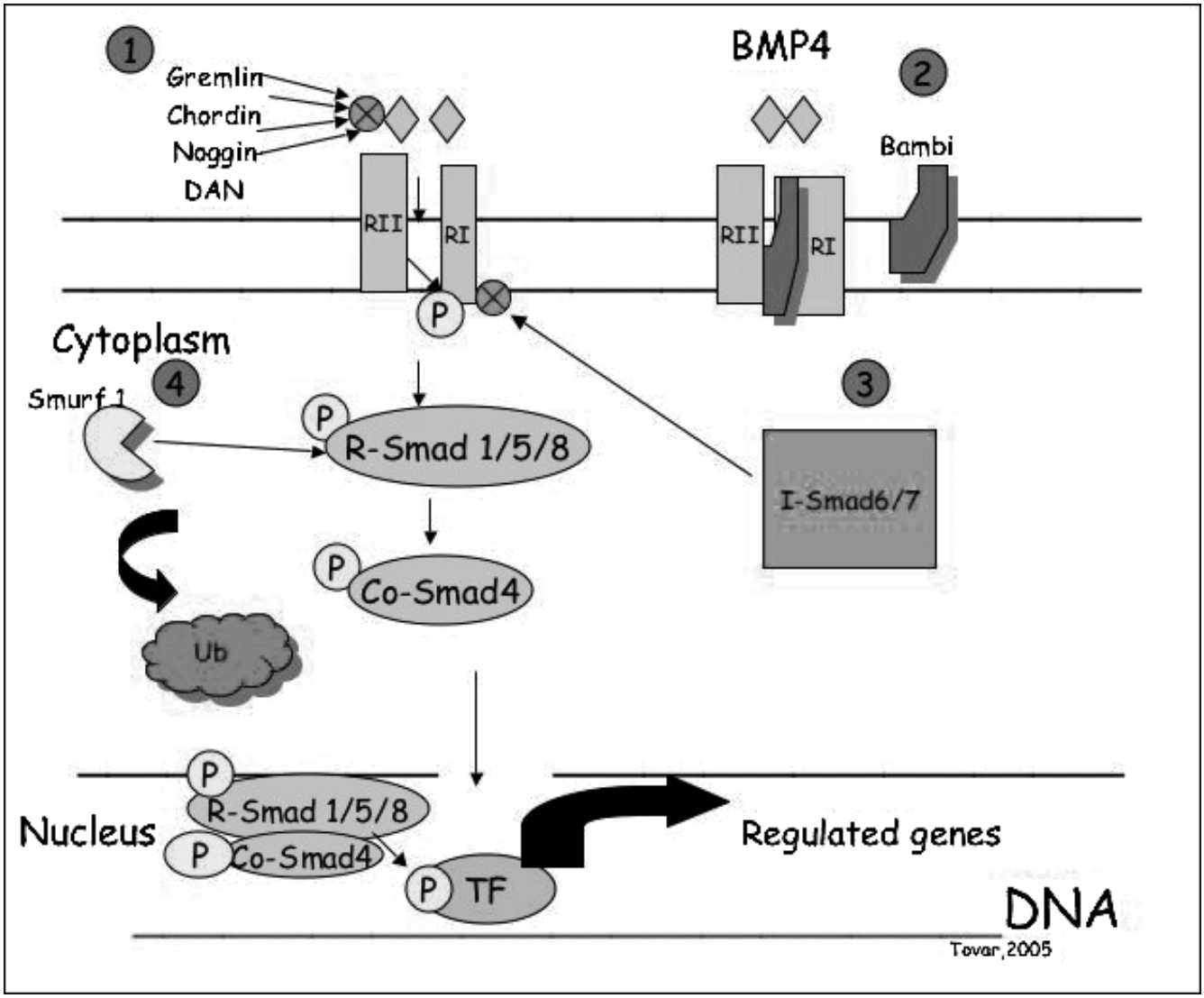


**Figure 1.** Schematic representation of the canonical BMP signaling pathway and mechanisms of signal inhibition. Signaling by BMP involves two types of transmembrane serine/threonine kinases termed type I (BMPR-I) and type II (BMPR-II) receptors. BMP signaling is conveyed from the cell membrane to the nucleus by the Smad family of proteins. Ligand-activated BMPR-I phosphorylates receptor Smad1, Smad5, or Smad8. Phosphorylated receptor Smads subsequently assemble with and form a heteromeric complex with a common Smad4 (Co-Smad4). The heteromeric complex consisting of a receptor Smad and the common Smad then translocates into the nucleus to regulate transcription of specific target genes. The biological activities of BMPs that are transduced *via* the canonical Smad signaling pathway can be inhibited *via* (1) extracellular control of ligand access to receptors by BMP antagonist–binding proteins (e.g., gremlin), (2) membrane expression of BAMBI, which competes with BMPR-I for ligand binding, (3) intracellular modulation of BMP signal transduction in target cells *via* inhibitory Smads, and (4) Smurf-1, which specifically targets Smad1 and Smad5 for ubiquitination and proteosomal degradation.

osteoprotegerin expression in mouse bone marrow–derived stem cells. Lastly, pressure-induced phosphorylation of p38 MAPK in epithelial cells was demonstrated to be mediated *via* Src and protein kinase C, and suppression of p38 MAPK function, achieved by using specific inhibitors, blocked the pressure-mediated phosphorylation of heat shock protein 27 (HSP27) (24). Clearly it would be of great interest to know whether BMPs signal *via* p38 in cells derived from ocular tissues.

