Minireview *Highlight article*

Effects of bone morphogenetic proteins on epithelial repair

Yu Hou[1,2,*], Yu-Xi He[1,*], Jia-Hao Zhang[1,2], Shu-Rong Wang[1] and Yan Zhang[1]

[1]Department of Ophthalmology, 2nd Hospital of Jilin University, Changchun 130041, China; [2]Norman Bethune Health Science Center of Jilin University, Changchun 130021, China

Corresponding author: Yan Zhang. Email: Zhangy66@jlu.edu.cn

*These authors contributed equally to this work.

Impact statement

Since epithelial injury is a common pathological situation in the clinical context, the repair of epithelial damage is very important. This article focuses on the bone morphogenetic protein (BMP) family and summarizes the roles of BMPs in epithelial injury, provides ideas for clinical epithelial injury, and promotes further development of this field. Specifically, the review provides new treatment ideas and enhances the breadth of treatment options. In the future, basic and clinical experiments based on the key proteins discussed in this article should be carried out to increase the cure rate of epithelial injuries.

Abstract

Epithelial tissue has important functions such as protection, secretion, and sensation. Epithelial damage is involved in various pathological processes. Bone morphogenetic proteins (BMPs) are a class of growth factors with multiple functions. They play important roles in epithelial cells, including in differentiation, proliferation, and migration during the repair of the epithelium. This article reviews the functions and mechanisms of the most profoundly studied BMPs in the process of epithelial damage repair and their clinical significance.

Keywords: Bone morphogenetic protein, epithelium, wound healing

***Experimental Biology and Medicine* 2021; 246: 2269–2277. DOI: 10.1177/15353702211028193**

Introduction

Epithelial tissues are widely distributed, with diverse structures and functions.

Considering that epithelial damage is a key component of various pathological processes, the repair of epithelial damage is crucial. Bone morphogenetic proteins (BMPs) are the largest branch of the transforming growth factor-beta (TGF-β) superfamily. They have been named for their ability to form ectopic bone; however, in addition to their regulatory effect on bone formation, recent studies have shown their regulatory effects on epithelial cells. Therefore, BMPs have a noticeable role in the process of epithelial tissue repair. This review considers the nine most extensively studied BMP family proteins among those that play a significant role in the repair of epithelial damage and discusses their effects on and clinical significance for epithelial tissue repair.

The process of epithelial repair

Damage repair includes regeneration and fibrosis. Depending on the degree of repair, regeneration is divided into complete regeneration and incomplete regeneration. Based on the prerequisites for repair to occur, there are physiological regeneration and pathological regeneration. This article focuses on the repair of the damaged epithelium, that is, on the pathological repair of the epithelium. If the damage is not deeper than the basement membrane of the epithelial tissue, the repair of the epithelium is complete, and the structure and function of the original epithelial tissue are completely restored. However, if the basement membrane of the epithelial tissue and the underlying connective tissue are destroyed, incomplete repair takes place and a scar is formed.

After the epithelial damage, local epithelial cells undergo necrosis. The damaged epithelial cells and other

damaged tissues instantly release a number of complex signals to regulate the proliferation and differentiation of epithelial cells and attract them to the trauma center. These signals can be physical or chemical. For example, damage of the surrounding epithelial cells leads to destruction of desmosomes and hemidesmosomes of the wound marginal epithelial cells, which eliminates physical tension. The wound marginal cells generate lipid mediators and activate membrane-associated kinases to increase the permeability of the cell membrane to calcium ions—an epithelial repair initiation signal. Then, under the action of certain cytokines, epithelial cells change their structure and reduce cell adhesion to the extracellular matrix and surrounding cells, establishing sufficient conditions for the proliferation and migration of the epithelial cells within the wound. A gradient of recruitment factors guides the new epithelial cells to gradually move to the center of the wound. When the epithelial cell sheets extending from the wound edges on both sides meet, the epithelial repair ends, and the injury repair enters other stages[1] (Figure 1).

Overview of BMPs

BMPs are a subfamily of TGF-β. BMPs were first discovered by Urist in 1965,[2] when they were shown to have the capacity to induce calcification of mouse cartilage *in vitro*[3] and bone formation in the non-skeletal parts of rats.[2]

In addition to their regulatory effect on bone formation, recent studies have shown that BMPs had a regulatory effect on epithelial cells. For example, the BMP pathway regulates the vertebrate mucociliary epithelium morphogenesis and differentiation,[4] and the inhibition of BMP-4 can regulate the stratification of corneal epithelium.[5] This review discusses the nine most thoroughly studied BMP family proteins that play a major role in the repair of epithelial damage, and sheds light on their effects on and clinical significance for epithelial tissue repair.

BMP signaling pathway

The BMP signaling pathway consists of three essential components: ligands, receptors, and the downstream signaling pathway inside cells (Table 1, Figure 2).

Ligands

Seven BMPs (from BMP-1 to BMP-7) were first identified.[6,7] Subsequently, more BMPs have been found, with the current total of more than 20 proteins.[8] According to the HUGO Gene Nomenclature Committee, BMPs include 11 types of molecules, such as BMP-1 to BMP-7, BMP-8A, BMP-8B, BMP-10, and BMP-15, while other proteins are put under the growth differentiation factor (GDF) name.

