Minireview

Bone morphogenetic protein signaling in inflammation

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Impact statement

By compiling findings from recent studies, this review will garner novel insight on the dynamic and complex role of BMP signaling in diseases of inflammation, highlighting the specific roles played by both individual ligands and endogenous antagonists. Ultimately, this summary will help inform the high therapeutic value of targeting this pathway for modulating diseases of inflammation.

Abstract

Bone morphogenetic protein signaling has long been established as a crucial pathway during embryonic development. In recent years, our knowledge of the function of bone morphogenetic protein signaling has expanded dramatically beyond solely its important role in development. Today, the pathway is known to have important homeostatic functions across multiple different tissues in the adult. Even more importantly, bone morphogenetic protein signaling is now known to function as a driver of diseases in the adult spanning different organ systems. In this review, we will explore the functions of bone morphogenetic protein signaling in diseases of inflammation. Through this exploration, we will highlight the value and challenges in targeting bone morphogenetic protein signaling for therapeutic interventions.

Keywords: Atherosclerosis, myocardial infarction, vascular inflammation, anemia of inflammation, endothelial injury, inflammatory arthritis

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Introduction

Bone morphogenetic protein (BMP) ligands are part of the transforming growth factor-β (TGF-β) superfamily. As their name suggests, BMPs were first observed in the pioneering work by Urist[1] in 1965 where their activity was found to induce ectopic bone formation. Although later Urist was able to isolate the bone inducing proteins,[2] it was not until two decades later that these proteins were individually cloned and characterized.[3] Since then, BMPs have been studied extensively outside of their established role in bone and cartilage and found to possess a multitude of functions in the embryonic development of other organ systems, including blood, heart, vasculature, brain, lung, kidney, and limbs. This review will focus on the emerging role BMPs play in inflammatory processes across organ systems in the adult.

Signaling and regulatory components in the BMP pathway

Subclassification of the more than 15 known BMPs based on phylogenetic analysis of amino acid and nucleotide similarity creates particular subgroups of these ligands: BMP2/4, BMP5/6/7/8, BMP9/10, and BMP12/13/14.[4] It is important to note that BMP1 does not function like the rest of the BMP family. Although able to induce bone and cartilage development, BMP1 is not part of the TGF-β superfamily of proteins. Instead, it is a procollagen C-proteinase that functions in collage maturation.[5] The rest of the BMP family of proteins function as signaling ligands that bind to target receptors on the cell surface.

Before being secreted into the extracellular space where they become active, BMPs are first synthesized as precursor proteins in the cytoplasm. These pre-pro-peptides consist of an N-terminal signal peptide that is required for secretion, a prodomain that plays an important regulatory role for the folding of the active protein, and a C-terminal part that contains the mature peptide that is capable of binding to and activating its receptors.[6] BMP precursors form dimers in the cytoplasm that are subsequently cleaved by convertases to generate the mature BMP ligand that is being secreted into the extracellular space.

Once secreted, BMP ligands bind to their receptors on the surface of target cells to form a heterotetramic complex

