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REVIEW

Regulation of bone morphogenetic protein 4 on epithelial tissue

Sitong Shen[1] · Shurong Wang[1] · Yuxi He[1] · Huicong Hu[1] · Boyuan Yao[1] · Yan Zhang[1]

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Abstract

Epithelial tissues provide tissue barriers and specialize in organs and glands. When epithelial homeostasis is physiologically or pathologically stimulated, epithelial cells produce mesenchymal cells through the epithelial-mesenchymal transition, forming new tissues, promoting the cure of diseases or leading to illness. A variety of cytokines are involved in the regulation of epithelial cell differentiation. Bone morphogenetic proteins (BMPs), especially the bone morphogenetic protein 4 (BMP4) has a variety of biological functions and plays a prominent role in the regulation of epithelial cell differentiation. BMP4 is an important regulatory factor of a series of life activities in vertebrates, which is also related to cell proliferation, differentiation and mobility, it also has relation with tumor development. This paper mainly reviews the mechanism of BMP4's regulation on epithelial tissues, as well as its effect on the growth, differentiation, benign lesions and malignant lesions of epithelial tissues, and expounds the function of BMP4 in epithelial tissues, to provide theoretical support for the research on reducing epithelial diseases.

Keywords Bone morphogenetic protein 4 · Epithelial tissue · Growth and differentiation · Benign lesions · Cancer

Abbreviations

BMPs	bone morphogenetic proteins
BMP4	bone morphogenetic protein 4
BMPRI, BMPRII	BMP type I and II receptors
Smad	drosophila mothers against decapentaplegic protein
r-smads	receptor-regulated Smads
coSmads	common partner Smads
P38 MAPK	P38 mitogen-activated protein kinase
ERK1/2	extracellular regulated protein kinase 1/2
JNK	c-Jun amino terminal kinase
PI3-K	phosphatidylinositol-3-kinase
PKB	serine/threonine kinase B
AT1s	type I alveolar cells
AT2s	type II alveolar cells
Sulf1	sulfatase sulf-1
OC1	cochlear tissues and a sensory epithelial cell line
NR_2B gene	aspartic acid receptor subunit gene
Foxn1	forkhead transcription factor 1
TNF-α	tumor necrosis factor
IFN-γ	interferon-γ
IL-8	active interleukin 8
BE	Barrett's esophagus
KLF4	kruppel-like factor
COPD	chronic obstructive pulmonary disease
ID3	inhibitor of differentiation 3
M1	classical activation of macrophages
M2	selective activation of macrophages
ID2	differentiation inhibitor 2

✉ Yan Zhang
zhangy66@jlu.edu.cn

[1] Department of Ophthalmology, the 2nd Hospital of Jilin University, Changchun 130041, China

Epithelial tissues and classification

Epithelial tissues consist of a large number of cells with regular shape and few intercellular stroma, referred to as epithelium. Epithelial cells have two polarities, one is called the free surface, facing the surface of the body or cavity organs, and the other is called the basal surface, facing deep connective tissues. There are no blood vessels in epithelial tissues, and they are rich in nerve endings that can sense various stimuli(Honda 2017) (Table 1).

Table 1 Characteristics and representative of different kinds of epithelium

Kinds of epithelium	Characteristics of epithelium	Typical epithelial tissues
Covering epithelium	1.Composed of regular dense epithelial cells and a small amount of intercellular stroma 2. Can evolve into glandular epithelium and sensory epithelium during the development of embryos.	Palatal epithelium Alveolar epithelium Corneal epithelium Airway epithelium Gastric epithelium Ovarian epithelium ...
Glandular epithelium	Specialized for secretory function	Urogenital sinus epithelium Breast epithelium Thymic epithelium...
Metastatic epithelium	The shape and level may vary with the contraction or expansion of the host organ	Ureteral epithelium Urinary epithelium Bladder epithelium...
Sensory epithelium	Specialized for special sensory functions	Sensory epithelium...