Initially, the ligand is translated into a precursor protein, which facilitates the targeted delivery of ligands. The precursor protein is cleaved to form a ligand monomer which must form a ligand homodimer or a heterodimer to function.[9,10] In the extracellular environment, ligands combine with extracellular matrix components to form latent ligands;[11] when needed, latent ligands are activated allosterically by integrins or enzymatically by proteases.

Receptors

Receptors of BMPs can be divided into two classes: type I receptor and type II receptor. The type I receptor contains ACVRL1 (also known as ALK1), ACVR1A (also known as

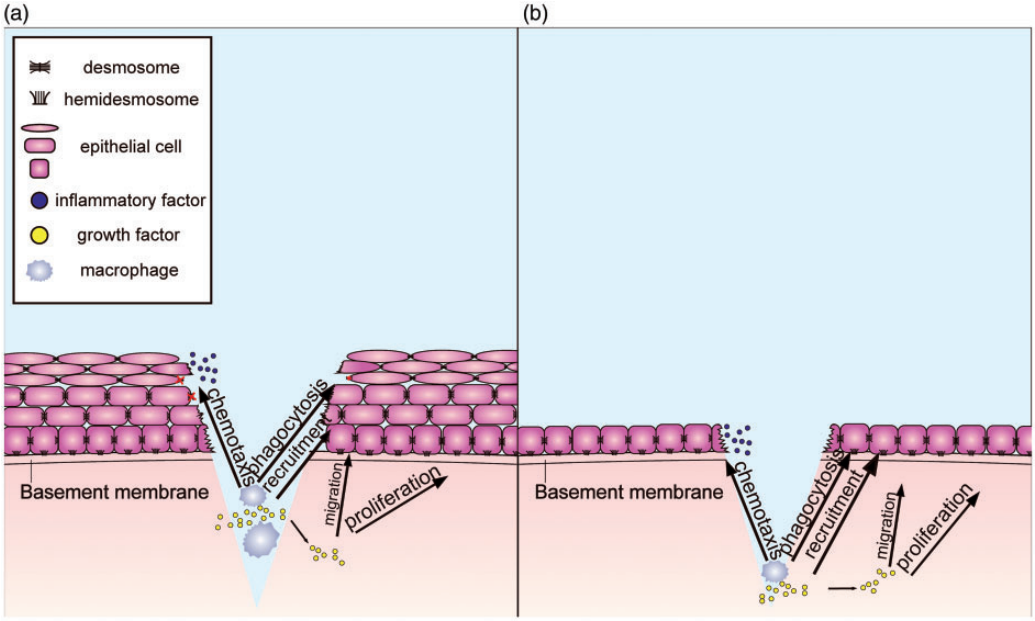

Figure 1. The repairing process of stratified epithelium (a) and monolayer epithelium (b). This figure demonstrates the repairing process of stratified epithelium and monolayer epithelium. The damage of epithelial cells leads to necrosis and the leakage of various inflammatory factors, which can attract many inflammatory cells, including macrophages. The red cross in this image refers to the elimination of physical tension, which can be an initiation signal for the regeneration of the epithelium. Macrophages clean out the trauma by phagocytosis, eating all the necrotic cells, foreign matters, and micro-organisms. Inflammatory cells release many cytokines that can promote the migration ability of cells close to the trauma and promote the proliferation ability of cells far away from the trauma. (A color version of this figure is available in the online journal.)

ALK2), BMPR1A (also known as ALK3), and BMPR1B (also known as ALK6). Type II receptor contains ACVR2A, ACVR2B, and BMPR2[11,12] (Table 1).

The signal transduction complex is composed of a ligand dimer, two type I receptors, and two type II receptors.[12] In ligand-induced receptor complexes, type II receptor subunits mainly phosphorylate and activate type I receptors. Type I receptors subsequently phosphorylate R-mothers against decapentaplegic homologues (R-SMAD) in the C-terminal domain.[11]

Table 1. BMP family members and their receptors.

Family member	Type I receptor	Type II receptor	Co-receptor
BMP-1	–	–	–
BMP-2	BMPR1A and BMPR1B	ACVR2, ACVR2B, and BMPR2	RGM
BMP-3	ACVR1B	ACVR2, ACVR2B, and BMPR2	–
BMP-4	BMPR1A and BMPR1B	ACVR2, ACVR2B, and BMPR2	–
BMP-5	ACVR1A, BMPR1A, and BMPR1B	ACVR2, ACVR2B, and BMPR2	–
BMP-6	ACVR1A, BMPR1A, and BMPR1B	ACVR2, ACVR2B, and BMPR2	RGM
BMP-7	ACVR1A, BMPR1A, and BMPR1B	ACVR2, ACVR2B, and BMPR2	–
BMP-8A	ACVR1A, BMPR1A, and BMPR1B	ACVR2, ACVR2B, and BMPR2	–
BMP-8B	ACVR1A, BMPR1A, and BMPR1B	ACVR2, ACVR2B, and BMPR2	–
BMP-10	ALK1	ACVR2 and BMPR2	Endoglin
BMP-15	BMPR1B	BMPR2	–

–: not applicable; ACVR: activin receptor; BMP: bone morphogenetic protein; BMPR: bone morphogenic protein receptor; RGM: repulsion guidance molecules; ALK1 as ACVRL1.

