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Review

Bone morphogenetic protein signaling pathway: an essential role in intestinal homeostasis and diseases

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Abstract

The bone morphogenetic protein (BMP) signaling pathway is a fundamental regulator of intestinal homeostasis, orchestrating the delicate balance between stem cell proliferation and epithelial differentiation along the crypt-villus axis. In opposition to the Wnt signaling pathway, BMP signaling promotes epithelial maturation and inhibits excessive stem cell expansion, thereby ensuring proper renewal and functional integrity of the intestinal epithelium. Both epithelial and mesenchymal cell populations actively contribute to BMP signaling; mesenchymal cells serve as a primary source of BMP ligands and antagonists, while epithelial cells predominantly express BMP receptors and downstream effectors. This dynamic epithelial-mesenchymal dialogue establishes and maintains the intestinal stem cell niche and structural organization of the crypts. Dysregulation of BMP signaling has been increasingly implicated in the pathogenesis of inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, as well as in colorectal cancer (CRC). In inflammatory conditions, modulation of BMP ligands and antagonists influences epithelial regeneration and immune responses, highlighting their potential anti-inflammatory and anti-fibrotic roles. Conversely, in colorectal carcinogenesis, alterations in BMP pathway components—including mutations in BMP receptors and Smad effectors, alongside aberrant expression of BMP antagonists like Gremlin-1—disrupt the balance of intestinal homeostasis, promoting tumor initiation, progression, and metastatic potential via both canonical and non-canonical signaling mechanisms. This review comprehensively summarizes the current understanding of BMP signaling in intestinal physiology and pathology, emphasizing the critical interplay between epithelial and mesenchymal compartments, and the impact of the genetic context and pathway modulators. Further elucidation of BMP pathway dynamics promises novel therapeutic strategies for intestinal diseases through targeted modulation of this pivotal signaling cascade.

Keywords: BMP signaling, BMP ligand, BMP antagonist, Smad, BMP receptor, Differentiation, Epithelial mesenchymal interaction, Inflammatory bowel diseases, Cancers.

1. Introduction

Discovered by *Urist* in 1965, the Bone Morphogenetic Proteins (BMPs) belong to the transforming growth factor (TGF-β) superfamily and were first described in bone metabolism [1,2]. Originally known for its ability to control osteoblast and osteoclast activity and to modulate bone formation, the BMP pathway has been partly studied for its involvement in morphogenesis and organogenesis [3]. In embryonic development, the BMP pathway controls the setting up of the embryo's symmetry axes, the generation of the different layers and the spatial and temporal regionalization of tissues [4,5]. The BMP pathway also participates in controlling cellular homeostasis in various adult tissues by regulating proliferation, differentiation and apoptosis. Because of this versatility, authors agree that it is most often referred to as the Body Morphogenetic Protein pathway [6].

In the gastrointestinal tract, the BMP pathway represents a key signaling pathway also involved in the intestinal crypt-villus morphogenesis, the gut looping and the maintenance of adult homeostasis by regulating intestinal stem cells renewal as well as epithelial differentiation [4]. As a result, a dysregulation in the BMP pathway could be associated to the development of several intestinal diseases, including intestinal inflammatory diseases and colorectal cancers [7–9].

In the first part, we will describe the intestinal crypt and its environment. Then, we will focus on the BMP pathway and the related actors in the intestinal tract to understand how the pathway regulates the intestinal cellular homeostasis. Finally, we will focus on how BMP pathway is implicated in intestinal diseases.

2. The intestinal epithelium and its main regulatory pathways

2.1. Intestinal crypt microenvironment

The small intestinal and colonic epithelia are continuously and rapidly renewing, with epithelial cells being completely replaced every four or five days. The turnover, which requires a perfect balance between self-renewal

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and differentiation signals, is ensured by intestinal stem cells (ISCs) [10]. Structurally, the intestinal epithelium is constituted of a single layer of cells forming alternating villi and invaginations, also called crypts [11]. In the colon, villi are absent. ISCs that initiate epithelial renewal are located in the lower third of the crypts [12]. Studies revealed that two types of stem cells are present in the crypt bottom: crypt base columnar cells (CBCs), which divide rapidly to progenitors (or transit-amplifying: TA cells) and at the fourth position, quiescent cells named « *+4 cells* » characterized by a slow dividing cycle [13–15]. The CBCs cells are marked by the leucine-rich repeat-containing protein-coupled receptor 5 gene (*Lgr5*$^{+}$). Then, five cell types are divided into two categories, which then derive from progenitors and ascend to the top of the villi or crypts of the colon. The absorptive cells or enterocytes/colonocytes, have a crucial role in nutrient absorption. The secretory cells are constituted of goblet cells, Paneth cells, enteroendocrine cells and tuft cells [16]. The tuft cells develop along the crypt-villus axis and are rather involved in antibacterial, hormonal and more recently in immune functions [17,18]. Enteroendocrine cells are specialized in hormone secretions and respond to both luminal and basolateral signals [19]. Paneth cells do not migrate up to the villus tip; instead, they remain in the transit-amplifying zone and can also intercalate between intestinal stem cells (ISCs) to support their maintenance. [10] (Fig. 1). They play essential role in epithelial defense, secreting antimicrobial peptides (alpha-defensins). In the colonic epithelium, renewal, organization, and cellular composition proceed similarly to the small intestine, except that Paneth cells are absent [20,21].

The cellular homeostasis is maintained by fine regulatory mechanisms that ensure a perfect balance between proliferation, differentiation and apoptosis. In particular, ISCs and progenitor cells are in permanent interaction with a complex microenvironment (called niche) that includes mesenchymal cells, lymphocytes and macrophages, endothelial cells, neuronal cells and Paneth cells. The niche provides essential regulatory cytokines and growth factors [12].