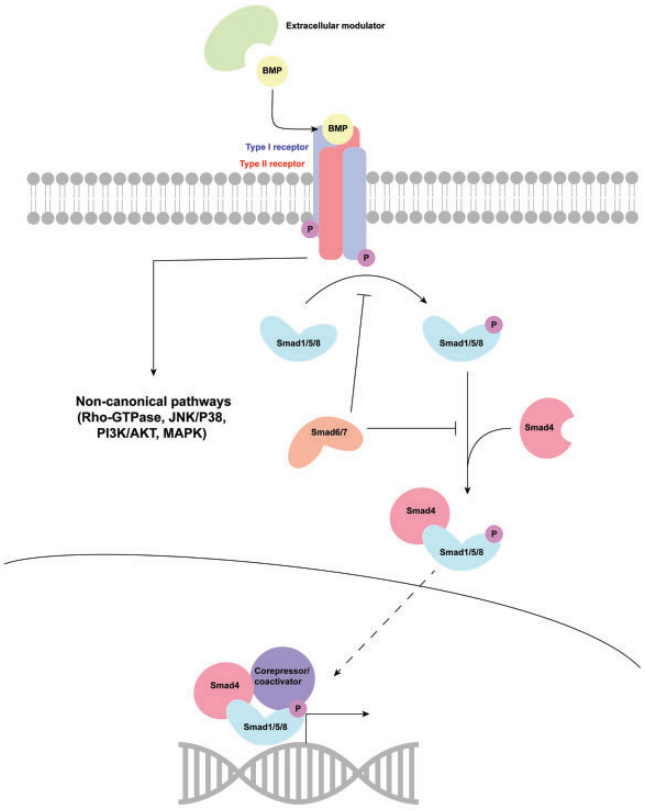

Figure 1. BMP signal transduction. Bone morphogenetic proteins transduce signals in target cells by binding to a heterotetramic complex composed of two dimers of type I and type II receptors. This allows the constitutively active type II receptor to transphosphorylate the type I receptor, causing conformational changes that lead to activation of both canonical pathways and non-canonical pathways like the Rho-GTPase, JNK/P38, PI3K/AKT, and MAPK pathways. Through the canonical pathway, ligand-receptor complex formation leads to phosphorylation of R-Smads (Smad1/5/8), which are then able to form complexes with co-Smads (Smad4). Together, the complex translocates into the nucleus where it associates with coactivators and corepressors to regulate gene expression. BMP ligands can be regulated both by extracellular modulators including protein antagonists and by intracellular modulators like inhibitory Smads (Smad6/7). Adapted from Wang et al.[45]

consisting of two dimers of type I and type II receptors[7] (Figure 1). This complex formation allows the constitutively active type II receptor to transphosphorylate the type I receptor, and activation of the type I receptor causes conformational changes that lead to phosphorylation of downstream proteins known as R-Smads (Smad1, Smad5, and Smad8). Activated, phosphorylated R-Smads in the cytoplasm subsequently form complexes with co-Smad (Smad4), and together, they translocate into the nucleus where they associate with coactivators and corepressors to regulate gene expression.[7] In addition to this so-called canonical signaling pathway, noncanonical BMP signaling pathways that are independent of Smads have also been identified. These include the Rho-GTPase, JNK/P38, and PI3K/AKT pathways in addition to various branches of the MAPK pathway.[8–10]

In addition to the diversity present in downstream signaling pathways, there also exists diversity within the interactions between BMP ligands and the membrane-bound BMP receptors. Both ligand-independent homodimerization and ligand-dependent heterodimerization of BMP type I receptors with effective signal transduction have been observed with certain type I receptor isoforms.[11] Moreover, certain heterodimeric complexes can only be assembled through binding with a specific BMP heterodimeric ligand.[12] Such complexities allow for an additional layer of signal regulation and coordination.

Adding to this complexity, BMP signaling is regulated by both intracellular and extracellular modulators. Extracellularly, BMP ligands are inhibited by proteins like Chordin, Noggin, and the Cerberus and Dan family of proteins, a protein family that includes Gremlin 2 (Grem2). While both Noggin and Grem2 possess a cysteine knot motif and form dimers,[13,14] their structure and the way they inhibit BMP ligands are very different. Noggin forms a head-to-head dimer that creates a clamp-like structure to bind to BMP dimers, inhibiting ligand activity by effectively masking the type I and type II receptor binding surfaces.[14] Grem2 forms a head-to-tail dimer,[13,15] and along its convex surface, one Grem2 monomer binds to a single monomer of the BMP dimer complex, where it interferes with the type II, but not the type I, receptor binding surface.[16] The other monomer of the Grem2 dimer is free to interact with another BMP dimer complex, and this second BMP dimer can then interact with another Grem2 dimer, creating a so-called "daisy chain" reaction. Grem2 demonstrates both a strong and broad inhibition of BMP ligands[17] and a strong specificity for the BMP subfamily of ligands within the TGF-β superfamily.[15]