The regulatory mechanism of BMP4 in epithelial tissues

Uptream signal pathways and sources of BMP4

BMP4 plays an important role in mesoderm differentiation and is regulated by its upstream pathways. Wnt/β-catenin signal (Fig. 1) is one of its upstream signal pathways(Kim et al. 2002),which may activate or inhibit BMP4 in different tissues or functions, and the correlation between them remains to be studied. BMP4 exists in many kinds of cells, and when the BMP4 in epithelial cells is activated, it migrates to mesenchymal cells, activates the downstream signaling pathway of BMP4 in mesenchymal cells, undergoes epithelial-mesenchymal transition(Li et al. 2019; Seppo Valnio et al. 1993), and regulates the growth and differentiation of epithelial cells through the paracrine sequence between mesenchymal and adjacent epithelium provided by BMP4 ligands(Kahata et al. 2018).

BMPs ligands and receptors

BMP ligands bind to BMP type I and II receptors (BMPRI, BMPRII), which show kinase activity and send signals that activate intracellular effectors, such as drosophila mothers against decapentaplegic protein (Smad) and signal branches of protein kinases, lipid kinases and small molecule kinases(Kahata et al. 2018). BMP4 binds to BMPRII and phosphorylates BMPRI to form a complex that activates its downstream pathway (Rahman et al. 2015).

Downstream signal pathways of BMP4

BMP4 is a member of the TGF-β family. TGF-β ligands express and secrete at sites where epithelial cells interact with mesenchymal cells, contributing to regulate the growth and differentiation of epithelial cells and regulate differentiated epithelial cells(Kahata et al. 2018).

BMPs have a series of downstream signaling pathways, Smad is one of the most important. Smad includes receptor-regulated Smads (r-smads), common partner Smads (coSmads) and path-restricted Smads(Miyazawa and Miyazono 2017). Activation of BMPRI regulates the phosphorylation of r-smads, among which the phosphorylation of Smad1, Smad5 and Smad8 has BMP signal specificity. Phosphorylated r-smads protein forms a complex with Smad4, a coSmad protein with BMP signal specificity. This complex enters the nucleus and binds to a variety of co-activators or co-inhibitors to regulate the transcription of target genes (Liu et al. 2017).

Smad-independent downstream signaling pathway is also an important pathway of BMP4. P38 mitogen-activated protein kinase (P38 MAPK), extracellular regulated protein kinase 1/2 (ERK1/2), c-Jun amino terminal kinase (JNK), phosphatidylinositol-3-kinase (PI3-K), and serine / threonine kinase B (PKB) are all downstream signals independent of Smad (Chen et al. 2004). BMP4 binding to receptor induces phosphorylation of downstream signals and up-regulates or down-regulates the expression of related factors (Li et al. 2013). Furthermore, it is involved in the regulation of cytoskeletal change, migration and cell survival, and can affect the transcription of target genes either alone or in coordination with the Smad pathway (Fig. 2).

Regulation of BMP4 on epithelium

Regulation of BMP4 on epithelial tissue growth

Regulation of BMP4 on the growth of covering epithelium

In the process of palatal development, if the integrity of the palatal epithelium is destroyed, it usually leads to