**Regulation of BMP Signaling.** BMP signaling is regulated at the cellular level by specific spatial and temporal control mechanisms. Most of the mechanisms to control BMP signaling are inhibitory. The biological activities of BMP that are transduced *via* the canonical Smad signaling pathway can be inhibited *via* (i) *extracellular* control of ligand access to receptors *via* BMP antagonist binding proteins or through the pseudoreceptor called the BMP and activin membrane–bound inhibitor (BAMBI) and (ii) *intracellular* modulation of BMP signal transduction. The interaction of BMPs and inhibitory mechanisms helps determine BMP action in specific cell contexts. The inhibitory molecules are summarized in Table 2. We will briefly review the extracellular and intracellular mechanisms to control BMP signaling (Fig. 1). A recent

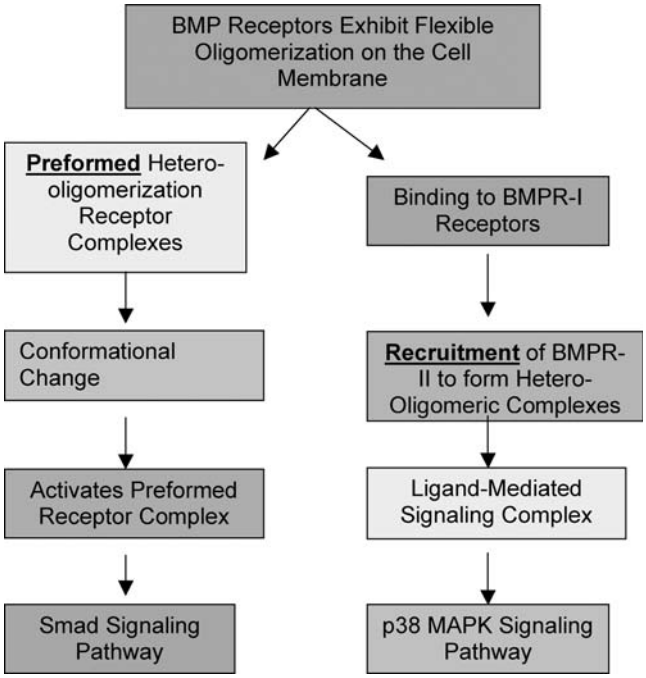


**Figure 2.** Schematic representation of the influence of the BMP receptor oligomerization pattern on signaling pathway activation. BMP receptor oligomers are present at the cell surface prior to ligand binding, with heterocomplexes of BMPR-II and BMPR-Ia and BMPR-Ib being the most prominent. This finding implies that if such complexes transduce specific ligand-induced signals, they should be mediated by conformational changes within the subunits in the complex upon ligand binding. Prior to ligand binding, a measurable level of BMP receptors is found as *preformed* hetero-oligomeric complexes. However, the majority of the receptors are *recruited* into hetero-oligomeric complexes after ligand addition. BMP binding to preformed receptor complexes activates the Smad signaling pathway, whereas BMP-induced recruitment of receptors activates a Smad-independent signaling pathway *via* p38 MAPK.

review on BMP inhibitory molecules has been published and should be consulted for greater details (3).

*Extracellular Inhibition of BMP Signaling.* In addition to spatial and temporal expression of BMPs and BMP receptors in tissues, it is now recognized that a very specific class of molecules, collectively referred to as BMP antagonist proteins, regulate BMP signaling (3, 25). Examples of BMP antagonist proteins include noggin, chordin, follistatin, and members of the DAN (differential screening-selected gene and members aberrative in neuroblastoma) family including cerebus, caronte, Drm/gremlin (GREM1 and GREM2), and Dan. These proteins contain a cysteine knot motif similar to that observed in other TGF-β superfamily members. The mechanism of inhibition appears to be direct binding to the BMP ligand by the antagonist, thus preventing BMP from interacting with the receptor complex (26). Because the concentration of the BMP is critical for various biological responses, the presence of antagonists is necessary to control the biological activity of BMPs. There is a fine balance between BMP activity and inhibition. This balance occurs through spatial and temporal expression of BMPs, BMP receptors, and BMP antagonist proteins. Previous reports suggested that BMP antagonist proteins are likely to play an important role in regulating multiple cell functions during early development and in adult tissues (27). It is now recognized that BMP antagonist proteins bind distinct BMPs with different affinities. For example, noggin binds BMP-2, BMP-4, BMP-5, and BMP-6 with various degrees of affinity, while Drm/gremlin binds BMP-2, BMP-4, and BMP-7 with high affinity. The expression of BMP antagonist proteins in ocular tissues has not been extensively studied.

Another extracellular mechanism to regulate BMP signaling is through BAMBI. This molecule acts as a pseudoreceptor. BAMBI structurally resembles BMPR-I, but BAMBI lacks the intracellular serine/threonine kinase domain (28). BAMBI competes with BMPR-IA and BMPR-IB for ligand binding, thus inhibiting the downstream signaling of the BMP ligand. It is possible that BAMBI functions as a dominant negative receptor (Fig. 1). Only a few studies have examined the expression of BMP antagonist proteins and BAMBI in ocular tissues (see below).

*Intracellular Inhibition of BMP Signaling.* The action of BMP on a target cell can also be controlled or modified by regulating the BMP signaling pathway within the target cell (29). The most widely studied mechanism of intracellular control of BMP signaling involves I-Smads (26–33). Inhibitory Smads (e.g., I-Smad6 and I-Smad7) are negative regulators of BMP signaling and regulate cellular responses through multiple mechanisms. I-Smads can physically interact with activated type I receptors and thus compete with R-Smads (e.g., R-Smad1, R-Smad5, and R-Smad8) (26, 27, 30, 31). In addition, I-Smads interact with activated R-Smads and prevent formation of the R-Smad/Co-Smad4 complex. It appears that I-Smad6 inhibits BMP signaling preferentially, while I-Smad7 inhibits both BMP and TGF-β signaling. Interestingly, Miyazono (11) reported that TGFβ superfamily ligands, including BMP, induce expression of I-Smads. This result suggests that I-Smads can act as part of an autocrine negative feedback loop.