The mesenchymal population resides within the extracellular matrix (ECM) and is closely related to the epithelium due to the spatial proximity. Including various cells such as fibroblasts, mesenchymal stem cells, pericytes or telocytes, mesenchymal cells are often classified according to single cell analysis and specific markers [22] (Table 1). It is important to note that these subtypes are not « *mutually exclusive to each other* » [12]. Indeed, although numerous studies have tried to group these cell types, a strict classification remains too complex depending on both cell markers, localization and morphological criteria [12,23]. Fibroblasts represent a major component of the stromal population [24]. They fulfill three main roles: (a) they are involved in the production of ECM components, (b) they play an important role in immune response and (c) they are actors in the maintenance of stem cell niche by sending and/or receiving signals to ISC niche cells. Among fibroblasts, myofibroblasts represent a specific subclass with contractile activity. In addition, trophocytes, telocytes or pericytes are today considered as fibroblasts with specific markers, locations and functions [25,26](Table 1). In the event of epithelial injury or inflammation, resting fibroblasts can turn into activated fibroblasts or myofibroblasts by expressing α-smooth muscle actin. During carcinogenesis, fibroblasts acquire a fairly similar phenotype to become cancer-associated fibroblasts (CAFs) able to play a part in all cancerization stages (proliferation, migration, invasion, metastasis process, angiogenesis and chemoresistance) to promote the tumor development [27]. But not surprisingly, due to their heterogeneity, one or more CAF subclasses could also have anti-tumorigenic abilities [28]. However, the transformation is not totally definitive and CAF can return closer to a normal phenotype [29]. In the mesenchymal compartment, immune cells also participate in several functions within the crypt environment. They can strongly interact with epithelial and dendritic cells to

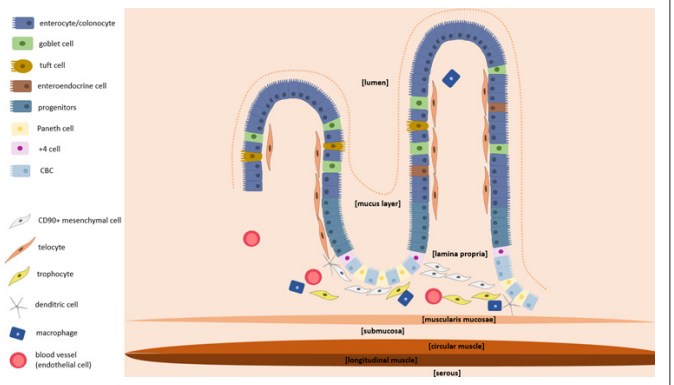

Fig. 1. Simplified schematic representation of the intestinal organization: structure of the intestinal epithelium and the surrounding ISC niche.

Table 1. Summary of the different subclasses of mesenchymal cells commonly found in small intestine and colon and the main agonists or antagonists of the Wnt and BMP pathways that they produce.

mesenchymal population name	main ligand production	references
Gli1^{+} mesenchymal cells (intestine and colon)	Wnt agonists and regulators (Wnt2, Wnt2b, Wnt4 and Rspo3)	[12,32]
CD34^{+} mesenchymal cells (intestine)	Wnt agonists and regulators (Rspo1, Rspo3, Wnt2 and Wnt2b)	[12,33]
CD90^{+} mesenchymal cells (colon)	Wnt agonists (Rspo3, Wnt2b) and Bmp antagonists (Grem1)	[12,34]
Pdgfra^{+} stromal cells (intestine and colon)	Wnt agonists	[12,35]
Pdgfra^{high} **Foxl1**$^{+}$ telocytes (intestine and colon)	- Wnt agonists at crypt base and top - Bmp ligands (Bmp5, Bmp7) and antagonists (Grem1)	[12,36–38]
Pdgfra^{low} trophocytes (intestine and colon) - Lo-1 (CD 81^{+}) - Lo-2(CD 81^{-})	- BMP antagonists (Grem1) and Rspo3 - Wnt agonists (Wnt4)	[12,38–40]
Ng2^{+} pericyte-like cells (intestine and colon)	Wnt agonists (Wnt2b and Wnt4)	[12,41]

(Gremlin 1: Grem1 / Rspodin1-3: Rspo1-3).

assure gut defense, but also with the mesenchymal populations [30]. Specific intestinal mesenchymal cells ($CD90^+$) express toll-like receptors detecting early pathogen patterns/presence and are able to produce proinflammatory cytokines to lead immune cells to the inflammatory site [31].

To remember: Under physiological conditions, the continuing renewal of epithelia represents the key to intestinal homeostasis, finely modulated by the interaction between the different cell types of the ISC niche.

2.2. Implications of the different signaling pathways in intestinal homeostasis

Several pathways are involved in the control of intestinal homeostasis. The main ones referenced are: Wingless-related integration site (Wnt) pathway, BMP pathway, Notch pathway, Hedgehog (Hh) pathway, Epidermal Growth Factor (EGF) pathway and Hippo pathway [12,42,43].

The Wnt pathway is a major signaling pathway involved in stem cell control and homeostasis (proliferation and cell fate) in many organs. Ligands are secreted by both epithelial and mesenchymal cells. Indeed, Paneth cells are described as Wnt3-ligand producing cells, whereas the surrounding stromal cells secrete Wnt2b, Wnt4 and Wnt5 [44,45]. The second pathway is the BMP pathway, which has a gradient and function opposed to the Wnt pathway, with an increasing gradient from the base of the crypt to the top of the villi in favor of cellular differentiation. BMP ligands are produced both by epithelial cells in the upper crypt (BMP2 and BMP7) and stromal cells around the epithelium, notably at the bottom of the crypts (BMP4) [46,47]. Notch pathway is a key signaling in stem cell maintenance and its activation plays a role in the fate of progenitor cells toward absorptive lineage via the Notch-Hes1-Elf3 cascade [10,43]. The Hh pathway is crucial in the development of crypt-villus axis and in the phenomenon of wound healing [48]. The EGF pathway regulates both ISC and epithelial proliferation. Finally, the Hippo pathway also appears to play an important role in intestinal homeostasis. Hippo is related to the regulation of 2 principal ligands: YAP and TAZ; the activation of Hippo leads to the sequestration of YAP and TAZ, themselves associated with stem cell and progenitors expansion and differentiation inhibition [49]. Hippo also intervenes in tissue regeneration. Importantly, all of these pathways are highly associated with each other and operate in a hudge network with many other pathways not mentioned here, to maintain homeostasis.