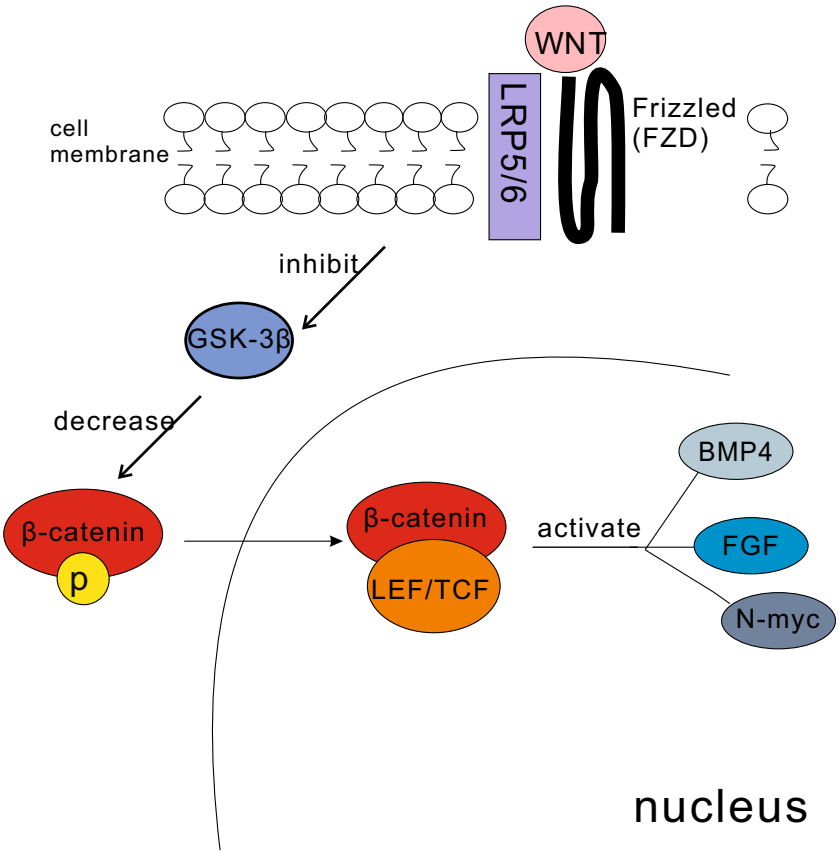

Fig. 1 This figure introduces the basic mechanism of WNT pathway. When the WNT pathway is opened, three proteins on the cell membrane bind, inhibiting the activity of corresponding kinases, reducing the phosphorylation of β-catenin. And β-catenin aggregates in the nucleus, BMP4 is its downstream pathway. In the formation and differentiation of lung, β-catenin plays an active role in BMP4, and then activates exogenous mesenchymal stem cells to differentiate into epithelial cells, regulating lung injury and repair. In corneal stratification, β-catenin inhibits BMP4

abnormal adhesion or fusion between the palatal framework connected with the adjacent structure, resulting in cleft palate defect (He et al. 2010). BMP4 is expressed in the prepalatal stroma to maintain the expression of Msx1 and promote the proliferation of anterior palatal epithelial cells and prepalatal stromal cells through the msx1-bmp4 positive feedback loop(Hilliard et al. 2005).

BMP4 also regulates the growth of upper and lower molars. BMP4 signals in the epithelium can activate BMP4 signals in the stroma, thereby promoting odontogenic proliferation of mesenchymal cells in the process of tooth morphogenesis and tooth formation (Seppo Valnio et al. 1993). Studies have shown that BMP4 can inhibit the activity of Dkk2, an antagonist of its upstream Wnt pathway, and synergize with Msx1 to promote the growth of epithelial cells and mesenchymal cells in the upper and lower molars (Jia et al. 2013).

There are type I alveolar cells (AT1s) and type II alveolar cells (AT2s) in alveolar epithelium (Fiaturi et al. 2018). After pneumonectomy, the compensatory regeneration of alveoli promotes the proliferation of AT2s, and new AT1s are formed to restore alveolar surface area and pulmonary function.BMP4 is active in most AT1s and AT2s in quiet adult lungs.BMP4 in AT2 helps to maintain its stability.However, at the early stage of pneumonectomy, the phosphorylated smad1/5/8 in AT2 decreases, making it sensitive to proliferation and differentiation signals, thus promoting the proliferation of AT2 cells and their differentiation into AT1 cells, thus promoting alveolar compensatory regeneration(Chung et al. 2018). Therefore, BMP4 can promote the growth of covering epithelium of multiple organs.