Smad ubiquitination regulatory factor (Smurf-1 and Smurf-2) is also an intracellular inhibitory molecule in target cells. These proteins are members of the ubiquitin enzyme family that participate in a cascade of ubiquitin transfer reactions. Specifically, the Smurfs are members of the E3 ubiquitin ligases. Smurf-1 targets R-Smad1 and R-Smad5 for ubiquitination and proteosomal degradation and appears to specifically control BMP signaling (30). Interestingly, Smurf-1 appears unique because it reduces the intracellular levels of R-Smads independently of BMP ligand stimulation. Thus, it appears that Smurfs control BMP signaling by acting at two different levels of the BMP-Smad signaling cascade: at the level of R-Smads and at the receptor level (25, 29). In addition, MAPK can phosphorylate the linker region of R-Smads and thus prevent nuclear translocation of the R-Smad/Co-Smad4 complex (31). A recent publication by Sapkota *et al.* (34) reported that Smad

**Table 2.** Human BMP Signaling Antagonist Proteins

| Protein location | Approved gene name | Approved gene symbol | Chromosome location | Sequence accession no. | Protein function |
|---|---|---|---|---|---|
| Cell membrane | | | | | |
| | BMP-activin-membrane-bound inhibitor homolog | BAMBI | 10q12.3-p11.2 | NM_012342 | Transmembrane pseudoreceptor blocks ligand binding to BMP receptors |
| Secreted | | | | | |
| | Chordin | CHRD | 3q.27 | NM_003741 | Binds BMP-2 and BMP-4 |
| | Chordin-like 1 (ventroptin) | CHRD1 | Xq.23 | NM_145234 | Binds BMP-4 |
| | Chordin-like 2 | CHRD2 | 11q.23 | NM_015424 | Inhibits BMP activity |
| | Noggin | NOG | 17q22 | NM_005450 | Binds BMP-2,-4 with high affinity |
| | Twisted gastrulation homologue | TWSG1 | 18p11.3 | NM_020648 | Forms a complex with BMP/chordin |
| | Gremlin 1 (DRM) | GREM1 | 15q11–13 | NM_013372 | Binds BMP-2 and BMP-4 |
| | Gremlin 2 (PRDC) | GREM2 | 1q43 | NM_022469 | Binds BMP-2 and BMP-4 |
| | Cysteine-rich secretory protein 10 (CoCo) | CRISPLD1 | 8q21.13 | NM_031461 | Blocks BMP and Wnt signaling |
| | Cerberus 1 | CER1 | 9p22-p23 | NM_005454 | Binds BMP-4 |
| | Dan | DAN | 1p36.12 | NM_005380 | Binds BMP-2 and BMP-4 |
| | Sclerostin domain containing 1 (USAG-1) | SOSTDC1 | 7q21.2 | NM_015464 | Binds BMP-2,-4,-6,-7 with high affinity |
| | Sclerostenosis | SOST | 17q12-q21 | NM-025237 | Binds BMP-6,-7 with high affinity |
| Intracellular | | | | | |
| | Smad6 | SMAD6 | 15q21-q22 | NM_005585 | Receptor Smad degradation |
| | Smad7 | SMAD7 | 18q21.1 | NM_005904 | Receptor Smad degradation |
| | SMAD-specific E3 ubiquitin protein ligase 1 | SMURF1 | 7q21.1-q31.1 | NM_020429 | Receptor Smad degradation |
| | SMAD-specific E3 ubiquitin protein ligase 2 | SMURF2 | 17q22-q23 | NM_022739 | Receptor Smad degradation |
| | Ring finger protein 111 | RNFIII | 15q21 | NM_017610 | Receptor Smad degradation |
| | STAM binding protein | STAMBP | 2p24.3-p24.1 | NM_006463 | I-Smad6 degradation |
| | Transducer of ERBB2, 1 | TOB1 | 17q21 | NM_005749 | Receptor Smad degradation |
| | Transducer of ERBB2, 2 | TOB2 | 22q12.3 | NM_016272 | Receptor Smad degradation |
| | v-ski sarcoma viral oncogene | SKI | 1q22-q24 | NM_003036 | Smad2 and Smad3 |
| | SKI-like (SnoN) | SKIL | 3q26 | NM_005414 | Smad2 and Smad3 |
| | Dachshund homologue 1 | DACH1 | 13q22 | NM_004392 | Smad4 inhibition |
| | Dachshund homologue 2 | DACH2 | Xq21.3 | NM_053281 | Smad4 inhibition |
| | CDKN1A-interacting zinc finger protein 1 | CIZ1 | 9q34.1 | NM_012127 | Antagonizes R-Smad1/5 transcription |

linker phosphorylation restricts R-Smad1 activity by allowing R-Smad1 to be recognized by Smurf-1. Besides initiating degradation, MAPK-dependent Smurf-1 binding caused R-Smad1 to be retained in the cytoplasm, thus preventing transport of the complex into the nucleus. In addition, the study showed that the Smurf-1 interaction with R-Smad1 inhibited R-Smad1 binding to nucleoporin Nup214, thus blocking entrance to the nucleus. Because BMP is known to increase Smurf-1 as well as I-Smads, these interactions indicate that cells exhibit an alternative autocrine mechanism to inhibit BMP signaling.

*Positive Regulation of BMP Signaling.* Other members of the TGF-β superfamily utilize accessory receptors or co-receptors to promote/enhance ligand binding and thus augment signaling. For example, SARA is an anchor/adaptor protein known to facilitate R-Smad interactions with TGF-β receptors. Until recently, accessory receptors or co-receptors had not been identified in BMP signaling. The first co-receptor for BMP signaling to be reported was CD44 (32). CD44 is a receptor for the extracellular matrix (ECM) macromolecule hyaluronan but also modulates R-Smad1 activation in the BMP-7 signaling pathway. R-Smad1 was shown to interact with the cytoplasmic domain of CD44, and perhaps CD44 anchors R-Smad1 for presentation to the BMP type I receptor. Disruption of the hyaluronan-cell interactions results in inhibition of BMP-mediated Smad1 phosphorylation (8) and may be a mechanism to change how a cell responds to BMP.