2.3. Localization of BMP pathway components and their interactions with epithelium and mesenchyme

The BMP subfamily currently consists of around thirteen BMP ligands clearly identified in humans [2,9]. BMP ligands are subdivided into groups according to their receptor affinity: BMP2/4; BMP5/6/7/8a/8b, BMP9/10, BMP12/13/14 (GDF5/6/7) and finally Bmp15 [50]. The most studied BMP ligand isoforms belong to Bmp2/4 and Bmp7 subfamilies. Briefly, the mechanism of the signal transduction is initiated by the binding of a BMP dimer (homodimer or heterodimer) to an heteromeric complex composed of type I and type II receptors. At present, four type I and three type II receptors have been identified, belonging to transmembrane serine-threonine kinase receptor family [51,52]. The binding can be inhibited by BMP antagonists as Gremlin 1 (Grem1), Chordin-like 1 (Chdl1) or Noggin. These antagonists do not act as competitors for BMP receptors but bind directly to specific BMP ligands. After the binding, the type II receptor, which is an active kinase receptor, phosphorylates the type I receptor and activates it. Finally, Smad1/5/8/9 proteins are phosphorylated by type I receptor and recruit the common effector Smad4 to form a transcriptional complex able to migrate into the nucleus to regulate directly or indirectly, via interaction with transcription factors, the different pathway targets [2,4,52,53] (Fig 2). The non-canonical pathway is also driven by the binding of BMP ligands to tetrameric receptor complex that results in the activation of other signaling pathways such as the MAPK pathway and phosphorylation of p38, ERK, JNK and Rho. The associated cellular modulations resemble those for the canonical pathways, i.e. cell growth, differentiation, migration, apoptosis, metabolism regulation, ect [3,54].

2.3.1. BMP ligand and antagonist expression in the intestine

2.3.1.1. In the small intestine

BMP4 is highly expressed in subepithelial mesenchymal cells adjacent to the ISC niche as well as in intravillus mesenchymal cells [46,55]. Small intestinal telocytes $Foxl1^+$ corresponding to myofibroblasts express BMP4, BMP5, BMP6 and BMP7 as well as the BMP inhibitors Grem1 and Chdl1 [36]. BMP2 is mainly expressed by mature enterocytes but was also detected in the lamina propria of the mouse intestine [56]. A parallel can be drawn between BMP2 and BMP7 since BMP7 colocalized with BMP2 and shared with the latter some functional similarities [56]. For its part, BMP6 is expressed at the villus tip in response to iron-sensing in mice small intestine [57]. A specific stromal CD34+ trophocyte produces the antagonist Grem1 [33]. Noggin, another BMP antagonist, is mainly expressed by mesenchymal cells belonging to the ISC niche and adjacent to the crypt, probably by pericryptal fibroblasts. The antagonist is also present in the cytoplasm of ISC [23,46].

2.3.1.2. In the colon

A first study of *Kosinski and al* reported the presence of BMP2, BMP5 and BMP7 at the top of the crypt and inversely an enrichment of BMP antagonists Grem1, Grem2 and Chrdl1 at the base of colonic crypt to antagonize BMP signaling in the ISC niche [58]. These data are consistent with a BMP gradient oriented from the base to the top of the crypt. A characterization of the cellular types associated with antagonist expression was performed by *in situ* hybridization. As a result, Chrdl1, Grem1, and Grem2 are primarily expressed by myofibroblasts and smooth muscle cells located in the basal part of the lamina propria and the muscularis mucosae, but not by epithelial cells. Several cell types producing the antagonist Grem1 have been identified, including trophocytes [39] or $CD90^+$ fibroblasts [34], newly identified as fibroblasts in close proximity to stem cells and enriched in Grem1 and other niche factors expression to support ISC maintenance and growth. Interestingly, even if mesenchymal cells are the main source of Grem1 transcripts, the Grem1 protein could be detected in Paneth cells at the base of the crypt [59]. Noggin,

another studied BMP antagonist, is found to be expressed, as BMP2, by mature epithelial cells in mice colon [47]. BMP2 is also detected in human and mice colonocytes, a localization consistent with its primarily role in epithelial cell differentiation [47,60]. BMP4 expression, for its part, is associated with mesenchymal cells located beneath and between the crypts in the colonic mucosa of mice [55]. *Brügger and al* have in addition found crypt top fibroblasts, identified as Pdgfra^{high} fibroblasts, as producers of BMP ligands including BMP2, BMP3, BMP4, BMP5 and BMP7 [26].

Interestingly, colocalization of two BMP ligands could have a specific impact of the BMP pathway. For example, BMP2 can heterodimerize with BMP7 to bind receptors and this heterodimer is more potent than BMP2 or BMP7 homodimer, which could lead to the enhancement of the BMP pathway [61]. In the same way, a coexpression of BMP ligands and antagonists within the same cell or nearby cells could indicate a paracrine or autocrine regulation of the pathway to maintain a perfect homeostasis at the cellular level.

2.3.2. BMP receptors

Together, Alk1 (or Acvr1), Alk2 (or Acvr1b), Alk3 (or Bmpr1a) and Alk6 (or Bmpr1b) represent the four type I receptors, while type II receptors consist of Bmpr2 (unique for BMP ligands), Acvr2a and Acvr2b (also shared with activins) [50,62]. Their structure allows differential affinity of the BMP ligands, and they possess a kinase activity essential for signal transduction. Finally, they are distributed according to a specific gradient along the crypt-villus axis. For example, Bmpr1a has a dominant expression in epithelial cells of intestinal villi, but its expression is lower in the proliferating zone [46] and similarly, Bmpr2 is highly expressed at the colon top [58].

2.3.3. BMP effectors and targeted genes

Smad1/5/8/9 effectors are located in epithelial cells along the crypt-villus axis [46]. Once phosphorylated and associated with Smad4, the Smad complex migrates into the nuclei of epithelial cells to activate canonically targeted genes, including downstream inhibitor of DNA-binding proteins (ID1-3), inhibitory Smads such as Smad6/7 and Vent2B [2,52,63–66] (Fig. 2).