Regulation of BMP4 on the growth of glandular epithelium

BMP4 can inhibit the growth of glandular epithelium in some organs. The prostate gland is a male-specific exocrine gland developed from the urogenital sinus of the lower urethra (Marker et al. 2003). Activation of androgen receptors in the urogenital sinus mesenchyma will regulate the formation of prostatic buds from the epithelial cells of the urogenital sinus (Cunha 1985). However, bud formation and branch morphogenesis of prostate are regulated by BMPs, among which BMP4 is an inhibitor of prostatic bud formation and branch morphogenesis (Keil et al. 2015). Studies have shown that in urogenital sinus, exogenous BMP4 inhibits testosterone-induced prostatic duct germination and epithelial cell proliferation. In the development of many organs, the regulation of heparan sulfate sulfonation is an important determinant of growth factor signal transduction. Extracellular sulfatase sulf-1 (Sulf1) inhibits prostate development (Kleinschmit et al. 2010), and BMP4 inhibits prostate development by

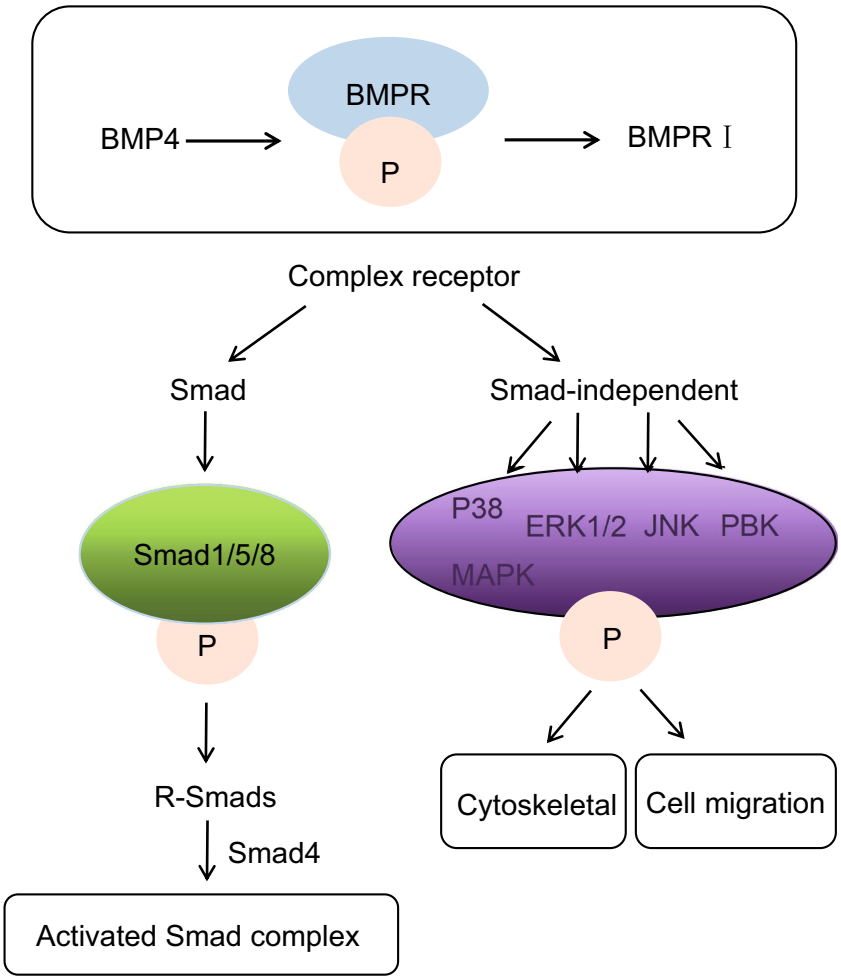

Fig. 2 BMP4 and its downstream pathways.

inducing the expression of Sulf1 (Buresh-Stiemke et al. 2012). Therefore, BMP4 can inhibit the proliferation of the urogenital sinus epithelium and thus inhibit the development of prostate.