Recent published reports have shown that DRAGON, a member of the repulsive guidance molecule (RGM) family, binds to BMP-2 and BMP-4 but not BMP-7 to enhance signaling (33). This glycosylphosphatidylinositol-anchored protein associates directly with BMPR-I and BMPR-II. DRAGON appears to be specific for BMP because it has no

effect on TGF-β signaling. Interestingly, a second member of the RGM family, RGMa, has also been recently identified as a co-receptor for BMP signaling (35). RGMa is a DRAGON homologue that enhances BMP but not TGF-β signaling *via* the canonical Smad signaling pathway. It is possible that both DRAGON and RGMa associate with BMP receptors, thus increasing overall binding of the BMP ligand to the BMP receptor complex. The net result would be the enhancement of BMP signal transduction. The presence of positive regulators of BMP signaling has not been studied in ocular tissues.

**BMP Target Genes.** More is known about BMP target gene regulation in bone than in ocular tissues. DNA microarray data have been reported for BMP regulation of osteoblasts (36), endochondral bone formation (37), and osteogenic signaling (38). Osteoprogenitor cells respond rapidly to BMP *via* signal transduction genes including *ID1–3*, *I-Smad6*, *I-Smad7*, *OASIS*, *Prx2*, *TIEG*, and *Snail*. Later responses include those that involve target genes related to osteoblast differentiation, including *Hey1* and *Tif7*. These are transcription factors involved in Notch and Wnt signaling. These data may indicate that BMP, Notch, and Wnt signaling are interrelated in osteoprogenitor cells as well as in other cells.

Smads have been reported to be mediators of the Id proteins (39). This family of proteins consists of helix-loop-helix (HLH) transcription factors (40). Because Id proteins lack a basic DNA-binding domain, they act as inhibitors of basic HLH transcription factors *via* heterodimerization (40, 41). Four different Id members (e.g., Id1–Id4) constitute this family. They have been reported to control a variety of cellular responses including cell growth, differentiation, apoptosis, and tumorigenesis (42). In addition, the activation of I-Smads clearly demonstrates that BMP can activate target genes responsible for controlling BMP signaling *via* a negative feedback loop.

Zwijsen *et al.* (43) listed 20 different target genes responsive to BMP activation. They have also identified I-Smad6 and I-Smad7 genes as targets for BMP activation. In addition, the BMP antagonist protein noggin is upregulated by BMPs. The bone matrix protein osteopontin and homeobox genes *MSX1*, *MSX2*, and *Tlx-2* are activated by BMPs. The *MSX2* gene has been reported to be critical for vascular calcification as well as for bone formation (44).

**Regulation of BMP Target Genes.** When the R-Smad/Co-Smad4 complex reaches the nucleus, Smads can regulate transcription of target genes by (i) directly binding to specific DNA sequences, (ii) interacting with other DNA-binding proteins, or (iii) recruiting transcriptional coactivators or corepressors (Fig. 1). The choice of target genes by an activated R-Smad-Co-Smad4 complex is made in association with specific DNA-binding co-factors. Because the MH-1 domain of the R-Smads is not selective, DNA-binding co-factors are critical in providing tight binding and specific recognition of the regulatory unit of the target genes. Signaling outcomes will be different in different cells depending on the presence of specific DNA-binding co-factors, coactivators, and/or corepressors. The types of nuclear proteins that have been reported to interact with BMP R-Smads include transcription factors (e.g., Runx, Menin, YY1, MyoD, Vent2, and OAZ), transcriptional coactivators, (e.g., p300, CREB binding protein, and GCN5) and transcriptional corepressors (e.g., c-Ski and SnoN). Recent reviews should be consulted for an in-depth understanding of the regulation of BMP target genes (1, 8). Nuclear proteins represent an additional mechanism to control cellular responses to BMPs. Nuclear proteins interacting with BMP R-Smads have not been studied in ocular tissues.

**Physiological Actions of BMP.** The existence of soluble factors that could induce ectopic bone and cartilage formation in muscle or subcutaneous sites was first reported in 1965 (45). Subsequently, it was determined that BMPs play essential roles in bone formation and bone cell differentiation. Most reports concerning the function of BMPs describe their trophic nature in the musculoskeletal system. However, the expression of BMPs and their receptors in many tissues other than bone have suggested that BMPs are also involved in the regulation of many biological processes unrelated to bone formation. BMPs can control a variety of cellular functions; therefore, this subfamily of TGF-β growth factors is considered to be pleiotrophic regulators.

In addition to bone and cartilage, various other organs are sites where BMPs and BMP receptors are present and/or act and include the ovary (46), brain (47), epididymis (48), pancreas (49), breast (50), and kidney (51). These proteins have been shown to regulate many fundamental biological processes such as cell proliferation, differentiation, apoptosis, cell migration, cell adhesion, embryonic development, and ECM synthesis (52). Detmer and Walker (53) demonstrated that BMPs act synergistically with hematopoietic cytokines in the differentiation of hematopoietic progenitors. Liu *et al.* (54) reported that BMP-7 affects functional recovery, glucose utilization, and blood flow following transient focal cerebral ischemia in rats. In addition, BMP-7 provides a neuroprotective function in the adult CNS. BMPs play a role in ECM expression and turnover as well as influence cellular cytoskeletal elements. BMP-4 binds to the basal lamina *via* type IV collagen and heparan sulfate proteoglycans (55). Thus, BMP bound to the basal lamina could influence cellular interactions in diverse tissues. There are inherent benefits for BMP binding to the basal lamina. For example, bound BMP molecules may be protected from proteolytic degradation. Alternatively, bound BMP may undergo controlled release and/or mediate local cellular alterations (56).

**Expression and Function of BMPs in Ocular Development and Differentiation.** Knockout studies have shown that BMPs are essential for early morphogenesis of the eye (51, 57–60). Several BMP family members are expressed during mouse eye development

(61). Most of the data pertaining to BMPs and embryonic development in ocular tissues relate to the lens and retina and are summarized in Table 3.