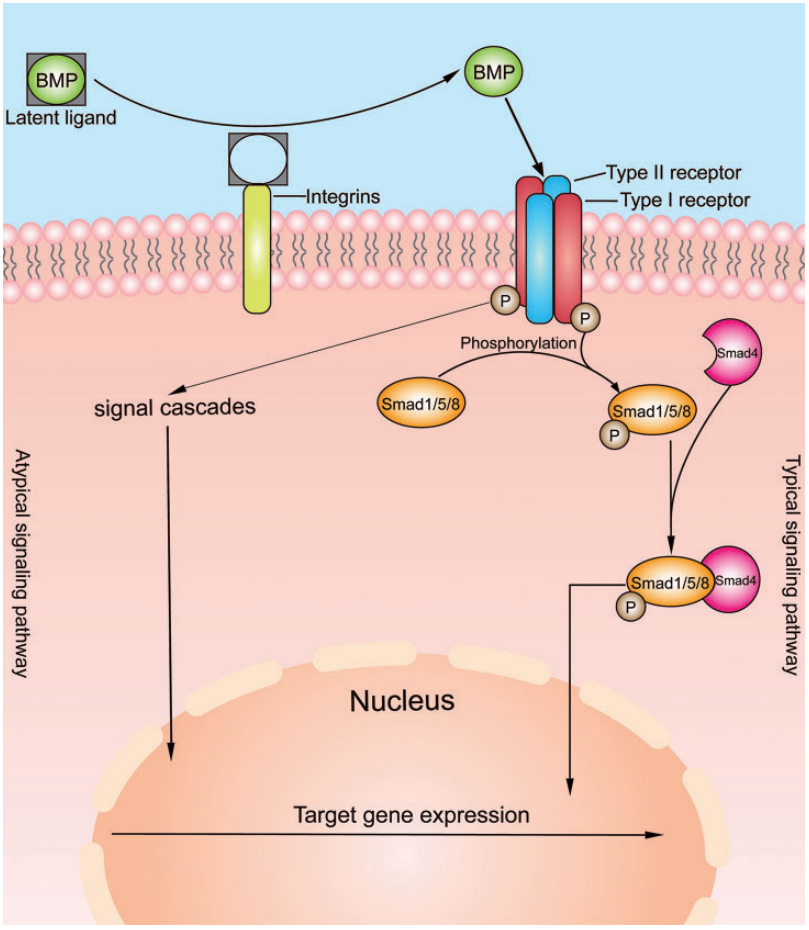

Figure 2. The molecular mechanism of the BMP signaling pathway. The BMP ligand outside cells can combine with the receptor complex formed by the type I and type II receptors. The complex activates either the typical pathway or the atypical pathway. In the typical pathway, the signal transduction complex phosphorylates the SMAD1/5/8. Being phosphorylated, the SMAD1/5/8 can bind to SMAD4 to form a complex, and then go through the nuclear membrane through the nuclear pore to regulate the expression of target genes. Moreover, the combination of BMP and its receptor can regulate other signal cascades to adjust the target gene expression (atypical pathway). (A color version of this figure is available in the online journal.)

Downstream signaling pathway

The activation of the signal transduction complex stimulates either typical or atypical downstream signaling pathways.

The typical downstream signaling pathway mainly involves SMAD signaling pathway. There are eight kinds of mammal SMAD proteins; six of them have a stimulatory effect (SMAD1 to SMAD5 and SMAD8—also known as SMAD9) and two have inhibitory effects (SMAD6 and SMAD7).[11] SMAD proteins consist of globular N-terminal and C-terminal domains, called MH1 and MH2 domains, respectively, separated by a flexible connecting region.[13,14] The activated type I receptors phosphorylate pathway-specific R-SMADs (SMAD1/5/8), which can combine with SMAD4 and translocate to the nucleus to regulate the expression of target genes and create a macro effect.[12]

The atypical signaling pathway always refers to the signal cascades that adjust gene expression after the activation of the signal transduction complex.

Effect of BMP-1 on epithelial damage repair

BMP-1 is a matrix protease. Although it does not belong to TGF-β family, its effect on epithelial damage repair is crucial. BMP-1 and another protein, mammalian tolloid-like 1, are co-released in various tissues and overlap in function. They are collectively known as BMP-1/tolloid-like proteinases (BTPs).

In case of a BTP gene knockout, mice showed signs of skin fragility.[15] In essence, BMP-1 promotes the synthesis of core proteoglycans, disaccharides, and laminin-332, which are the main components of the epithelial basement membrane, required for matrix components. At the same time, mice with BMP-1-like protein gene knockout suffered from slow wound healing after skin trauma. It has been shown that BMP-1-like protein activates TGF-β. However, the real reason for slower wound healing is the defective laminin-332 rather than the reduced activity of TGF-β.[16,17] Defects in laminin-332 causes dysfunction of hemidesmosomes and leads to the connection failure between the epithelial cells and the basement membrane, which in turn causes slow healing and fragile skin.