3. Role of BMP pathway in intestinal physiology: stem cell regulation and differentiation of epithelial cells

3.1 BMP pathway in the stem cell niche control

The BMP pathway plays a crucial role in the regulation of ISC niche, as well as in the repression of ISCs proliferation. Indeed, the loss of epithelial or mesenchymal BMP can lead to an hyperproliferation of ISCs with an expansion of crypt formation [46,67,68]. Due to the strong involvement of the Wnt pathway in epithelial proliferation, the authors investigated the potential interaction between Wnt and BMP pathways and suggested that BMP pathway was able to inhibit β-catenin translocation (a transcriptional coactivator of the Wnt pathway) to control and repress stem cell renewal. Using a model of conditional inactivation of *Bmpr1a* in mice and the phosphorylation of low-density lipoprotein receptor-related protein 6 (LRP6) as a marker of Wnt signaling activity, *He et al* demonstrated that Wnt signaling is necessary for ISC self-renewal but is no sufficient. The BMP pathway is also necessary for β-catenin activity regulation in ISC niche through PI3K –Akt signaling to ensure a balanced control and limit the ISC self-renewal [46]. In this way, the dialogue between mesenchymal cells as regulators and epithelial cells as regulated cells to maintain ISC renewal appears essential [36,37,39]. The importance of the dialogue in the regulation of cellular proliferation and homeostasis control via BMP signaling was further confirmed in a recent study. In a coculture model, colonic fibroblasts were able to activate the epithelial BMP signaling in colonocytes and decrease epithelial growth through the BMP4 paracrine ligand [69].

In 2017, a study investigated the role of BMP signaling pathway in the regulation of ISCs independently of the Wnt pathway. Interestingly, it was demonstrated that inhibition of *Bmpr1a* in the intestinal epithelium and more specifically in ISCs led to (a) an expansion of Lgr5+ cells, (b) an increase in Paneth cells number and (c) an acceleration of the epithelial cells turnover rate. The study of the Wnt pathway combined with the use of exogenous BMP4 pointed out the direct impact of the BMP pathway on Lgr5+ signature genes rather than an impact through the inhibition of β-catenin nuclear translocation [70].

3.2. BMP pathway in differentiation and cell zonation along the crypt-villus axis

A mouse model of *Bmpr1a*-deleted epithelium highlighted the role of epithelial BMP pathway in the differentiation of epithelial cells of the secretory lineage. In mutant mice, goblet cells showed a lack of maturity and smaller mucus granules, but without any change in *Muc2* expression. The number of enteroendocrine cells was significantly decreased by 75% and for goblet, enteroendocrine and Paneth cells, the mRNA levels of specification and differentiation genes were down-regulated. In contrast, the loss of epithelial BMP receptor did not affect absorptive lineage. If the epithelial BMP signaling seems to have an important impact on epithelium architecture, the study also highlights the role of mesenchymal BMP in crypt shaping and its dialogue with epithelial cells [71].

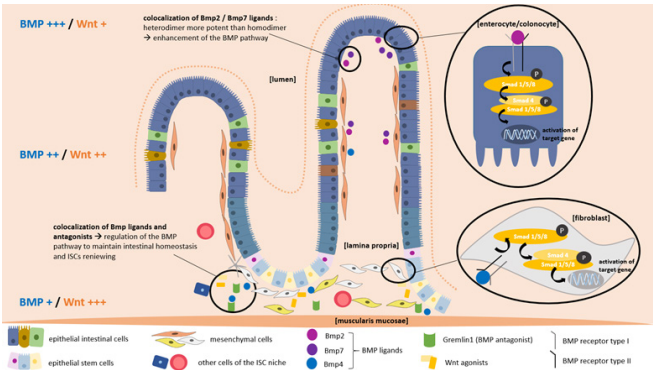

Fig. 2. Schematic representation of the BMP and Wnt pathway in the intestine: Epithelial and mesenchymal cells are the main producer cells of BMP ligands, including BMP2, BMP4 and BMP7, with a specific zonation along the crypt-villus axis. The mesenchymal population primarily expresses BMP antagonists, including Grem1, Noggin, and Chdl1, which directly bind to BMP ligands. Wnt agonists are also produced by mesenchymal cells to maintain ISC renewal. The BMP pathway signal transduction is briefly described in an enterocyte on the right. These different actors allow to have a perfect balance between BMP and Wnt opposed gradients and to maintain intestinal homeostasis.

Concerning the spatial and temporal control related to the BMP pathway, a first *in vivo* study demonstrated that the BMP gradient is able to control gene expression depending on enterocytes and goblet cells and therefore determine a specific related functional state for these two types of epithelial cells along the villus axis. Gene expression will rather concern lipid processing for enterocytes and antimicrobial activities for goblet cells, conferring further therapeutical issues through zonal modulation on the BMP pathway in the intestinal epithelium [72]. Similarly, a recent study performed in mouce small intestine showed that the localization of BMP2 and BMP4 expression had an impact on intestinal epithelial cell differentiation program and, consequently, on the associated function. Indeed, BMP2 expressed at the top of villi is involved in adhesion features of mature enterocytes, whereas BMP4 expression, more central, regulates lipid absorption and metabolism [56].

To remember: In the adult intestine, the BMP pathway is involved mainly in ISCs proliferation control and epithelial cell differentiation and maturation. The BMP gradient and the specific localization of the BMP actors have a crucial role in the related function of target genes.

4. Role of BMP pathway in intestinal pathology: inflammatory bowel diseases (IBD) and colorectal cancer (CRC)

4.1. Implications of BMP pathway in IBD

IBD, including Crohn's disease (CD) and ulcerative colitis (UC), represent two very studied, frequent diseases reaching about 10 million patients worldwide (*EFCCA, 2021*). It is now largely accepted that CD is caused by a brutal and abnormal activation of the immune system, damaging the intestine and affecting the different segments of the digestive tract. UC, for its part, mainly damages the colon and rectum [73]. Usually, animal models are obtained to study IBD disease either (a) by adding dextran sulfate sodium (DSS) in drinking water or (b) by rectal instillation of 2,4,6-trinitrobenzenesulfonic acid (TNBS) [74].