*Lens.* BMP ligands and BMP receptors play critical roles in lens development (62–68). For example, gene deletion of BMP-4 and BMP-7 influences both lens induction and eye development (51, 57–60, 63, 69). Furuta and Hogan (57) reported that BMP-4 is required for the optic vesicle to manifest its lens-inducing activity by regulating downstream genes and/or serving as one component of multiple inductive signals. Other reports have indicated that BMPs contribute to differentiation of lens fiber cells (63–65, 69).

Beebe *et al*. (66) demonstrated that BMPs and the gene encoding BMPR-IA are essential to lens development. Lenses with targeted deletion of BMPR-IA were smaller than normal, had thin epithelial layers, and lens fiber cells were vacuolated and degenerated shortly after birth. As might be expected, phosphorylated R-Smad1 was reduced in the absence of BMPR-IA. De Iongh *et al*. (67), reported BMP receptor expression in rat lens development. Reverse transcriptase polymerase chain reaction of RNA from postnatal lenses showed distinct expression of BMPR-II and BMPR-IA but not of BMPR-IB. *In situ* hybridization also showed specific localization of these BMP receptors in the ectoderm, lens pit, optic vesicle, and perioptic mesenchyme during early lens formation. However, during subsequent lens differentiation the receptors became increasingly restricted to the lens epithelium and to the equatorial region, including the germinative and translational zones. These are the areas where cells proliferate and begin differentiation. Receptor expression declined rapidly with further fiber differentiation and maturation.

Belecky-Adams *et al*. (70) demonstrated that BMPs participate in the differentiation of chick embryo lens fiber cells. They reported that phosphorylated R-Smad1 localizes to the nuclei of elongating lens fiber cells. In addition, transduction of chicken embryo lenses with constructs that expressed the secreted BMP antagonist noggin, delayed lens fiber elongation, and increased cell death in lens epithelium. The BMP antagonist noggin also inhibited the elongation of lens cells into fiber-like cells when cells were exposed to vitreous humor. Previous studies have indicated that the retina produces factors that promote lens cell differentiation. Therefore, BMPs may be present in the vitreous humor.

Faber *et al*. (65) demonstrated that BMP signaling is required for development of primary lens fiber cells in the mouse. Noggin could suppress primary fiber cell elongation and mouse lens size in explant culture. When dominant negative BMPR-IB was expressed in transgenic mice, the mice showed defects in the differentiation of primary lens fiber cells. These studies suggested that BMP ligand and BMP signaling are important for this aspect of lens development. The authors also used anti–BMPR-II and anti–p-Smad antibodies to demonstrate that equatorial lens fibers have BMP signaling mechanisms and are capable of responding to BMP ligands.

*Retina.* Liu *et al*. (68) reported two distinct requirements for BMPR-IB in mammalian retinal development. First, a targeted deletion of the *BmprIb* gene in mice resulted in failure of ventral ganglion cells to enter the optic nerve. In addition, Liu *et al*. demonstrated a significant elevation of apoptosis in the inner retina during postnatal development. BMP and BMP receptors are expressed by adult retinal-pigmented epithelium (RPE), with BMP-2 and BMP-4 acting as negative growth regulators (71). Their down-regulation might be part of the reparative response allowing other positive growth regulators to stimulate proliferation. Murali *et al*. (72) deleted BMPR-IA within the developing mouse retina, but this led to no detectable eye abnormalities. However, further reduction of BMP signaling by deleting BMPR-IB resulted in abnormal dorsoventral patterning. Further, double BMPR-IA/BMPR-IB mutants had severe eye defects, including failure of retina neurogenesis. The BMP-4 antagonist ventroptin altered expression patterns of several genes in the retina as well as the projection of the retinal axons to the tectum (73).

Belecky-Adams and Adler (70) demonstrated that BMPs, BMP receptors, and BMP antagonist proteins might have a role in the patterning and/or differentiation of the retina. Using *in situ* hybridization, they identified BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP receptors, and BMP antagonist proteins noggin and chordin in the chick embryonic eye. Interestingly, examination of mRNAs showed that they had a spatially restricted pattern of expression. BMP receptors were localized in the ventral portion of the retina and optic stalk. The BMPs and BMP antagonists localized to other regions of the retina or RPE. Trousse *et al*. (74) conducted studies to demonstrate that BMP-4 mediates apoptotic cell death in the developing chick eye. They determined that local BMP-4 was responsible for apoptosis in the dorsal optic cup. In addition, adding the BMP-4 antagonist noggin reduced the rate of cell proliferation in the dorsal optic cup.

Using developing chicken and mouse retina whole mounts, Franke *et al*. (75) reported a significant amount of programmed cell death in the ganglion cell layer following exogenous treatment with BMP-4 and TGF-β. Both pathways did not interact at the ligand, receptor, or Smad protein level but rather at the transcriptional level. Specifically, the signaling pathways converged at the level of the TGF-β immediate-early response gene TIEG and the transcriptional coactivator Gcn5.

*Other Ocular Tissues.* BMP signaling is required for the development of the ciliary body (76). Noggin can block BMP signaling in the mouse eye, and this blockade result in the failure of the formation of the ciliary process. Interestingly, expression of noggin promoted differentiation of retinal ganglion cells. Chang and colleagues (77) showed that a heterozygous deficiency of BMP-4 resulted in anterior segment dysgenesis, elevated intraocular pressure (IOP),