Intracellularly, BMP signaling is regulated by a variety of mechanisms. Specific miRNAs can regulate expression of various components of the BMP signaling pathway,[7] whereas specific intracellular phosphatases like protein phosphatase 1 can dephosphorylate both phosphorylated R-Smads and phosphorylated type I receptors.[18,19] Moreover, a class of inhibitory Smads or I-Smad (Smad6 and Smad7) play an important role in negative feedback inhibition of BMP signaling.[20] The complexity stemming from the many downstream signal transducers, both canonical and noncanonical, and the multiple layers of regulation allow BMP signaling to coordinate and precisely modulate a wide range of biological processes.

BMP signaling is crucial for development

Since their initial discovery, BMPs have been extensively studied in embryonic development utilizing primarily mouse, zebrafish, and frog models. Such studies have found that BMP signaling is indispensable for numerous developmental processes. Deletion of BMP2, BMP4, or BMP10 is embryonically lethal,[21–23] and loss of BMP7 or BMP11 results in death shortly after birth.[24,25] Similarly, deletion of BMP-responsive receptors, BMPR1-A, ActR1A, and BMPR2[26–28] or knocking out of downstream transducers like Smad1, Smad5, Smad4, and the inhibitory Smad7 are also embryonically lethal.[29–32]

In particular, BMP4 is critical during early gastrulation as its function is required for the differentiation and formation of the mesoderm,[22,33] from which arises a number of tissues and cell types, including vascular, cardiac, skeletal,

and smooth muscles, and definitive hematopoietic stem cells (HSCs) – cells that will continue to supply blood cells into adulthood. Moreover, BMP4 is important to the function of the HSC microenvironment with deficiencies leading to reductions in both HSC function and numbers.[34]

BMP2 is necessary for further mesoderm development and is important for the proper development of the heart and the amnion and chorion.[21] In the heart, BMP2 is critical for endocardial cushion formation, development of the valves, and myocardial patterning,[35,36] whereas BMP10 is essential for cardiac growth and chamber maturation.[23] BMP signaling is also important for controlling the differentiation of cardiac progenitor cells into cardiomyocytes.[37,38] At the early stages of embryonic development, BMP signaling is critical to the proper generation of left/right axis patterning, affecting tissues including the developing heart.[39–42] Moreover, in the central nervous system, BMP signaling is important for directing neuronal differentiation and autoregulation of neurogenesis.[43,44] These and other studies have revealed the essential role BMPs play in normal development in these and many other biological systems, including reproductive and endocrine organs.[45]

Similarly, BMP antagonists also play important roles during embryonic development. In mice, Chordin is crucial for neural induction,[46] and both Noggin and Chordin have important but overlapping roles in development of the forebrain and left-right axis patterning of the developing embryo.[47] Additionally, Noggin is necessary for the development of the axial skeleton in mice.[48] Deleting Chordin leads to stillborn mice, while Noggin knockout mice die at birth.[47,48] In contrast, Grem2 is required for atrial development and cardiac laterality in zebrafish,[49] but it appears to be dispensable for mouse development.[50]

BMP signaling in inflammatory processes

Developmental studies in genetic models have cemented the critical roles of BMP signaling throughout embryogenesis. More recent studies have investigated the role of BMP signaling in adult pathophysiological conditions, revealing a broad influence on homeostasis and disease states such as pulmonary hypertension, cancer, and anemia.[51,52] Recent discussions about BMP involvement in other diseases have been reviewed elsewhere.[45,53,54] Here, we will focus on the emerging roles of BMPs as key mediators of a variety of inflammatory conditions.