However, the mechanism by which BMP-1 promotes the maturation of laminin-332 still needs to be proved. As a hydrolase, BMP-1 cuts and processes the precursor of laminin-332, that is, the cutting of the laminin-γ2 peptide chain leads to laminin maturation, while the untreated protein has no activity.[15–20] Many intracellular factors can promote or enhance the role of BMP-1; for example, integrin α3β1 can upregulate the expression of BMP-1 gene,[20] while procollagen c protease enhancer 1 can be combined with BMP-1 to enhance its processing ability of collagen.[21]

In conclusion, as an extracellular protease, BMP-1 plays a key role in the repair of the epithelium. As a protease, on the one hand, BMP-1 reestablishes epithelium mainly by the cleavage of the laminin-332 precursor. The maturation of laminin-332, core proteoglycans, and disaccharides is a significant process of the basement membrane reformation, which is the prerequisite for epithelial cells to adhere, proliferate, and migrate. On the other hand, BMP-1 can rescue other BMP ligands from the latent complex and activate other members in the BMP family.[22] It exerts a variety of significant effects, including the synthesis or degradation of extracellular matrix proteins, the activation or inactivation of cytokines and growth factors, the cleavage of other substances that play an important role in the deposition of collagen, the interaction between the cell and the extracellular matrix, and the differentiation regulation of cell phenotypes.[23,24]

Effect of BMP-2 on epithelial damage repair

BMP-2 is the main member of the BMP family. In the damaged epidermal area, it can promote the expression of frizzled proteins in keratinocytes and make keratinocytes more sensitive to the WNT signaling pathway. Thus, it strongly activates the WNT pathway and inhibits the degradation of β-catenin to give it more opportunities to enter the nucleus, which promotes the expression of target genes, increases the migration and regeneration capacity of cells, and accelerates the repair of epithelium.[25]

Many related molecules are also involved in the regulation of BMP-2. Tumor necrosis factor-α (TNF-α) upregulates the expression of BMP-2 and its receptors, which in turn causes BMP-2 to induce TNF-α to downregulate the amount of E-cadherin; these actions increase the ability of cell migration, promote epithelial–mesenchymal transformation (EMT), and accelerate tissue repair.[26–28]

BMP-2 has been shown to promote the EMT process.[29] However, in another environment, BMP-2 can significantly reverse TGF-β1-induced α-smooth muscle actin (α-SMA), fibronectin, and zinc fingers protein SNAI1 upregulation and E-cadherin downregulation, thereby reversing the EMT process induced by TGF-β1 and reducing renal interstitial fibrosis.[30] The differences between the two environments likely stem from the differential effects of the involved factors; nevertheless, in both environments, BMP-2 has an inseparable role in the repair of epithelial damage.

BMP-2 also participates in the repair of vascular endothelium. BMP-2 can increase the migration ability of endothelial cells through the signaling pathway SMAD1/5/8/Id1 to form a tube and complete the repair of blood vessels.[31] BMP-2-transduced endothelial progenitor cells effectively improve the permeability of blood vessels and promote endothelial repair.[32] BMP-2 is also involved in scar formation during the repair of damaged epidermis;[33] it can also repair the endothelium and has a certain ability to promote cell differentiation.[34]

In general, BMP-2 shows different characteristics in different conditions. In one condition, it can promote the secretion of frizzled proteins, which makes keratinocytes more sensitive to the WNT signaling pathway. BMP-2 also prevents β-catenin from being degraded and favors its translocation to the nucleus, thereby upregulating E-cadherin to increase the migration capacity of the epithelial cells. In other words, BMP-2 promotes the EMT process. In the other condition, BMP-2 can inhibit the TGF-β1-promoted EMT.

Effect of BMP-4 on epithelial damage repair

The role of BMP-4 protein in normal tissues is to inhibit epithelial cell proliferation[35] and maintain a relatively constant number of cells in the tissue. After the epithelial tissue is damaged, BMP antagonists are secreted to temporarily stop the effect of BMP-4 and increase the proliferation ability of the epithelial cells. In the early stage of repair, the accumulation of epithelial cells increases along the basement membrane. When the cell density reaches a certain level, active compression of cells occurs, expelling apoptotic cells and restoring density.[36]

Under inflammatory conditions in the urethra, BMP-4 can combine with BMPRIA and BMPRIB to send out signals to regulate the differentiation and regeneration of the urethral epithelial cells in the injured area.[37]

Thymus endothelial cells can produce BMP-4; when the thymus is acutely damaged, BMP-4 acts on thymic epithelial cells by enhancing their expression of Foxn1. Foxn1 is a key transcription factor involved in the development, maintenance, and regeneration of thymic epithelial cells, and its downstream targets such as DII4 are the key mediators of thymic cell development and regeneration. Previous studies have confirmed the importance of the BMP-4 pathway in endogenous tissue regeneration and provided a potential clinical pathway for enhancing T cell immunity.[38]