4.1.1 BMP pathway in acute phase of inflammation

In an *in vivo* study in mice, acute DSS treatment caused a significant decrease in *Bmpr1a* and *Bmp4* mRNA levels in the colonic mucosa. In the same study, specific deletion of *Bmpr1a* receptor in the mouse mucosa significantly increased the extent of inflammation and intestinal damage. Further *in vitro* investigations in human fibroblastic cells have shown the ability of cytokines IL-1β and TNF-α to inhibit *Bmp4* expression, a ligand that seems to have anti-inflammatory properties [55]. Similarly, it has been demonstrated that during the first 3 days of DSS-treatment in mice, Smad4 and BMP4 protein expressions were increased, followed by a decrease on day 7. Intraperitoneal administration of BMP4 recombinant protein in these mice improved many parameters after 3 days: (a) reduction of activity index score (based on stool consistency, fecal blood and weight loss) and (b) reduction of histology score (evaluation of immune cells infiltration and intestinal architecture). The increase of colonic epithelium proliferation and regeneration by modulation and maintenance of $Lgr5^+$ ISCs renewal is attributed to the up-regulation of *ID3* gene in mice and could probably be mediated by the non-canonical BMP pathway. This suggests a new role for BMP4, still poorly investigated [75].

Targeted deletion of *Bmpr1a* in $Foxl1^+$ colonic telocytes was also studied. After deletion, mice were subjected to an acute DSS treatment, followed or not by a recovery protocol. During the acute inflammation, total depletion of goblet cells was observed, leading to mucus layer disturbance, resulting in bacterial infiltration and a lower recovery ability [76]. The role of the BMP pathway in goblet cell differentiation was already discussed after epithelial deletion of *Bmpr1a* and associated with an impaired terminal differentiation but not with a change in the cell fate [71]. After recovery, a change of telocyte localization was noticed with a move toward the top of the crypt and therefore distant from stem cell niche [76]. A loss or a downregulation of the dialogue between ISCs and mesenchymal cells could explain the delay in healing when compared to controls. The epithelial modulation in response to mesenchymal deletion of *Bmpr1a* underlines the importance of the dialogue between mesenchyme and epithelium in the intestinal barrier function during both inflammation and healing.

In 2003, a first investigation measured the effect of BMP7 on the healing process of IBD in rats. TNBS-induced UC was performed intracolonically, followed by a therapeutic phase with intravenous BMP7 administration at 3 concentrations (30, 100 and 250 µg/kg) during different time intervals. A prophylactic model was used with a BMP7 treatment before colitis induction. The results indicate a better preservation of intestinal architecture in case of both BMP7 treatment and prophylaxis compared to the control group. Moreover, BMP7 showed an impact on proinflammatory genes with a decrease in mRNA level of *IL-6*, 2 days before colitis induction [77]. In 2012, *Maric et al* observed a significant decrease in *Bmp7* expression in the acute phase, after 2 and 5 days of TNBS acute colitis induction in rats [78].

4.1.2 BMP pathway in chronic phase of inflammation

These authors also investigated the BMP pathway during chronic colitis (14 and 30 days after TNBS colitis induction in rats) [78]. By monitoring the expression of BMP ligands, a significant decrease and increase of mRNA levels of *Bmp6* and *Bmp2* were observed, respectively, during the chronic phase. In the same study, the BMP7 therapy resulted in reduction of *Bmp2* and up-regulation of *Bmp4* gene expression, but also in *Smad6* and *Smad7* mRNA level downregulation. Interestingly, a relation was established with the mesenchyme since exogenous BMP7 improved the proliferation of mononuclear cells of the lamina propria and increased expression of *Smad1* and *Smad8* effectors during inflammation, thereby maintaining the BMP pathway active. In this way, the antagonist *Noggin* was increased both in acute and chronic phases and its level was restored to normal level after BMP7 treatment [78]. A last study performed in 37 CD patients showed that BMP7 was overexpressed in CD patient tissues compared to control tissues and correlated to the increase in *TGF-β1* gene expression [79]. One probable hypothesis reported an anti-fibrotic role for BMP7 related to the limitation of TGF-β1-induced epithelial to mesenchymal transition [80].

Finally, a recent study performed in human IBD colonic tissues reported an increase in *Grem1* mRNA and protein levels in inflamed tissue compared to the corres-

ponding non-inflamed tissue. The increase was correlated with that of two stem cell markers *Aldh1a* and *Oct4,* in UC patients. In inflamed UC tissues, the increased proliferation of *Oct4+* mesenchymal stem cells was combined with their aberrant differentiation into myofibroblasts still expressing *Oct4* stem cell marker. Moreover, these differentiated cells also exhibited high levels of PD-L1, a well-known immunosuppressive molecule that may contribute to their pathological phenotype [9,81]. In contrast, another study suggested a beneficial role for increased *Grem1* expression in IBD. Using a mouse genetic recombination model, the effects of *Bmp4* overexpression were found to be opposite to those of *Grem1* overexpression in ulcerative colitis. Not surprisingly, they noticed that *Bmp4* manipulation was associated with an impaired regeneration because this ligand mainly inhibited the dedifferentiation of progenitor cells and the maintenance of stem cells, whereas *Grem1* acted in favor of proliferation and epithelial reparation. However, the authors pointed out the risk of developing epithelial hyperplasia with a long-term *Grem1* overexpression [82].

To remember:

Current evidence highlights the complexity and fine regulation of the BMP pathway during both acute and chronic intestinal inflammation. We can summarize the emerging roles of BMP pathway components as follows:

1. **During the acute phase of inflammation:**

- BMP4 and BMP7 exhibit anti-inflammatory effects, associated with the downregulation of pro-inflammatory cytokine expression and production.

2. **During the chronic phase of inflammation and regeneration:**

- BMP7 plays a beneficial anti-fibrotic role by supporting the integrity of the epithelial barrier and modulating mononuclear immune cells.
- In contrast, increased expression of the BMP antagonist Grem1 has a paradoxical effect: it contributes to short-term epithelial regeneration but, over the long term, leads to aberrant and harmful differentiation of mesenchymal stem cells, resulting in epithelial hyperproliferation.