BMP signaling promotes the inflammatory phenotype of endothelial cells in atherosclerosis

Atherosclerosis has long been viewed as an inflammatory disease.[55–57] Plaque formation begins with initial endothelial dysfunction that leads to accumulation of lipids in arterial intima and infiltration of immune cells. Markers of dysfunction include upregulation of cell surface molecules such as E-selectin, VCAM-1, and ICAM1, which play essential roles in the roll on, adhesion, and recruitment of immune cells.

Typically, inflammatory cytokines such as TNF-α and IL-1 induce cell adhesion receptors in endothelial cells, but they also induce expression of BMP ligands in endothelial cells.[58] Many studies have pointed out that BMPs further promote the inflammatory phenotype of endothelial cells. In particular, BMP4 is selectively expressed in endothelial cells of atherosclerotic lesions in human coronary arteries.[59] Moreover, BMP4 is upregulated in endothelial cells in response to shear stress and increases endothelial expression of membrane adhesion molecules, leading to enhanced leukocyte adhesion.[59,60] Likewise, BMP2 also upregulates expression of adhesion molecules and promotes leukocyte adhesion.[50,61] Some of these pro-inflammatory effects may be further accentuated in diabetes,[58] a known risk factor for atherosclerosis. In addition to enhancing adhesion of inflammatory cells, BMP2 also induces chemotaxis of monocytes, key immune cells implicated in the pathogenesis of atherosclerotic plaques, and impairs their differentiation into anti-inflammatory M2 macrophages.[62] The recruitment of these pathogenic inflammatory cells is further enhanced through BMP-mediated impairment of endothelial barrier function.[63]

Consequently, inhibiting BMP signaling with extracellular protein inhibitors such as the BMP-binding endothelial regulator protein BMPER and Noggin, or with small molecule chemical inhibitors such as DMH1 suppresses vascular inflammation and lessens recruitment of leukocytes.[63–67] Taken together, these studies suggest that BMP signaling promotes vascular inflammation through direct effects on the endothelium and infiltrating leukocytes and that blocking BMP signaling attenuates the inflammatory response. Thus, BMPs and downstream effectors of BMP ligands may be attractive therapeutic targets for managing inflammatory vessel diseases including atherosclerosis.

BMP signaling in vascular calcification

A clinically relevant consequence of chronic inflammation in atherosclerosis is vascular calcification. This results from a highly regulated process where non-osteoblastic cells, including vascular smooth muscle cells (VSMCs) and pericytes, differentiate into osteoblast-like cells that mineralize the vascular matrix in the tunica media through abnormal deposition of calcium phosphate.[68] Highlighting the similarities between calcification and bone formation, recent evidence suggests an important role for BMP signaling in this pathological process.

VSMCs typically exist in the tunica media as quiescent, differentiated cells, and function to maintain vascular tone through their contractile abilities. However, they are also able to enter a synthetic state characterized by proliferation and production of extracellular matrix,[69] and such a transition is accompanied by loss of cell markers associated with contractility.[70] Expressed in calcified human atherosclerotic plaques,[71] BMP2 inhibits proliferation in VSMCs[72,73] and induces loss of contractility markers once growth arrest has been established.[74]

This suggests either a role for BMP2 in VSMCs that is dependent on proliferation status or one that facilitates along a continuum in promoting the transdifferentiation process. Moreover, BMP2 also induces expression of genes in VSMCs that are crucial for osteogenic differentiation and bone formation, including Msx-2 and Runx2.[75–78]

Deficiency in these genes leads to defects in osteoblast differentiation and large defects in both endochondral and intramembranous ossification.[77,79,80] Recent studies confirm the role of Runx2 and Msx-2 in the osteogenic conversion of VSMCs.[77,81] These studies highlight the molecular similarities between the processes of vascular calcification and bone formation, and taken together, strongly posit a role for BMP signaling in vascular calcification. Moreover, studies have shown that BMP inhibition can also attenuate vascular calcification.[67,82–84]