Gremlin is one of the main endogenous antagonists of BMPs.[39,40] BMP signaling is combined with BMP receptors (BMPRs), especially BMP-4 and BMP-7 with BMPRIA and BMPRII. BMPRs are mainly expressed in the nuclei of human lens epithelial cells. Increasing the concentration of gremlin does not affect the content of BMP-4 in the cells, but it affects the expression of BMPR. Specifically, when the concentration of gremlin increases, the expression of BMPRIA increases, while the expression of BMPRII decreases. BMP-4 inhibits the expression of α-SMA, fibronectin (Fn), and type I collagen through its downstream SMAD1/5 pathway, thereby inhibiting the migration ability of cells. Therefore, BMP-4 inhibition may play an important role in cell migration during wound healing.[41]

The repair function of BMP-4 on epithelial cells mainly involves the role of its downstream pathway SMAD. BMP-4 and its downstream pathways can control the proliferation and migration of epithelial cells and can regulate the fate of epithelial progenitor cells.[42]

Above all, BMP-4 protein plays a different or even opposite role in the epithelium when the body is in two different stages, physiological or pathological. Under physiological conditions, the BMP-4 protein plays an inhibitory role to maintain cell concentration and cell turnover rate in the epithelial tissue. Under pathological conditions, BMP-4 often promotes cell division and differentiation to repair the damaged epithelial tissue.

Effect of BMP-5 on epithelial damage repair

As a growth factor, BMP-5 is activated for various reasons. It can be activated during embryonic development or induced by tissue damage in adult animals. In case of a fracture, skin injury, or lung injury, gene expression of the affected area is changed to activate BMP-5, which is necessary for starting or accelerating the process of tissue repair and regeneration.

BMP-5 affects the fate of epidermal stem cells.[43–46] In damaged skin areas, the signaling cascade involving BMP-5 activates epidermal stem cells and progenitor cells, thereby enabling epithelial cells to proliferate and cells at the wound edge to migrate. In the lungs, BMP-5 can promote the proliferation of club cells in damaged epithelial tissues, re-epithelialize the airway, and complete or accelerate the repair of damaged parts of the lung epithelium.

BMP-5 exerts autocrine signaling in the epithelium of the fallopian tube isthmus of cattle.[47] An *in vitro* wound healing experiment showed that BMP-5 stimulated cell responses, induced apoptosis of the injured cells, and enhanced migration of the regenerated cells rather than cell proliferation.[48]

BMP-5 also has a certain effect on the regeneration of animal ears,[43–46] and genetic studies have shown that BMP-5 plays an indispensable role in maintaining the number of normal epidermal stem cells.[44,46] Indeed, BMP-5 plays an important role both in maintaining the steady-state of various tissues under normal conditions and in repairing tissues after injury.[49]

Above all, as a growth factor, BMP-5 is activated in the damaged epithelium to promote the regeneration regulated by epidermal stem cells; at the same time, it can induce the migration of the regenerated cells. In normal epithelial tissue, it maintains the density and stability.

Effect of BMP-7 on epithelial damage repair

In the damaged corneal tissue, the expression of BMP-7 mRNA increased under the action of substance P and nerve growth factor. Exogenous BMP-7 stimulates and activates the TGF-β signaling pathway and cell cycle pathway. After BMP-7 treatment, the ability of the epithelial cells to move and migrate was enhanced, and the activation of MAPK cascade protein in epithelial cells and stromal cells was accompanied by an increase in phosphorylation of cofilin. The expression of zinc finger E-box-binding homeobox also changed, and when BMP-7 acted on stromal cells, α-SMA upregulation was favored. After BMP-7 stimulation, corneal epithelial cells and stromal cells were also observed to increase the level of epidermal growth factor receptor phosphorylation. Taken together, BMP-7 has a very important function in corneal epithelial repair.[50]

BMP-7 also plays a role in the development of lacrimal glands. During the repair or development of the lacrimal gland, BMP-7 is expressed in the glandular bud epithelium and interstitial tissue. In the lacrimal gland interstitium, BMP-7 promotes the proliferation and aggregation of mesenchymal cells; moreover, it promotes the interstitial expression of connexin 43, cadherin, and α-SMA to stimulate branching of the glands. In the epithelium of lacrimal gland buds, BMP-7 also promotes cell proliferation.[51]

BMP-7 also plays an important role in lung injury caused by long-term ingestion of silica dust. Without drug

Table 2. The comparison of functions and pathways of the BMP family members.

BMPs	Molecular type	Function	Pathway
BMP-1	Matrix metalloproteinase	Provided by inflammatory cells; hydrolysis, modification, and maturation of the adhesion protein-332 in the basement membrane of epithelial cells, and promotion of the maturation of extracellular matrix components to provide a stable extracellular environment for the repair of epithelial damage	None
BMP-2	Growth factor	Regulation of EMT, promotion of migration and proliferation	SMAD 1/5/8/Id1 pathway WNT signal cascade
BMP-4	Growth factor	Maintaining the density of epithelial cells in epithelial tissue, inhibiting cell proliferation and migration when in the physiological situation; promoting epithelial cell differentiation and regeneration when in the pathological situation	SMAD 1/5 pathway
BMP-5	Growth factor	Inducing the proliferation and differentiation of epithelial cells Inducing stem cell differentiation, maintaining tissue homeostasis, and accelerating tissue repair	Not clear so far
BMP-7	Growth factor	Promotion of the migration of epithelial cells Promotion of the proliferation of epithelial cells	Inhibition of SMAD 2/3 pathway, upregulation of SMAD 1/5 pathway
BMP-9	Growth factor	Anti-inflammatory function Promotion of the EMT process Promoting cell proliferation and survival, inhibiting epithelial cell apoptosis Maintaining the density of epithelial cells in epithelial tissue	SMAD 1/5/8 pathway, p38 MAPK, and PI3K/AKT signal cascade SMAD 1/5
GDF-7	Growth factor	Promotion of EMT Promotion of epithelial cells development	Not clear so far
GDF-6	Growth factor	Promotion of EMT	Not clear so far
GDF-5	Growth factor	Promotion of EMT Inhibition of the proliferation of epithelial cells	Not clear so far