4.2. Role of BMP pathway in CRC

CRC is the third most common incident and second deadliest cancer worldwide [83]. In a majority of CRC cases, including both sporadic and hereditary cancers, the mutation of *Adenomatous Polyposis Coli (APC)*, a tumor suppressor gene, occurs in about 90% of the time as the first and initiating mutation. Consequently, the Wnt pathway is overactivated and leads to hyperproliferation of epithelial cells during the initiation of carcinogenesis [84]. The balance between the Wnt and BMP pathways, as a key to intestinal homeostasis, is then lost in favor of the Wnt pathway, requiring further study of the BMP pathway during colorectal carcinogenesis.

4.2.1. BMP pathway in hereditary syndromes and genetic predispositions to CRC initiation

The BMP pathway is strongly involved in the development of hamartomatous polyposis syndromes, including Juvenile Polyposis Syndrome (JPS) and Hereditary Mixed Polyposis Syndrome (HMPS). These syndromes are characterized by germline mutations that can be transmitted to the progeny. The genetic analysis of JPS patients showed that *SMAD4* and *BMPR1a* germline mutations are found in about 50 to 60% of JPS cases [67,85–87]. Histologically in mice, it was observed that germline mutation of *Bmpr1a* led to an aberrant expansion of the stromal compartment, whereas *SMAD4* mutation was more associated with epithelial changes (hyperplasia or even foci of dysplasia). An interesting study carried out on JPS patients confirmed these data by comparing histological phenotype between patients having *SMAD4* or *BMPR1a* germline mutations with those with sporadic juvenile polyps [88]. In contrast, in a polyposis patient's cohort, *BMPR2* gene was found to be a potential novel candidate involved in CRC development. Using CRISPR-Cas9 method in SW837 human colorectal cells, the inactivation of three *BMPR2* selected variants promoted cell proliferation and one variant had a total depletion of BMP pathway functions [89]. The HMPS, for its part, is caused by a mutation leading to an aberrant *GREM1* epithelial overexpression. This BMP antagonist, usually produced by subepithelial fibroblasts, here inhibits the BMP pathway along the epithelium, causing the formation of ectopic crypt foci with increased progenitor cells in HMP patients. The mutation could, in addition, act in synergy with hyperactivation of Wnt pathway during colorectal carcinogenesis. The possibility of an epithelial *GREM1* surexpression also exists in serrated colorectal cancers, a kind a sporadic equivalent of HMPS polyps [90,91].

Unrelated to polyposis syndromes, studies have investigated potential predisposition genes for hereditary CRC risk. In 2011, in a cohort of human patients, *BMPR1a, BMPR1b, BMPR2, BMP2, and BMP4* were classified as CRC risk genes, whereas *BMPR2, BMPR1b* and *BMP2* were rather associated with the risk of developing rectal cancer. Evaluation of the interaction with other genetic factors identified a correlation between BMP pathway genes and the tumor phenotype of methylated CpG island, but also with microsatellite instability and *KRAS* mutation [92].

Additionally, Allaire *et al*. investigated the stromal inactivation of the Bmpr1a receptor in myofibroblasts of the mouse large intestine. They observed (a) polyps formation, (b) stromal remodeling and important expansion of myofibroblasts and fibroblasts number and finally (c) modulation of ECM, immune cells and microenvironment with higher secretion of growth factors but also cytokines including Il-6 and Il-1β [93]. Similarly, *in vivo* in mice, the *Bmpr1a* receptor deletion has been evaluated in two subsets of mesenchymal cells (fibroblasts and myofibroblasts) and in endothelial cells. Only the fibroblastic deletion led to (a) expansion of stromal populations, (b) epithelial proliferation and (c) specific serrated polyp formation. Interestingly, the *Bmpr1a* deletion in mice was associated with *Cxcl12* upregulation in intestinal and colonic stromal cells, associated with epithelial hyperproliferation and serrated polyp formation. Interestingly, in the more advanced phase of CRC, *Ma et al* found that fibroblast-derived Cxcl12 is able to drive proliferation and invasion of cancerous cells through *PTEN* expression and PI3K/Akt signaling [94]. Inhibition of BMP colonic pathway using deletion of stromal *Bmpr2* in mutant mice resulted in epithelial hyperplasia and hamartomatous polyps, but only in the colon. Mutant mice have developed several symptoms like intestinal bleeding and epithelial hyperplasia, suggesting the importance of the dialogue between both

epithelial and mesenchymal cells, even if the central role in initiation of hamartomatous polyps is rather associated with a deficient stromal environment [95]. In parallel, the specific deletion of *Bmpr1a* receptor has also been performed in the epithelium of mice in two studies. In the first one, the deletion led to an impaired differentiation of secretory cells but not to initiation of crypt formation [71]. In the second study, an increase in epithelial cell proliferation but not to hamartomatous polyps associated with JPS was observed [93].

In definitive, these data highlight the importance of the mesenchymal BMP signaling in polyp formation and CRC initiation. BMP deletion in the mesenchymal compartment leads to expansion of a reactive stroma with a probable increase of *Cxcl12* mRNA level or pro-inflammatory cytokines, but also strongly disrupts the dialogue with epithelial cells (Fig. 3).

4.2.2. Sporadic CRCs and evolution of the BMP pathway during promotion and progression

The involvement of the BMP pathway in CRCs may also occur not only during initiation stages, demonstrating the complexity of the pathway. Indeed, a study performed on human colonic tissues showed that the loss of *BMPR2* and *SMAD4* gene expression was associated with the progression of the disease because these genes were no longer detected in advanced cancer tissues in comparison with adenoma ones [96]. In another similar study, the loss of *BMPR2* expression was rather associated with microsatellite instable cancers, while an impaired *SMAD4* expression was correlated to stable microsatellites [97]. These first data indicate that the BMP pathway seems to switch off between adenoma and cancer steps. These results are consistent with an upregulation of *GREM1* expression in patients tumor tissues in comparison with normal ones [98].