BMP signaling in tissue fibrosis

Another consequence of chronic vascular inflammation involves induction of processes leading to extracellular matrix (ECM) protein deposition in the adjacent tissue. Under normal conditions, this process functions to repair and preserve tissue architecture and functional integrity after injury. However, pathological dysregulation of inflammation can lead to excessive deposition and an aberrant process of tissue fibrosis that impairs normal organ function. A myriad of profibrotic cytokines released by infiltrating leukocytes act to directly activate fibroblasts, upregulate production of the fibrogenic cytokine TGF-β, increase ECM protein synthesis, and reduce degradation of matrix proteins through downregulating expression of matrix metalloproteinases.[85,86]

Because of this intimate relationship between inflammation and fibrosis, canonical BMP signaling may initially play an indirect positive role through promoting the recruitment of infiltrating leukocytes by endothelial cells into the tissue and thus enhancing the magnitude of the profibrotic signal elicited by these cells. Interestingly, within the tissue itself however, BMP7, through a Smad-dependent antagonism of downstream TGF-β signaling,[87] exerts anti-fibrotic effects. While BMP7 is downregulated in pathological fibrosis of organs, its exogenous administration or overexpression is both anti-fibrotic and functionally protective in disease models of chronic kidney disease,[88–94] liver fibrosis,[95] and pulmonary fibrosis.[87,96–98] The differential roles of BMP signaling in tissue fibrosis, from enhancement at the endothelial level through leukocyte recruitment to regulation at the interstitial tissue level through antagonism of TGF-β signaling, reflect not only the specialized roles served by individual BMP ligands, but also points to a built-in regulatory element that modulates the overall effects of BMP signaling in promoting tissue fibrosis through inflammation.

BMP signaling in endothelial to mesenchymal transition

In addition to these molecular processes, endothelial to mesenchymal transition (EndMT) is a cellular process activated in response to inflammation that significantly contributes to the resulting consequences of vascular calcification and tissue fibrosis. In response to inflammatory cytokines, endothelial cells undergo a phenotypic conversion from a differentiated endothelial cell state to a more undifferentiated mesenchymal fibroblast-like cell state. During this process, these cells lose cell-to-cell adhesions and endothelial markers like CD31 and gain mesenchymal characteristics, including ECM protein production and markers like α-smooth muscle actin and fibroblast specific protein 1.[99,100] The resulting multipotent mesenchymal cell is able to differentiate and contribute to multiple different cell types to serve needed functions. Under pathological conditions, it can contribute to the fibroblast population within the tissue to help promote fibrosis in circumstances such as after acute or chronic injury,[101–104] or it can also contribute to an osteoprogenitor cell population that underly the pathophysiology of vascular calcification.[105]

The process of EndMT in the adult is well known to be activated by TGF-β signaling,[99–103] while signaling through the BMP subfamily of ligands, in particular BMP2 and BMP4, is well known to induce EndMT during embryonic development.[35,106] In the adult, these ligands likely function similarly to promote this developmentally active programming. This is supported by *in vitro* evidence demonstrating treatment of cultured endothelial cells with either BMP4 or TGF-β2 induced acquisition of mesenchymal stem cell-like features.[107] Moreover, inhibition of canonical BMP signaling by DMH1 a dorsomorphin analogue which specifically inhibits activation of Smad1/5/8,[108,109] also inhibits EndMT *in vitro*. In addition, BMP6 has also been shown to pathologically promote EndMT in a disease model of cerebral cavernous malformation both *in vitro* and in *in vivo*.[110] Interestingly, BMP7 inhibits EndMT both *in vitro* and *in vivo*.[104,111] The discrepancy can be explained by the observation that an interaction between activated Alk2 and activated Alk5 BMP receptors is necessary for EndMT.[107] Administration of either TGF-β2 or BMP4 activates both receptors to allow an interaction, whereas BMP7 solely activates Alk2, preventing the necessary Alk2-Alk5 interaction. Taken together, these findings demonstrate the important and complex role BMP signaling plays in endothelial function and disease pathology beyond the initial inflammatory response.