SMAD: drosophila mothers against decapentaplegic protein; EMT: epithelial–mesenchymal transition; Id: inhibitors of differentiation; MAPK: mitogen-activated protein kinase; AKT as protein kinase B; GDF: growth differentiation factor.
This table lists the main functions of the BMP family members mentioned in this review and the downstream signaling pathways of these molecules. The pathway does not correspond to the function.

intervention, the damaged alveolar epithelial cells are affected by the SMAD2/3 pathway, which in turn causes fibrosis of the entire lung and endangers life. The presence of BMP-7 blocks the SMAD2/3 pathway, upregulates the SMAD1/5 pathway, reduces the aggregation of type I and type III collagen, and prevents fibrosis of the damaged alveolar epithelium.[52]

In addition, BMP-7 inhibits the EMT process; it exerts an anti-invasive effect by inhibiting the expression of integrin induced by TGF-β.[5] BMP-7 has an inhibitory effect on TGF-β-induced fibrosis; this effect is mediated not by inhibiting the phosphorylation of TGF-β receptor but rather by inhibiting the related genes in the process of EMT (zinc finger transcription coding gene 1, zinc finger transcription coding gene 2, zinc finger protein Snai1, zinc finger protein Snai2, N-cadherin, vimentin, and type I collagen) and significantly reversing the decline in E-cadherin caused by TGF-β1.[53] BMP-7 also has a role in regulating the fate of epithelial progenitor cells.[54]

In summary, the effect of BMP-7 on epithelium mainly involves promoting the proliferation and migration of epithelial cells, stromal cells, and mesenchymal cells, and inhibiting collagen aggregation by regulating a series of signaling pathways. These mechanisms are prominent in damaged corneal tissue, lacrimal glands, and alveolar epithelium.

Effect of BMP-9 on epithelial damage repair

BMP-9, also known as GDF-2, is close to BMP-10 in genetic structure and is also one of the main members of BMPs. Studies have shown that BMP-9 has anti-inflammatory effects in human epithelial cells and endothelial cells cultured *in vitro* and participates in the repair of epithelial damage.[55] In normal epithelial tissues, similar to other BMPs, BMP-9 can maintain the normal density and number of epithelial cells; in contrast, under pathological conditions, such as injury or cancer, BMP-9 induces cell growth, promotes EMT in epithelial cells, and increases migration ability.[56] BMP-9 has a strong EMT-promoting function;[57–61] therefore, it has the ability to enhance the migration of wound margin cells after epithelial tissue injury and accelerate the repair of epithelial tissue. BMP-9 also has the ability to promote cell proliferation and survival in epithelial cells. In breast epithelial cells, BMP-9 inhibits epithelial cell apoptosis via its downstream SMAD1/5 signaling pathway.[62] BMP-9 regulates the cell cycle and survival ability of epithelial cells through its downstream SMAD1/5/8, p38MAPK, and PI3K/AKT signaling

cascade. Among them, the growth-promoting effect of BMP-9 on epithelial cells mainly comes from the MAPK signaling cascade rather than from PI3K, although PI3K is often involved in regulating the cell survival and proliferation ability.[61]

In summary, BMP-9 can promote the proliferation and migration of epithelial cells through SMAD1/5/8, p38MAPK, and PI3K/AKT signaling cascades in pathologic conditions and some physiological conditions. In the normal epithelial tissue, BMP-9 maintains the density of epithelial cells by inhibiting proliferation and migration caused by contact inhibition.

Effects of BMP-12, BMP-13, and BMP-14 on epithelial damage repair

BMP-12, BMP-13, and BMP-14 are highly similar in gene structure, so these three factors are discussed together in this article.

BMP-12 is also known as GDF-7. Studies have shown that the presence of BMP-12 promotes the growth and development of seminal vesicle epithelial cells, maintains their viability, and controls the ratio of basal epithelial cells to luminal epithelial cells. BMP-12 is necessary for the growth of seminal vesicle epithelial cells, either as a permission signal for the growth of seminal vesicles or through cooperation with several other molecules to control the development of seminal vesicle epithelium.[63]

BMP-13 is also known as GDF-6. At present, the functions of BMP-13 in the epithelium are not clear enough, but it is undeniable that it plays an important role in the process of EMT, which can increase the migration ability of cells.[64,65]

BMP-14, also known as GDF-5, has been reported to inhibit the proliferation of corneal epithelial cells, but the mechanism is not yet clear.[66] BMP-14 also promotes the EMT process, which plays an important role in the repair of epithelial tissue damage.[67]

In conclusion, although the effects of these three types of BMP family members on the epithelium have not been thoroughly studied, they can still be shown to have a critical role in epithelial repair. Similar to other members of the BMP family, BMP-13 and BMP-14 have the same capacity to promote EMT. Moreover, BMP-14 can inhibit the proliferation of epithelial cells. Conversely, BMP-12 can promote the growth and the development of epithelial cells.