In contrast, other studies have demonstrated that BMP ligands are overexpressed in advanced colorectal cancer tissues, conferring a pro-oncogenic role to the BMP pathway. Indeed, in two different studies on patient cohorts, BMP7 was found to be highly increased in CRC tissues in comparison with peripheral non-tumoral mucosa [99]. In the second study, the *BMP7* overexpression was correlated with a worse prognosis and liver metastasis [100]. The same results were obtained for BMP9, which was significantly up-regulated in human carcinoma compared to adenoma and to normal colonic mucosa [101] and for *BMP4* with a significantly higher expression in colorectal cancer tissues in comparison with normal colon tissue [102]. In both cases, high BMP ligand expression was correlated with the poorest prognosis in patients (98,99). In contrast, *BMP3* expression (classified as a Bmp antagonist) was down-regulated in sporadic CRC tissue samples in comparison with the normal colonic mucosa and independently of the microsatellite stability status [103]. BMP ligand role was also assessed and discussed in colorectal cancerous cell lines. Table 2 presents the different studies with various conclusions according to the experimental conditions.

Even if the BMP pathway could be inhibited in advanced colorectal cancer tissues in comparison with adenomas, the establishment and progression of the tumor is rather associated with an increase in BMP ligand and Grem1 antagonist expression in both the epithelial and mesenchymal compartments. However, it is still unclear on this day whether the increase is rather the cause and result of the carcinogenesis process or rather the consequence of an activation of a defense mechanism.

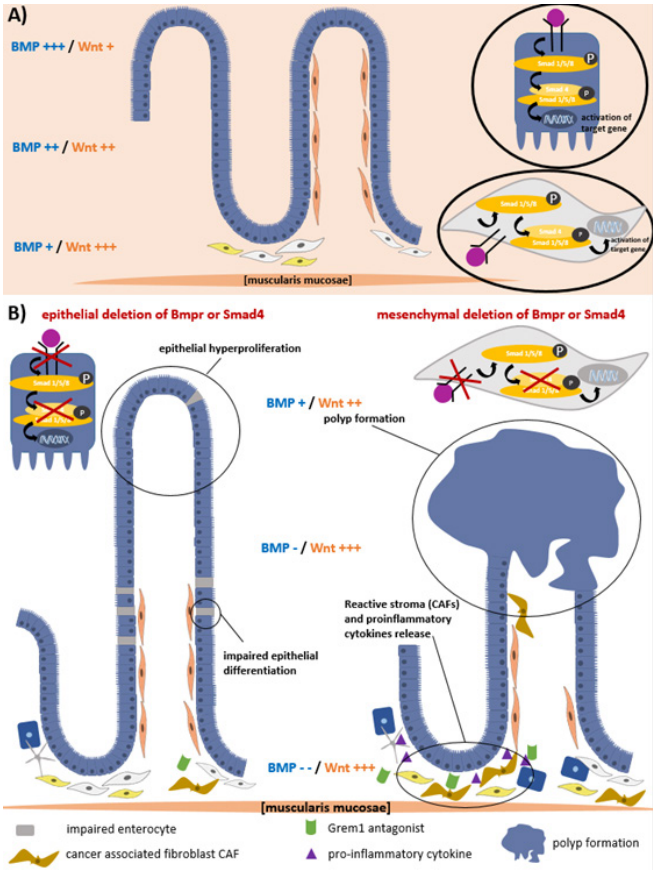

Fig. 3. Schematic representation of the impact of BMP pathway deletion (Bmpr/Smad) in the epithelium or the mesenchyme: (A) representation of the balance between the Wnt and BMP pathways. (B) Bottom left, a deletion of epithelial Bmpr or Smad4 is associated with impaired differentiation and increased proliferation. Bottom right, a mesenchymal deletion leads to a reactive stroma, an inflammatory context and sporadic or hamartomatous polyps in the intestine.

4.2.3. A track to explain the paradoxicality of the BMP pathway: the genetic status

The Smad4 status plays an important role in the modulation of BMP pathway, as first observed in Table 2. The impact of a BMP pathway activation has been evaluated in both *SMAD4*-negative and positive CRC cells and also in human colonic tissues. In *SMAD4* negative cells, the activation of BMP signaling resulted in increased EMT, migration and invasion abilities, whereas in *SMAD4*-positive cells, the same action led cells to a more epithelial phenotype. Activation of BMP signaling in *SMAD4*-negative cells seemed mediated by the activation of the non-canonical Rho/ROCK/LIMK pathway. Very interestingly, these data were confirmed in humans because patients with both *SMAD4* mutation and active Bmp receptors had the poorest prognosis [113]. Further investigations demonstrated that under *SMAD4*-negative status, the activation of BMP pathway was no longer inhibiting Wnt signaling but was even able to activate this pathway, which correlated with an association between *SMAD4* deletion and higher β-catenin level. In p53-mutated cells, BMP had no influence on Wnt signaling, but *p53* wild type was mandatory for BMP to inhibit Wnt signaling. *SMAD4* and

Table 2. Summary of *in vitro* studies on BMP actor's role and cellular mechanisms involved in advanced colorectal cancer model.