BMP4 can also inhibit the growth of breast epithelium. The formation of dorsal ventral boundary is the key to determine body plan during embryonic development. When Tbx3 gene is overexpressed in the mammary gland formation region, it promotes prolongation of the dorsal ventral boundary and exhibits epithelial thickening of the characteristics of the mammary ectoderm. Bmp4 negatively regulates Tbx3 and inhibits the growth of breast epithelium, thereby limiting the growth of breast epithelium to a specific location (Cho et al. 2006). Therefore, BMP4 has a certain inhibitory effect on the growth of glandular epithelium.

Regulation of BMP4 on the growth of sensory epithelium

BMP4 promotes the apoptosis of cochlear sensory epithelial cells and inhibits the growth of cochlear sensory epithelium. Cochlear tissues and a sensory epithelial cell line (OC1) are continuously growing sensory epithelial cells of the cochlea. BMP4 and its receptors are highly expressed in the sensory area of the developing rat cochlea and are involved in the regulation of hair cell development (Zheng et al. 2008). Studies have shown that excessive intracellular calcium ion loading can lead to the disorder of calcium channels leading to cell apoptosis (Huber et al. 2018). BMP4 can increase intracellular calcium ion concentration, thereby inhibiting DNA synthesis and promoting the apoptosis of OC1 cells. In addition, aspartic acid receptor subunit gene (NR_2B gene) is a part of the brain N-methyl-D-aspartate nerve endings. It is highly expressed in the sensory epithelial cells of the cochlea, which can promote the apoptosis of OC1. BMP4 promotes the apoptosis of cochlear sensory epithelial cells and inhibits the growth of cochlear sensory epithelium by increasing the expression of NR_2B gene (Chen et al. 2014).

Regulation of BMP4 on epithelial tissue differentiation

Regulation of BMP4 on the differentiation of covering epithelium

BMP4 can promote the differentiation of corneal epithelial cells into layers. The cornea is a transparent tissue located on the anterior surface of the eye, consisting of layered non-keratinized epithelium, thick matrix scattered over keratinocytes, and monolayer endothelium (Zieske 2004). The activity of Wnt/β-catenin signal in corneal stromal cells was negatively correlated with the stratification and proliferation of corneal epithelial cells. When the Wnt/β-catenin signal is removed, its inhibition on BMP4 is removed, and the expression of BMP4 is increased as a paracrine factor to enhance the expression of P63 in corneal epithelial stromal cells. P63 is necessary to initiate epithelial stratification and maintain the proliferation potential of basal keratinocytes during corneal and skin development (Zhu et al. 2014). Therefore, BMP4 can promote the stratification and proliferation of corneal epithelial cells (Zhang et al. 2015).

Regulation of BMP4 on the differentiation of glandular epithelial

The embryonic epithelial thymus gland is originated from the endoderm of the third pharyngeal sac. Under the influence of forkhead transcription factor 1 (Foxn1), it eventually differentiates into functional thymic epithelial cells. Foxn1 is a key transcriptional regulator for thymic epithelial differentiation (Swann et al. 2017). At the early stage of embryonic development, the primitive endoderm signals the adjacent mesenchyma to induce BMP4 expression, which in turn activate the expression of Foxn1 and induce the differentiation of thymic epithelium (Neves et al. 2012). When BMP signal in thymic embryo is suppressed, thymus will be dysplastic(Soza-Ried et al. 2008), which further proves that BMP4 can promote the differentiation of thymic epithelium.

Regulation of BMP4 on the differentiation of metastatic epithelium

BMP4 can promote the proliferation and differentiation of ureteral epithelial cells and induce the formation of mesenchymal cells. The ureter is an important part of the urinary system, which ensures the effective discharge of urine from the renal pelvis to the bladder (Bohnenpoll et al. 2017a). Sonic hedgehog factor is an important signal for growth and differentiation of ureteral epithelial cells. Secreted by ureteral epithelium, sonic hedgehog factor activates its downstream pathway and induces the expression of Forkhead transcription factor 1 (Foxf1) in mesenchymal tissue. Foxf1 activates and maintains the expression of BMP4, which regulates the proliferation and differentiation of ureteral mesenchymal and epithelial cells (Bohnenpoll et al. 2017b; Haraguchi et al. 2012). Therefore, BMP4 plays a crucial role in the differentiation of ureteral epithelium as a downstream signal. BMP4 plays a role in promoting epithelial differentiation in different types of epithelial tissues of different organs.