**Table 3.** Summary of BMP, BMP Receptor, and BMP Antagonist Protein Expression by Embryonic Ocular Tissues

| Author | Tissue | BMP, BMP receptor, BMP antagonist | Animal |
|---|---|---|---|
| Luo *et al.* (1995) | Lens | BMP-7 | Mouse |
| Karsenty *et al.* (1998) | Lens | BMP-7 | Human |
| Belecky-Adams *et al.* (2002) | Lens | pSmad1, noggin | Chick |
| Faber *et al.* (1999) | Lens | Noggin, BMPR-IB, BMPR-II, pSmad | Mouse |
| de Iongh *et al.* (2004) | Lens | BMPR-IA, BMPR-IB | Rat |
| Beebe *et al.* (2005) | Lens | BMPR-IA, pSmad1, noggin, follistatin | Mouse |
| Zhao *et al.* (2002) | Ciliary body | Noggin, BMP-7 | Mouse |
| Furuta and Hogan (1998) | Optic cup/lens | BMP-4 | Mouse |
| Liu *et al.* (2003) | Retina | BMPR-IB, BMP-2, BMP-4 | Mouse |
| Murali *et al.* (2005) | Retina | BMPR-IA, BMPR-IB | Mouse |
| Sakuta *et al.* (2001) | Retina | Ventropin | Chick |
| Belecky-Adams and Adler (2001) | Retina | BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP receptors, noggin, chordin | Chick |
| Trousse *et al.* (2001) | Retina | BMP-4, noggin | Chick |

and optic nerve abnormalities. The anterior segment abnormalities were similar to those seen in human patients with developmental glaucoma. Thus, BMP signaling may be involved in conditions associated with human glaucoma. Examination of BMPs and BMP receptors in other ocular tissues during development is needed.

**Expression and Function of BMPs in Adult Ocular Tissues.** It has been recognized only recently that BMPs have a functional role in adult tissues. This realization has opened new areas of study and has demonstrated new functions for BMPs that were not previously appreciated. There has been very little information published concerning the role of BMPs in the postnatal eye. BMPs are expressed in a variety of ocular tissues including the cornea, trabecular meshwork, optic nerve head, and retina. Results that involve these tissues are summarized below and in Table 4.

*Cornea.* Wall *et al*. (78) were the first to report the presence of a BMP in the cornea. They localized BMP-6 in a variety of epithelial tissues in the mouse, including skin, bronchiolar tissue, and cornea. In contrast, the limbus and conjunctival epithelium of the adult mouse did not express BMP-6. BMP-2 and BMP-4 mRNA and proteins were expressed in cultured human corneal epithelial cells, keratocytes, and corneal endothelial cells (79). Each major cornea cell type was positive for BMP-2 and BMP-4 in experiments using immunohistochemistry and fresh frozen human corneas. BMP-2 and BMP-4 stimulated apoptosis of corneal fibroblasts. In addition, Mohan *et al.* (79) reported that human corneal epithelial cells, keratocytes, and endothelial cells also expressed mRNA for BMPR-IA, BMPR-IB, and BMPR-II. The presence of all three BMP receptors in rat corneal and conjunctival epithelium, keratocytes, and corneal endothelium was reported by Obata *et al*. (80). It is possible, if not likely, that BMP-2 and BMP-4 may control other corneal cell functions.

Kim *et al*. (81) studied the effect of BMP-2 and BMP-4 on corneal fibroblast chemotaxis. During early corneal wound healing, apoptosis of stromal keratocytes is followed shortly by repopulation of the anterior stroma with either activated keratocytes or myofibroblast-like cells. BMP-2 and BMP-4 are cytokines that bind to heparin and thus may be released from epithelial cells or the epithelial basal lamina upon corneal injury. Thus, BMP-2 and BMP-4 may stimulate migration and mitosis of keratocytes to re-establish normal cell numbers. Kim *et al*. (81) suggested that BMP and other cytokines are sequestered in the cornea basal lamina and serve as a reservoir to be released following injury to the cornea. In 1999, You *et al*. (82) added BMP-3, BMP-5, and BMP-7 to the list of BMP family members present in the human cornea. Using both *ex vivo* and cultured epithelial and stromal cells, they also confirmed the presence of BMPR-IA, BMPR-IB, and BMPR-II. They reported pronounced differences in expression of BMP in the human cornea, with high levels of BMP-5 and BMP-7 and lower levels of BMP-2 and BMP-4.

A few papers have addressed the role of BMPs in corneal cell differentiation and potential therapeutic uses for BMPs. You and Kruse (83) reported that activin A but not BMP-7 increased α-smooth muscle actin and actin-binding proteins such as smooth muscle myosin, α-actinin, and vinculin during myofibroblast differentiation. They also demonstrated that BMP-7 induced R-Smad1 and that R-Smad1 induction was inhibited by the BMP antagonist follistatin. Saika *et al*. (84) demonstrated the therapeutic effect of BMP-7 on a corneal alkali injury model in the mouse. Resurfacing of the burned cornea by invading conjunctival epithelium was accelerated by adenoviral transduction of BMP-7. In addition, exogenous BMP-7 suppressed the generation of myofibroblasts and the appearance of monocytes and macrophages. Furthermore, exogenous BMP-7 resulted in the activation of R-Smad1, R-Smad5, and R-Smad8. They suggested that BMP-7 is an effective treatment for alkali burns of the cornea.

It is known that limbal epithelium participates in the regeneration of cornea throughout life. One interesting aspect of BMP signaling was reported by Zhao *et al*. (76), who showed the neural potential of cells isolated from the

**Table 4.** Summary of BMP, BMP Receptor, and BMP Antagonist Protein Expression by Adult Ocular Tissues

| Author | Tissue | BMP, BMP receptor, BMP antagonist | Animal |
|---|---|---|---|
| Wall *et al.* (1993) | Cornea | BMP-6 | Mouse |
| Mohan *et al.* (1998) | Cornea | BMP-2, BMP-4, BMPR-IA, BMPR-IB, BMPR-II | Human |
| Obata *et al.* (1999) | Cornea | BMPR-IA, BMPR-IB, BMPR-II | Rat |
| Kim *et al.* (1999) | Cornea | BMP-2, BMP-4 | Human |
| You *et al.* (1999) | Cornea | BMP-3, BMP-5, BMP-7, BMP receptors | Human |
| You and Kruse (2002) | Cornea | BMP-7, Smad1, follistatin | Human |
| Saika *et al.* (2005) | Cornea | BMP-7, Smad1/5/8 | Mouse |
| Toyran *et al.* (2005) | Cornea | BMP-7 | Human |
| Mathura *et al.* (2000) | Retina, RPE | BMP-2, BMP-4, BMPR-II | Human |
| Yu *et al.* (2004) | Retina | BMP-4, Smad4 | Mouse |
| Shen *et al.* (2004) | Retina | BMP-7 | Human |
| Wordinger *et al.* (2002) | Trabecular meshwork | BMP-2, BMP-4, BMP-5, BMP-7, BMP receptors | Human |
| Wordinger *et al.* (2002) | Optic nerve head | Follistatin, Drm/gremlin, chordin, BAMBI | Human |