In vitro cell lines	BMP actor and effect	Observed effects and activated pathways
- SW480 and DLD1 cells (mutated K-RAS) **- CT26 cells** [104]	Bmp2 **Benefical** and **Deleterious**	- Inhibition of cell growth during sshort-termexposure to Bmp2 - Resistance, induction of invasion (loss of E-cadherin cell-to-cell contact) and epithelial to mesenchymal transition during long-term exposure for surviving cells Induction of MET by Bmp2 blockade → involvement of PI3K/Akt pathway
- SW480 cells - Smad4 null cells [105]	Bmp2 treatment **Beneficial** and **Deleterious**	- Biphasic response with a decreased growth during 48h and then an increased proliferation. Decrease *PTEN* mRNA and protein levels after 36h and 84h, respectively →relayed by non-canonical pathway RAS/ERK
- HCT116 and SW620 cells STAT3- silenced or overexpressed [106]	Bmp2 **Deleterious**	- Increase of cancer stem cell proliferation, increase EMT and up-regulation of STAT3 expression - In STAT3 knockdown cells, inhibition of EMT decreased proliferation and EMT
- HCT116 and HEK-93 cells [107]	Bmp2 **Benefical**	- Inhibition of proliferation and migration of cancer cells, induction of apoptosis -Suppression of *in vivo* tumor growth of human cancer cells in xenograft
- HT29 and DLD-1 cells [102]	Bmp4 **Deleterious**	Prevention of colorectal cancer cells apoptosis and promotion of tumor growth by autocrine Bmp4 → aberrant activation of Wnt/β-catenin and MAPK/Erk pathway
- HCT116 cells overexpressing BMP4 [108]	Bmp4 **Deleterious**	- Increased migration and invasion abilities of HCT116 cells and protection from apoptosis →Regulation of urikase plasminogen activator UPA system activity to promote malignancy of cancerous cells
- SW480 cells overexpressing BMP4 and Smad4-negative [109]	Bmp4 **Deleterious**	- Change in SW480 cell morphology and increase in spreading, adhesion, EMT, migration and invasion abilities → loss of Smad4 involved in progression of colorectal cancer cells, non-canonical pathways not yet investigated
- chemoresistant colorectal cancer stem cells from humans (CRC-SCs) Smad4 negative or positive [110]	Bmp4 **Benefical**	-Differentiation and inhibition of tumorigenic capacity of CRC-SCs. Effect is ineffective in *Smad4* negative cell line. - Enhancement of cytotoxic effect of chemotherapy → inhibition of PI3K/AKT pathway and antagonization of Wnt proliferative effects
- NCM460 cells **- SW620 and SW480 cells** **- HT29 cells** [111]	Grem1 **Deleterious**	- Increased *Grem1* mRNA level mesenchymal like cell > epithelial like cell > normal colon cell - Repression of tumor cell growth, angiogenesis and EMT in *Grem1* silencing in mesenchymal-like cells → hypothesis of BMP/Smad and VEGF independent pathways
- SW480 and SW620 cells [112]	Grem1 **Deleterious**	Increased Grem1 production by fibroblastic cells in coculture in response to paracrine signals from colon cancer cells, resulting in BMP inhibition and EMT
- HCT116 and SW480 cells [98]	Grem1 **Deleterious**	Promotion of invasion, migration, EMT and endoplasmic stress → modulation of ATF4 and ATF6 through activation of PI3K/Akt pathways and antagonization of Bmp2 pathway

The different cell lines are human colorectal cancer cell lines, except for NCM460, that derives from normal epithelial cells.

p53 mutations also affected the chemosensitivity status [114]. Indeed, the importance of the BMP pathway in chemotherapy was demonstrated by using SMAD4-expressing CT26 and *SMAD4*-null SW620 colorectal cell lines. *Smad4* deletion was able to induce a resistance to 5-FU, which was confirmed *in vivo* through the activation of the non-canonical PI3K/Akt/CDC2 cascade, leading to inhibition of cell cycle arrest and apoptosis [115]. In a more recent meta-analysis conducted on 10 studies and about 4400 patients, *SMAD4* mutation was associated with poor prognosis and aggressiveness of CRC, but also with the *RAS* status [116]. Interestingly, an *in vitro* study on SW480 colon cancer cell lines (transfected with small interfering RNA against KRAS) showed that oncogenic *KRAS* downregulated Bmp4 through non non-canonical ERK pathway [117]. In conclusion, the *SMAD4* status clearly drives the BMP signaling pathway during carcinogenesis, but *p53, KRAS* and the role of other cancer-related genes

have to be further explored. Their silencing during promotion stages led to a more deleterious impact of the BMP pathway that seems to be due to activation of non-canonical pathways.

To remember:

- The BMP pathway plays a key role in polyposis syndromes JPS and HMPS and CRC initiation. Deletion of BMP receptors and *SMAD4* effector in the mesenchymal compartment is associated with a higher risk of developing CRC.

- The BMP pathway could be inactivated in advanced stages of the CRC, consistent with a Grem1 expression upregulation. But BMP ligands (BMP4, BMP7 and BMP9) may be found to be overexpressed in CRC tissues/cells in correlation with the poorest survival rate.

- The *SMAD4* status is crucial. Under Smad4 negative status, non-canonical BMP pathways (including pAkt, p38MAPK or pERK) are associated with progression, aggressiveness and higher chemoresistance of the tumor. Under *SMAD4* positive status, Bmp ligands could have, on the opposite, therapeutic properties by promoting differentiation of colorectal cancer cells and enhancing response to chemotherapy treatment.

Conclusion

In conclusion, the balance between the Wnt and the BMP pathways, strongly integrating the importance of the dialogue between epithelial and mesenchymal populations, is crucial for maintaining intestinal homeostasis. In inflammatory bowel diseases (IBD) and colorectal cancers (CRC), the balance between signaling pathways is disrupted, often resulting in the overactivation of Wnt signaling. While increased expression of the BMP antagonist Grem1 in IBD is associated with epithelial regeneration, in CRC it contributes to uncontrolled epithelial hyperproliferation. The BMP pathway itself may remain active in these contexts; however, activation of non-canonical BMP signaling pathways frequently exerts deleterious effects. Despite advances, several critical questions remain unresolved: (a) What is the precise role of non-canonical BMP signaling in the intestine under both physiological and pathological conditions, and how and when are these pathways engaged? (b) What are the distinct functions of various BMP ligands? Evidence points to their specific spatial expression along the crypt-villus axis as a key factor, but further investigation is particularly needed for Bmp7 and Bmp9, which are overexpressed in CRC tissues yet remain poorly characterized. (c) What roles do the diverse BMP modulators play? Beyond the antagonists discussed, other regulators—including extracellular factors such as follistatin, membrane-bound modulators, and intracellular inhibitors like Smad6 and Smad7—have mechanisms of action that remain largely unknown.

Definitively, the complexity of such an important pathway in the intestine pathophysiology requires further investigations to study the exact role of the BMP pathway in *in vitro* and *in vivo* models by considering the disease step and the environment but also the genetic context and the effect of the numerous modulators.

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