Comparison of the functions of BMPs in the repair of epithelial damage

Through their downstream SMAD pathway, BMPs can produce various effects on epithelial tissue, including the cell proliferation and differentiation ability and cell migration ability required when the epithelial tissue is damaged. Table 2 compares the specific functions and mechanisms of several BMPs in the process of epithelial damage repair.

Conclusions

Although BMP-1 is not a BMP family member, it plays an indispensable role in epithelial tissue repair. The remaining BMPs use related pathways to connect and directly act on damaged epithelial tissue cells to increase their proliferative and migration ability to promote epithelial tissue repair. However, the mechanisms of action of many of these factors on epithelial damage repair remain unclear, and more research is needed.

AUTHORS' CONTRIBUTIONS

All the authors participated in this review. HY composed this review, HYX revised this review, ZJH and WSR retrieved literature for this review, and ZY provided the idea for this review.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

FUNDING

This work was supported by Jilin Provincial Science and Technology Department International Science and Technology Cooperation Project (No. 20200801016GH). Jilin Medical and Health Talents Special Project (Nos. 2019SCZT052, 2019SCZT057), the Outstanding Young Teacher Training Program of Jilin University (Nos. 419080500586, 419080520252), Youth Talent Training Project of Jilin Provincial Department of Finance (No. 3D5197389429), Jilin Province Traditional Chinese Medicine Science and Technology Support Project (No. 2019134), the Mechanism of BMP4 Inhibiting Corneal Neovascularization (No. 3R2196623429), Course Cases Base of Professional Degree Graduate (No. 419100200379), Jilin University Young Teachers and Students Professional Discipline Project (2020-JCXK-26), Technical Research Project of Jilin Provincial Department of Education (JJKH20201103KJ), Jilin University Basic Research Business Expense Project (45119031C004), and the Jilin Province Health Special Project (2020SCZT089, 2020SCZT025).

ORCID iD

Yan Zhang https://orcid.org/0000-0002-6149-4054

REFERENCES

1. Haensel D, Dai X. Epithelial-to-mesenchymal transition in cutaneous wound healing: where we are and where we are heading. *Dev Dyn* 2018;**247**:473–80
2. Urist MR. Bone: formation by autoinduction. *Science* 1965;**150**:893–9
3. Nogami H, Urist MR. A morphogenetic matrix for differentiation of cartilage in tissue culture. *Proc Soc Exp Biol Med* 1970;**134**:530–5
4. Cibois M, Luxardi G, Chevalier B, Thomé V, Mercey O, Zaragosi L-E, Barbry P, Pasini A, Marcet B, Kodjabachian L. BMP signalling controls the construction of vertebrate mucociliary epithelia. *Development* 2015;**142**:2352–63
5. Zhang Y, Yeh L-K, Zhang S, Call M, Yuan Y, Yasunaga M, Kao WWY, Liu C-Y. Wnt/β-catenin signaling modulates corneal epithelium