Regulation of BMP4 on benign lesions of epithelium

Regulation of BMP4 on benign lesions of covering epithelium

Inflammatory response can remove harmful factors in tissues, but uncontrolled inflammatory response will lead to tissue damage. If inflammatory factors can not be removed in time, acute inflammation will turn into chronic inflammation, causing serious consequences (Khedoe et al. 2013). Gastric epithelial cells are monolayer columnar epithelium, which will release a large amount of cytokines and chemokines when stimulated by inflammation. Peptides such as tumor necrosis factor (TNF-α), Interferon-γ (IFN-γ), and active interleukin 8 (IL-8) can promote and maintain the injury of gastric mucosa (Obonyo et al. 2002). BMP4 was not expressed in normal human gastric antrum tissues, but was abundantly expressed in inflammatory gastric antrum tissues infected by Helicobacter pylori (Bleuming et al. 2006). In the gastric mucosa, the signals are generated by BMP target gastric epithelial cells, and BMP4 in gastric mucosa cells can inhibit the expression of IL-8, thereby slowing down gastric inflammation. In addition, BMP4 is also expressed in the respiratory epithelium, and TNF-αincreases the expression of BMP4 in the respiratory tract, thereby activating the downstream Smad pathway to reduce the IL-8 induced by TNF-αand alleviate the inflammatory response (Li et al. 2014). Therefore, activation of BMP signals, including BMP4, can inhibit the expression and release of inflammatory cytokines in covering epithelial cells (Takabayashi et al. 2014).

Barrett's esophagus (BE) is a dermal metaplasia in which the normal squamous epithelium in the distal esophagus is replaced by columnar epithelium. The most abundant bile acids in the patients' reflux fluid are deoxycholic acid and deoxycholic acid (Taddei et al. 2014). When exposed to deoxycholic acid, the expression of BMP4 in esophageal squamous epithelium increases, activating the expression of kruppel-like factor (KLF4) in its downstream pathway and inducing the metaplasia transformation in the process of BE formation (Yan et al. 2016).

Human airway epithelium is pseudostratified columnar epithelium, and basal cells are stem cells of human airway epithelium, which can differentiate into ciliated cells and secretory cells (Rock et al. 2010). Smoking may lead to chronic obstructive pulmonary disease (COPD), which is characterized by morphological changes in airway epithelium,

including basal and intermediate cells proliferation, reduction of ciliated cells, goblet cell proliferation and squamous epithelial metaplasia (Shaykhiev et al. 2013). Studies have shown that BMP4 expression is very low in normal airway epithelium. However, in the airway epithelium of smokers with copd, BMP4 type I receptors increase and play a role in regulating BMP4. BMP4 inhibits normal basal cells from differentiating into mucociliary epithelial cells and secretory cells, and induces squamous metaplasia by activating the downstream Smad pathway (Zuo et al. 2019). Therefore, BMP4 promotes morphological changes of airway epithelium and induces the occurrence of airway epithelial diseases.

In summary, BMP4 can both slow down the inflammatory response of the covering epithelium and induce corresponding benign lesions by inducing epithelial metaplasia or differentiation.

Regulation of BMP4 on benign lesions of metastatic epithelium

Urinary epithelium is a kind of metastatic epithelium. When the urethra is infected or injured by inflammation, the expression of Shh signal in basal cells and Wnt signal in stromal cells are up-regulated, and the expression of BMP4 is promoted, thus promoting the regeneration and injury repair of urinary epithelium and restoring the barrier function of urinary epithelium (Wang et al. 2017). Urinary tract infection is caused by urinary pathogenic *Escherichia coli* infection, and urinary tract infection will reduce the expression of BMP4 and the activity of downstream pathway Smad1, thereby leading to dysdifferentiation of urinary epithelial cells (Mysorekar et al. 2009). Therefore, BMP4 plays an important regulatory role in the repair of urethral epithelial injury.