limbal epithelium of the adult cornea. The acquisition of neural properties by these cells is regulated by BMP-4 signaling and may arise from transdifferentiation or reprogramming of limbal stem cells. Limbal stem cells may possess default neural potential that is suppressed *in vivo* by BMP-4 signaling.

Using immunohistochemistry, Toyran *et al.* (85) examined the expression of BMP-7 in normal human eyes and eyes with osseous metaplasia. Intraocular bone formation can occur in long-term retina detachment and inflammation. It is believed that ectopic ossification may originate in osteoprogenitor stem cells that are dormant within the soft tissues. With stimulus from BMPs, these cells differentiated into osteoblasts that produced osteoid that may calcify (85). The RPE metaplasia that surrounded areas of intraocular ossification exhibited moderate BMP-7 immunoreactivity. Mild BMP-7 staining was observed in metaplastic areas not associated with osseous formation. Interestingly, a significant decrease in BMP-7 labeling was seen in corneal keratocytes in eyes with osseous metaplasia. Therefore, BMP-7 may have an important role in intraocular ectopic bone formation.

The therapeutic effects of BMP-7 in the treatment of corneal alkali injury have been reported by Saika *et al.* (84). They reported that overexpressing BMP-7 *via* adenoviral gene transfer was an effective treatment in mice. Interestingly, BMP-7 had an antagonistic effect on TGF-β–regulated tissue fibrosis but stimulated resurfacing of the cornea *via* invading conjunctival epithelial cells.

*Trabecular Meshwork and Optic Nerve Head.* Our laboratory was the first to report the expression of BMP mRNA and proteins in the adult human trabecular meshwork (TM) and optic nerve head (ONH) (86). In addition, all three BMP receptors (BMPR-IA, BMPR-IB, and BMPR-II) as well as several BMP antagonists were expressed in both of these tissues (86). Not only do TM cells and ONH cells secrete BMPs, but also they are capable of responding to exogenous BMP-4 *via* R-Smad phosphorylation (87).

BMP expression in the TM and ONH may be associated with the pathogenesis of glaucoma. Elevated IOP is an important risk factor in the development of glaucoma as well as in the progression of glaucomatous damage (88). Elevated IOP is due to increased resistance of aqueous humor outflow and appears to be associated with a number of morphological and biochemical changes in the TM (89). There is an accumulation of ECM material in the glaucomatous TM, and this increase may be due to disruption of the normal balance between ECM deposition and degradation (89, 90). In glaucoma, aqueous humor levels of TGF-β2 are elevated, and this increase may contribute to the accumulation of ECM in the TM and increased aqueous outflow resistance. We recently reported that TGF-β2 stimulates the production of the ECM component fibronectin, a finding similar to what occurs in the glaucomatous TM (91). In addition, we demonstrated that BMP4 blocked the TGF-β2 induction of fibronectin in TM cells, and this result suggests that BMPs can modulate the effects of TGF-β2 in TM cells (87). The BMP antagonist gremlin, which is expressed in the TM, reversed the BMP-4 antagonism of TGF-β2. To determine whether there may be defects in the BMP signaling pathway in glaucoma, we compared the expression of BMP-associated genes in normal TM cells with that in glaucomatous TM cells. The expression of gremlin mRNA and protein was greater in glaucomatous TM cells than in normal TM cells. The addition of recombinant gremlin to the medium of perfusion-cultured human eyes caused a significant rise in IOP, mimicking one of the central features of glaucoma (87). These results (summarized in Fig. 3) are consistent with the hypothesis that in primary open angle glaucoma, elevated Drm/gremlin expression by TM cells inhibits BMP-4 antagonism of TGF-β2 and this inhibition leads to increased ECM deposition and elevated IOP (87).

Fuchshofer *et al.* (92) have demonstrated the antagonistic effect of BMP on TGF-β2 signaling. They demonstrated that BMP-7 could inhibit TGF-β2 stimulation of a number of proteins associated with the ECM including connective tissue growth factor, thrombospondin-1, fibronectin, collagen types IV and VI, and PAI-1. BMP-7 alone had no effect. It is possible that new therapies centered on

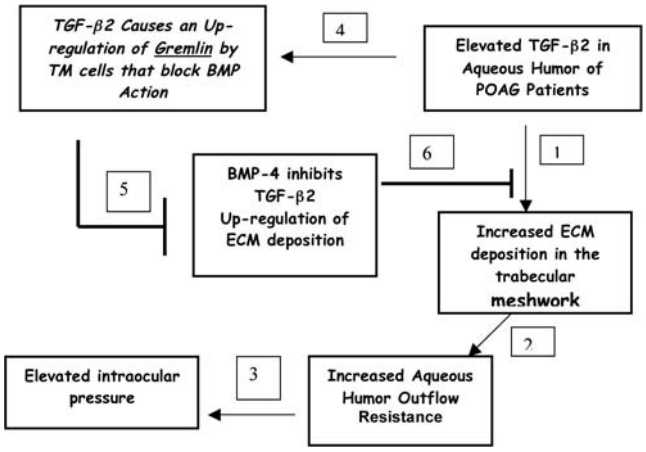


**Figure 3.** Schematic representation of the interactions of BMP-4, TGF-β2, and gremlin within the TM. Elevated TGF-β2 in the aqueous humor of glaucomatous patients leads to increased ECM deposition in the TM (1 in the figure), increased resistance of aqueous humor outflow from the TM (2 in the figure), and elevated IOP (3 in the figure). In addition, elevated TGF-β2 levels appear to cause an upregulation of the BMP antagonist gremlin by the TM cells (4 in the figure). Gremlin is known to bind directly to BMP-4 and prevent its biological activity (5 in the figure). Thus, the ability of BMP-4 to counterbalance the effect of TGF-β2 in the TM is inhibited (see 6 in the figure).