BMP signaling regulates the inflammatory response following cardiac ischemic injury

Inflammation is a critical component of tissue repair following acute or during chronic tissue injury. For example in the heart, the systemic inflammatory response following myocardial infarction (MI) allows infiltration of immune cells into the heart to help clear cellular debris, and this acute process is essential to proper tissue healing and repair.[112–116] Our group and others have measured BMP expression in the heart and found that BMP2 is upregulated following MI in mice.[50,117] Our results show that BMP2 is transiently induced during the inflammatory phase and promotes a pro-inflammatory phenotype in endothelial cells[50] (Figure 2). This upregulates expression of adhesion molecules and increases the number of infiltrating inflammatory cells in the heart. Moreover, we found that the acute inflammatory cytokine TNF-α upregulates BMP2 expression endothelial cells and the two work synergistically to promote the inflammatory phenotype in endothelial cells.

BMP2 also upregulates the expression of its own antagonist Grem2 (Figure 2), and consequently, Grem2 expression, but not expression of other BMP antagonists, follows

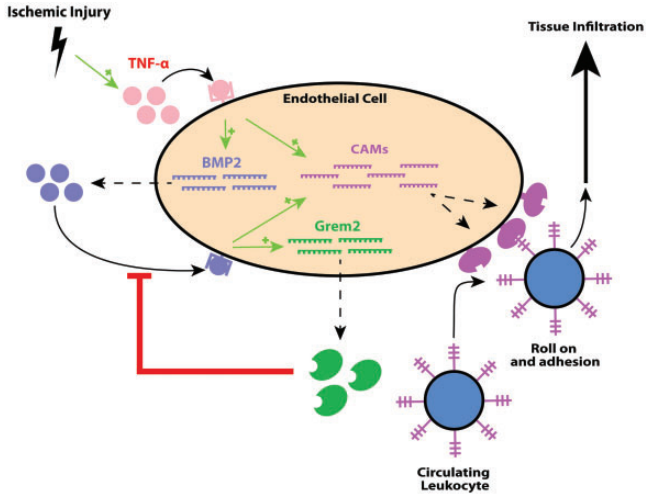

Figure 2. BMP signaling regulates the endothelial inflammatory response after ischemic injury. Ischemic injury induces local TNF-α production which promotes expression of BMP2 in endothelial cells. The two signaling proteins upregulate expression of cell adhesion molecules (CAMs), which enhances recruitment and infiltration of circulating leukocytes into the tissue. BMP2 also induces expression of its antagonist Grem2, creating a negative regulatory loop that regulates BMP activity to limit tissue inflammation.

the increasing levels of BMP2 following MI. This temporal coordination of BMP regulation is important in modulating tissue inflammation as shown by gain or loss of Grem2 function in mice. Specifically, loss of Grem2 function by homologous recombination promoted pro-inflammatory changes in endothelial cells and led to both greater levels of infiltrating inflammatory cells in the heart and worsened functional outcomes following MI.[50] Administering DMH1 rescued this pro-inflammatory phenotype. Moreover, cardiac-specific overexpression of Grem2 limited tissue inflammation and improved functional recovery.[50] These findings build upon earlier studies demonstrating the role BMPs have in promoting vascular inflammation through eliciting changes in endothelial cells that promote leukocyte recruitment. In addition, they introduce endogenous regulatory mechanisms highlighting the crucial role of endogenous BMP antagonists in limiting inflammation and the therapeutic value of regulating BMP signaling.

BMP signaling in chronic inflammatory arthritis

At the intersection of bone pathology and inflammation, studies of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) offer unique opportunities to explore the role of BMPs in inflammatory processes related to a system in which they already have an established presence. The pathogenesis of both diseases involves immune-mediated inflammatory processes. RA is characterized by synovial inflammation, progressive joint damage, and bone loss, while AS is characterized by chronic enthesitis, initial bone destruction, and aberrant bone repair leading to spinal fusion and dysfunction.