Reconstruction of the bladder is also associated with structural restoration of the bladder epithelium and detrusor. When damaged, under the stimulation of mesenchymal stem cells, Hh ligands (mainly Shh) were increased in bladder epithelial basal stem cells, thereby promoting the production of Hh target gene product BMP4. BMP4 transmits paracrine stimulation to bladder epithelium to promote the repair of bladder epithelium and smooth muscle layer (Pokrywczynska et al. 2019). Therefore, BMP4 plays a repair role in the lesion of transitional epithelium.

Regulation of BMP4 on benign lesions of glandular epithelium

BMP plays an important role in the formation of submandibular glands by regulating the synthesis of extracellular matrix. During the development of submandibular gland, epithelial cells grow and germinate. The initial bud divides and elongates to form a network of epithelial stems with buds at the top and mesenchymal substances derived from neural crest around it (Miao et al. 2019). The development of submandibular gland will be affected if there are obstacles in the formation of branches. BMP4 inhibits the size and number of buds and their further branches, thus inhibiting the development of submandibular glands (Hoffman et al. 2002). It can be speculated that BMP4 inhibits the development of glands by inhibiting the growth of glandular epithelium, thus leading to diseases..

Regulation of BMP4 on malignant lesions of epithelium

Regulation of BMP4 on malignant lesions of covering epithelium

Ovarian cancer is the most fatal cancer among gynecological malignancies. Most ovarian cancer originates from ovarian epithelium, which forms a continuous monolayer of cells and attaches to the surface of the ovary through the basement membrane composed of fibronectin, collagen type IV and laminin. Ovarian epithelium secretes vitreous binding protein and integrin to enhance cell adhesion (Auersperg et al. 2001; Shepherd and Nachtigal 2003). Studies have shown that Hedgehog signaling produced in ovarian cancer cells can regulate the production of BMP4 by mesenchymal stem cells associated with ovarian cancer, which in turn enhances Hedgehog signaling (Coffman et al. 2016). BMP4 can not only regulate the expression of extracellular matrix components and integrin, but also promote the expression of inhibitor of differentiation 3 (ID3), thus promoting the migration and morphogenesis of ovarian cancer cells (Shepherd et al. 2008; Theriault et al. 2007).

In addition, odontogenic tumors are a group of tumors that derived from the tooth formator or its remnants and can only be found in the jaw or associated soft tissue. Increased expression of BMP4 in odontogenic tumors can promote its occurrence (Swarup et al. 2018).

Rgulation of BMP4 on malignant lesions of metastatic epithelium

Bladder epithelium is a metastatic epithelium in which BMPs plays an important role in regulating homeostasis through fine regulation of Wnt and Hedgehog signals. In this process, BMPs induce differentiation of urothelial cells (Shin et al. 2014). Data shows that BMP4 signals generated by bladder cancer cells can induce the polarization of monocytes/macrophages to the M2 phenotype (Martinez et al. 2017). Macrophages can be divided into two polarization types according to their phenotypes and the polarization factors they secrete, namely, classical activation (M1) and selective activation (M2) of macrophages. The macrophages secreting pro-inflammatory factors are mainly M1 macrophages, while M2

Table 2 Different roles and corresponding pathways of BMP4 in different epithelial tissues

Epithelial tissue and related phenomena		Involved pathways and genes	The function of BMP4
Growth	Covering epithelium	Msx1-BMP4	Promote the growth of multiple organ epithelium
	Glandular epithelium	BMP4-Sulf1/Tbx3	Inhibit the growth of glandular epithelium
	Sensory epithelium	BMP4-Ca2 + NR2B	Inhibit the growth of cochlear sensory epithelium
Differentiation	Covering epithelium Glandular epithelium	Wnt /β-catenin Foxn1-BMP4	Promote epithelial differentiation
	Transitional epithelium	Foxf1-BMP4	
Benign lesions	Covering epithelium	Smad, Inhibition of IL-8 expression	Slow down the inflammatory response and induce morphological transformation of epithelium
	Glandular epithelium	Unknown	Inhibiting glandular development
	Transitional epithelium	Smad	Promote repair of epithelial injury
Malignant lesions	Covering epithelial	Wnt、Hedgehog	Promote cancer development
	Glandular epithelium	Smad	Promote/inhibit cancer development
	Transitional epithelium	Wnt、Hedgehog	Promote cancer development