BMP antagonism of TGF-β2 may promise to be a new treatment for glaucoma.

*Retina.* Little information exists about a role for BMPs and BMP receptors in the adult retina. Mathura *et al.* (71) have suggested a role for BMPs in the adult RPE. These authors determined the relative level and localization of BMP mRNA in the adult retina and RPE. BMP-2, BMP-4, and BMPR-II mRNA were detected in adult bovine RPE and mouse retinal neurons. They also noted that oxygen-induced ischemia caused a decrease in BMP-4 mRNA. In addition, mice with inherited photoreceptor degeneration had decreased BMP-4 mRNA expression in the retina and RPE. Mathura *et al.* (71) concluded that BMP-2 and BMP-4 might act as negative growth regulators in the retina and the RPE. They speculated that these modulators are down-regulated in injury and that this downregulation thus allows tissue repair.

Yu *et al.* (93) utilized wild-type (rod-dominant) mice and neural retain leucine zipper knockout (*Nrl-/-*) (cone only) mice to examine altered expression of BMP/Smad genes. Using custom cDNA microarray technology, they reported that BMP/Smad signaling pathway genes are expressed in the mature wild-type retina and that this expression is significantly altered in the *Nrl-/-* mouse. They further demonstrated that BMP-4 and Co-Smad-4 are expressed in mature rod photoreceptors in the mouse. They speculated that BMP/Smad pathways participate in cell-cell communication in the mature mouse retina.

Shen *et al.* (94) determined the effect of BMP-7 on horizontal cells cultured from adult human retina. BMP-7 was detected in all retinal layers, with greatest expression in the inner and outer nuclear layers. BMP-6 and BMP-7 suppressed the kainite receptor current but enhanced AMPA receptor current; BMP-2 had no effect. This action of BMP was rapid and occurred in less than a second. Thus, it appeared that BMPs rapidly regulate two ionotropic glutamate receptors.

Interestingly, Vogt *et al.* (95) reported that BMP-4 enhanced the secretion of vascular endothelial growth factor (VEGF) by human RPE cells. Cells treated with BMP-4 had higher VEGF in the conditioned medium, and the response was dose-dependent and time-dependent. The authors suggested that BMP-4 may be involved in the regulation of ocular angiogenesis associated with diabetic retinopathy *via* stimulation of VEGF by RPE cells.

The role of elevated glucose in the expression of the BMP antagonist protein gremlin has been reported by Kane *et al.* (96). *In vitro* gremlin protein expression by bovine retinal pericytes was induced by elevated glucose. In addition, Kane *et al.* used the streptozotocin-induced diabetic mouse to show that gremlin was elevated in the retina. Further, they reported that gremlin expression was modulated by hyperglycemic induction of the MAPK pathway. Together the results suggested that gremlin may have a role in diabetic retinopathy *via* the inhibition of BMP signaling.

*Conjunctiva.* The expression of BMPs and their receptors was recently reported by Andreev *et al.* (97). They reported that various BMPs and activin A are components of the conjunctival cytokine meshwork regulating tissue homeostasis and wound healing. In particular, BMP-6 and activin A are associated with conjunctival scarring. They suggested that the control of BMP signaling may be important in managing postoperative conjunctival scarring responses in patients with glaucoma.

**Conclusions and Future Directions.** BMPs represent a significant subfamily of the TGF-β superfamily of growth factors. It is now clear that numerous adult and embryonic nonosseous tissues express BMP and BMP receptors. A growing list of functions controlled by BMPs is being discerned and includes morphogenesis, cell proliferation, differentiation, apoptosis, and development. Both canonical (e.g., Smad) and noncanonical (e.g., p38) signaling pathways have been described. Of particular importance is the fact that BMP signaling is very tightly controlled by extracellular and intracellular mechanisms.

It is clear from this review that there are significant gaps in our understanding of the role of BMPs and BMP signaling in embryonic and adult ocular tissues. Expression of BMPs in embryonic ocular tissues has not always been followed with significant studies in adult ocular tissues. For example, studies of BMP and BMP receptor localization have mainly concentrated on the embryonic lens and retina (Table 3). However, few if any studies on BMP expression and function in the adult lens have been reported. Similarly, expression of BMPs in adult ocular tissues does not always correlate with embryonic patterns. For example, studies of

BMP and BMP receptor localization have mainly concentrated on the adult cornea (Table 4). It is also clear that the majority of embryonic studies have utilized the mouse and chick with few human studies reported. The reverse is true with respect to adult ocular tissues: numerous studies of adult human ocular tissues have been reported.

As new information abut other embryonic and adult tissues is reported, it will be important to discern whether similar functions occur in ocular tissues. For example, is the pattern of BMP receptor oligomerization reported in other cell types also important for BMP signaling in ocular tissues? It is now recognized that BMPs play a role in the pathophysiology of several diseases in the adult. These diseases include kidney, cerebrovascular, pulmonary hypertension, arthritis, osteoporosis, and cancer. Are specific ocular disease states correlated with the expression, or lack of expression, of BMPs and/or BMP receptors?

Important advances have been made with respect to specific BMP signaling pathways. These pathways include both the canonical (e.g., Smad) and noncanonical (e.g., MAPK) pathways. Little information has been reported with respect to signaling pathways in ocular tissues. A deeper understanding of the BMP signaling pathway in ocular tissues will help us elucidate the role of BMPs in the molecular mechanisms of ocular diseases. This understanding may lead to new novel therapeutic treatments and strategies.

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