BMP signaling appears to be beneficial in RA but not in AS. BMP2 and BMP6 are expressed in synovium from RA patients, and expression in patient-derived fibroblast-like synoviocytes *in vitro* becomes strongly up-regulated in response to pro-inflammatory cytokines IL-1β, TNF-α, or IL-17.[118,119] However, BMP4 expression in synoviocytes decreases in response to TNF-α,[118] aligning with clinical studies observing lower BMP4 mRNA levels in the synovium of RA patients relative to controls.[120]

The pro-inflammatory cytokines IL-17 and TNF-α induce a pro-inflammatory phenotype within synoviocytes marked by increased expression of pro-inflammatory cytokines IL-6 and GM-CSF, increased expression of the chemokine IL-8, and increased production of metalloproteinases MMP2 and MMP3. Expression and activity of these products are strongly implicated in the pathogenesis of RA.[121,122] Blocking BMP signaling with the canonical BMP inhibitor DMH-1 further augments this response and potentiates the induction of the pro-inflammatory phenotype in synoviocytes.[118] On the contrary, inducing BMP signaling with exogenous BMP6 reduced the expression of these products and interfered with the induction of a pro-inflammatory phenotype in synoviocytes.

In an *in vivo* model of AS, however, blocking BMP signaling through systemic gene transfer of the BMP antagonist Noggin slowed the initiation and progression of disease through regulating pathological bone remodeling.[123] The discrepancy in the role of BMP between these two disease states warrants further exploration and may be explained by the inherent differences between the disease pathophysiology of RA and that of AS. Moreover, it is likely that outcomes depend on cellular context, antagonistic effects of specific BMP subgroups such as BMP2/4 against BMP6/7, or differential activation of canonical versus non-canonical BMP signaling pathways. Nonetheless, these studies suggest not only an important role for BMP in well-recognized inflammatory diseases, but also in regulating inflammatory processes that drive disease.

BMP signaling in anemia of inflammation

Regulation of circulating iron is coordinated by several key proteins. As the sole exporter of intracellular iron, ferroportin functions to release intracellular iron in intestinal epithelial cells, hepatocytes, and macrophages into the circulation. An excess in circulating iron stimulates the expression of hepcidin in the liver, and releasing the protein into the circulation allows it to bind ferroportin to induce its internalization and degradation.[124] Likewise, a deficiency in iron also suppresses hepcidin expression. This negative feedback control allows for appropriate circulating iron stores, and perturbations to this system can have clinical consequences. Inflammatory cytokines such as IL-6 that are generated by a variety of diseases, including infection or autoimmune disorders, induce the hepatic expression of hepcidin, and the resulting reduction in circulating iron leads to anemia.[125]

Induction of hepcidin in response to inflammatory stimuli and, thus, iron levels is dependent on BMP signaling. During homeostasis, BMP6 is the predominant BMP ligand that functions in iron homeostasis and transduces its signal through the BMP coreceptor, hemojuvelin.[124,126,127] Expression of BMP6 in the liver is regulated by serum iron levels reflecting dietary intake,[128] and deficiency in

BMP6 leads to hepcidin deficiency and subsequent iron overload in tissues and organs.[129] It appears that other BMP ligands are unable to compensate for loss of BMP6 *in vivo* despite their ability to induce hepcidin expression in hepatocytes in vitro.[130] BMP2, however, may at least play a partial redundant role in inducing hepcidin expression. Hepcidin induction by either acute or chronic iron loading does not require BMP2, although hepcidin induction in either scenario is submaximal and relatively blunted.[131] On the other hand, intact BMP6 function is absolutely critical to hepcidin induction by acute iron loading. Additionally, inhibition of BMP6 but not BMP2/4 significantly decreases hepcidin levels and increases serum iron.[126] Moreover, BMP2 appears to be able to induce hepcidin expression independent of hemojuvelin, though at a lower efficiency.[124]