macrophages play a major role in reducing inflammation and tissue repair. Among them, M2 macrophages are beneficial to the growth of cancer cells (Zaki et al. 2011). Therefore, BMP4 can promote the development of bladder cancer by inducing macrophage polarization to the M2 phenotype.

Regulation of BMP4 on malignant lesions of glandular epithelial

BMP4 promotes the development of breast cancer. BMP4 and BMP7 are overexpressed in breast cancer and enhance the migration and invasiveness of breast cancer cells. If BMPR2 is inhibited, the phosphorylation of the downstream signaling pathway smad1/5/8 of BMP4 is also inhibited (Owens et al. 2012), further demonstrating the promoting effect of BMP4 on the progress of breast cancer.

In addition, BMP4 has an inhibitory effect on lung adenocarcinoma. Adriamycin can induce premature senescence of lung cancer cells. Adriamycin induces up-regulation of BMP4 expression, thereby activating the Smad pathway, acetylating histone acetylase p300 in the promoter regions of P16 and P21, and mediating senescence of lung cancer cells (Su et al. 2009).

It is worth noting that BMPs are major regulators of development and play an important role in carcinogenesis. BMP4 plays a dual role in the regulation of cancer cells, either inhibiting or stimulating the occurrence and metastasis of cancer cells, depending on the tissue and the type of cancer. BMP4 can induce the development of ovarian cancer, odontogenic tumor, bladder cancer, breast cancer, urethral cancer and prostate cancer, as well as inhibit the occurrence of lung adenocarcinoma, liver cancer (Zhang et al. 2012)and gastric cancer (Shirai et al. 2011). Therefore, the role of BMP4 in the development of cancer in different organs remains to be studied.

Conclusion

Since the regulation of BMP4 on epithelial tissues has been discovered, the research on BMP4 has become more and more extensive. This article reviews the regulation mechanism of BMP4 on epithelial tissue, and summarizes the regulation of BMP4 on epithelial growth, differentiation, benign lesions and malignant lesions according to different epithelial types (Table 2)

The upstream and downstream pathways of BMP4 and their roles in different diseases remain to be studied. At present, studies have shown that myofibroblasts can increase the expression of BMP4 in the esophagus and promote epithelial growth in the form of esophageal myofibroblast - paratrophic secretion (Zhang et al. 2018). Thymic endothelial cells can also promote the expression of BMP4 after injury and promote thymic regeneration through Foxn1 and its downstream target (Wertheimer et al. 2018).Despite the pathways mentioned in this review, BMP4 also has differentiation inhibitor 2(ID2) and other downstream pathways. In liver cancer cells, BMP4 promotes cell proliferation, inhibits cell differentiation, and promotes cell proliferation by affecting the expression of ID2, a downstream pathway protein that binds to helical transcription factors (Ma et al. 2017). Studying the BMP4 pathway is helpful to enhance or inhibit its function and fully exert its physiological effects.

BMP4 may promote or inhibit cancer in different tissues, and the study on the mechanism of BMP4 action may help us further clarify the relationship between BMP4 and cancer. In addition, BMP4 can be used to produce more real organ-like organs, which can be used in induced pluripotent stem cells, embryonic cells and other organ-like organs to promote the formation of organ-like organs (Mills et al. 2017), which may be helpful for organ culture and transplantation. Therefore, the role of BMP4 in different epithelial tissues and its corresponding mechanisms have broad research prospects.

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Compliance with ethical standard

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Conflict of interest The authors declared that they have no conflicts of interest to this work.

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