At the receptor level, the BMP type II receptors ActR2a and BMPR2 perform redundant roles in transducing signals to induce hepcidin expression. Deficiency in both receptors is required to reduce levels of hepcidin *in vivo* and is necessary to reduce BMP6-mediated induction of hepcidin expression as well as basal levels of hepcidin expression *in vitro*.[132] In addition, both of the BMP type I receptors Alk2 and Alk3 are individually necessary for hepcidin induction by BMP2 stimulation in culture and also for hepcidin induction by iron challenge *in vivo*.[133] However, when compared to a liver-specific deletion of Alk2, liver-specific deletion of Alk3 results in a much more severe iron overload phenotype and near abolishment of both basal BMP signaling and hepcidin expression. This suggests differential functions of these receptors with Alk3 individually promoting basal levels of BMP signaling and hepcidin expression, and Alk2 being a necessary component in addition to Alk3 only in the context of promoting hepcidin expression in response to BMP signal transduction and iron. This may be the result of the unique ability of Alk3 receptors to homodimerize and transduce signals for inducing hepcidin expression in the absence of ligand binding.[11] Downstream, Smad4 is also required for mediating hepcidin expression.[134]

The important roles of these BMP signaling mediators during homeostasis are also evident in response to inflammatory stimuli. Deficiencies in either BMP6 or hemojuvelin, and not in BMP2,[131] lead to impaired induction of hepcidin and hypoferremia in response to inflammation compared to normal controls,[124,129] but inflammatory induction of hepcidin persists in isolated or combinatory deficiencies of either when compared to baseline.[135] This suggests that inflammation may induce hepcidin through pathways independent of BMP signaling. Nonetheless, inhibiting BMP signaling with BMP antagonists or LDN-193189, an inhibitor of BMP type I receptor ameliorates anemia of inflammation and iron deficiency in mice.[135,136] These findings are consistent with observations that hepatocyte-specific deletion of BMP type I receptor, Alk3, attenuates phenotype of anemia of inflammation in mice.[137] Taken together, these studies suggest a pivotal role for BMP6 as a regulator of circulating iron both in homeostasis and chronic inflammatory conditions that warrants therapeutic considerations.

Conclusion and future directions

In the recent decade, our understanding of the role of BMP signaling has expanded beyond its initially discovered role in the skeletal system and outside its prominent and crucial roles in development. It is now well-recognized that BMPs are essential to a plethora of different processes throughout the body in the adult both during homeostasis and in disease states. Components of BMP signaling are prominently emerging as direct coordinators of inflammatory processes across various cell types from immune cells to endothelial and connective tissue cells. As the general role of inflammation in disease continues to develop and the intersection between immunology and other medical fields continues to grow, defining the multifaceted roles of BMP signaling in inflammation will allow greater insight into the molecular mechanisms that drive disease.

Already, recent studies have uncovered insight into the nonredundant roles of both specific BMP ligands and BMP antagonists that possess context-specific functions such as BMP6 in the regulation of circulating iron in response to inflammation, BMP2 and BMP4 in mediating inflammatory phenotype of endothelium in response to stress or tissue injury, and Grem2 in limiting post-injury tissue inflammation. This likely reflects the functional heterogeneity that exists among BMP ligands and their antagonists. Thus, special precautions should be taken regarding designing interventions targeting BMP signaling as broad inhibition of all BMP ligands to limit endothelial or tissue inflammation may also perturb iron homeostasis. With the increasing availability of small molecule BMP inhibitors and a recent pre-clinical study successfully utilizing such a compound,[138] it may be worth considering their pharmaceutical value and position to be clinically approved in the future. However, before moving forward into clinical applications, it will be important to design compounds to control specificity for the regulation of only certain BMP ligands to maximize efficacy while minimizing adverse off-target consequences.

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DECLARATION OF CONFLICTING INTERESTS

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