stratification via inhibition of Bmp4 during mouse development. *Development* 2015;**142**:3383–93
6. Ducy P, Karsenty G. The family of bone morphogenetic proteins. *Kidney Int* 2000;**57**:2207–14
7. Even J, Eskander M, Kang J. Bone morphogenetic protein in spine surgery: current and future uses. *J Am Acad Orthop Surg* 2012;**20**:547–52
8. Carreira AC, Alves GG, Zambuzzi WF, Sogayar MC, Granjeiro JM. Bone morphogenetic proteins: structure, biological function and therapeutic applications. *Arch Biochem Biophys* 2014;**561**:64–73
9. Gray AM, Mason AJ. Requirement for activin a and transforming growth factor–beta 1 pro-regions in homodimer assembly. *Science*1990;**247**:1328–30
10. Sun PD, Davies DR. The cystine-knot growth-factor superfamily. *Annu Rev Biophys Biomol Struct* 1995;**24**:269–91
11. David CJ, Massagué J. Contextual determinants of TGFβ action in development, immunity and cancer. *Nat Rev Mol Cell Biol* 2018;**19**:419–35
12. Salazar VS, Gamer LW, Rosen V. BMP signalling in skeletal development, disease and repair. *Nat Rev Endocrinol* 2016;**12**:203–21
13. Shi Y, Massagué J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell* 2003;**113**:685–700
14. Martin-Malpartida P, Batet M, Kaczmarska Z, Freier R, Gomes T, Aragón E, Zou Y, Wang Q, Xi Q, Ruiz L, Vea A, Márquez JA, Massagué J, Macias MJ. Structural basis for genome wide recognition of 5-bp GC motifs by SMAD transcription factors. *Nat Commun* 2017;**8**:2070
15. Muir AM, Massoudi D, Nguyen N, Keene DR, Lee SJ, Birk DE, Davidson JM, Marinkovich MP, Greenspan DS. BMP1-like proteinases are essential to the structure and wound healing of skin. *Matrix Biol* 2016;**56**:114–31
16. Amano S, Scott IC, Takahara K, Koch M, Champliaud MF, Gerecke DR, Keene DR, Hudson DL, Nishiyama T, Lee S, Greenspan DS, Burgeson RE. Bone morphogenetic protein 1 is an extracellular processing enzyme of the laminin 5 gamma 2 chain. *J Biol Chem* 2000;**275**:22728–35
17. Veitch DP, Nokelainen P, McGowan KA, Nguyen TT, Nguyen NE, Stephenson R, Pappano WN, Keene DR, Spong SM, Greenspan DS, Findell PR, Marinkovich MP. Mammalian tolloid metalloproteinase, and not matrix metalloprotease 2 or membrane type 1 metalloprotease, processes laminin-5 in keratinocytes and skin. *J Biol Chem* 2003;**278**:15661–8
18. Chang Y-C, Gordon MK, Gerecke DR. Expression of laminin 332 in vesicant skin injury and wound repair. *Clin Dermatol* 2018;**2**:115
19. Mokos ZB, Jović A, Grgurević L, Dumić-Čule I, Kostović K, Čeović R, Marinović B. Current therapeutic approach to hypertrophic scars. *Front Med* 2017;**4**:83
20. Longmate WM, Lyons SP, DeFreest L, Van De Water L, DiPersio CM. Opposing roles of epidermal integrins alpha3beta1 and alpha9beta1 in regulation of mTLD/BMP-1-mediated laminin-gamma2 processing during wound healing. *J Invest Dermatol* 2018;**138**:444–51
21. Massoudi D, Germer CJ, Glisch JM, Greenspan DS. Procollagen C-proteinase enhancer 1 (PCPE-1) functions as an anti-angiogenic factor and enhances epithelial recovery in injured cornea. *Cell Tissue Res* 2017;**370**:461–76
22. Ge G, Greenspan DS. Developmental roles of the BMP1/TLD metalloproteinases. *Birth Defects Res C Embryo Today* 2006;**78**:47–68
23. Hsieh Y-Y, Tung S-Y, Pan H-Y, Yen C-W, Xu H-W, Deng Y-F, Lin Y-J, Hsu W-T, Wu C-S, Li C. Upregulation of bone morphogenetic protein 1 is associated with poor prognosis of late-stage gastric cancer patients. *BMC Cancer* 2018;**18**:508
24. Malecaze F, Massoudi D, Fournie P, Tricoire C, Cassagne M, Malbouyres M, Hulmes DJ, Moali C, Galiacy SD. Upregulation of bone morphogenetic protein-1/mammalian tolloid and procollagen C-proteinase enhancer-1 in corneal scarring. *Invest Ophthalmol Vis Sci* 2014;**55**:6712–21
25. Yang L, Yamasaki K, Shirakata Y, Dai X, Tokumaru S, Yahata Y, Tohyama M, Hanakawa Y, Sayama K, Hashimoto K. Bone morphogenetic protein-2 modulates Wnt and frizzled expression and enhances the canonical pathway of Wnt signaling in normal keratinocytes. *J Dermatol Sci* 2006;**42**:111–9
26. François S, Eder V, Belmokhtar K, Machet M-C, Douay L, Gorin N-C, Benderitter M, Chapel A. Synergistic effect of human bone morphogenic protein-2 and mesenchymal stromal cells on chronic wounds through hypoxia-inducible factor-1 α induction. *Sci Rep* 2017;**7**:4272
27. Yan C, Grimm WA, Garner WL, Qin L, Travis T, Tan N, Han YP. Epithelial to mesenchymal transition in human skin wound healing is induced by tumor necrosis factor-alpha through bone morphogenic protein-2. *Am J Pathol* 2010;**176**:2247–58
28. Zhang F, Zhang X, Meng J, Zhao Y, Liu X, Liu Y, Wang Y, Li Y, Sun Y, Wang Z, Mei Q, Zhang T. ING5 inhibits cancer aggressiveness via preventing EMT and is a potential prognostic biomarker for lung cancer. *Oncotarget* 2015;**6**:16239–52
29. Inai K, Burnside JL, Hoffman S, Toole BP, Sugi Y. BMP-2 induces versican and hyaluronan that contribute to post-EMT AV cushion cell migration. *PLoS One* 2013;**8**:e77593–e93
30. Yang YL, Ju HZ, Liu SF, Lee TC, Shih YW, Chuang LY, Guh JY, Yang YY, Liao TN, Hung TJ, Hung MY. BMP-2 suppresses renal interstitial fibrosis by regulating epithelial-mesenchymal transition. *J Cell Biochem* 2011;**112**:2558–65
31. Wang P, Zhang L, Yao J, Shi Y, Li P, Ding K. An arabinogalactan from flowers of Panax notoginseng inhibits angiogenesis by BMP2/Amad/Id1 signaling. *Carbohydr Polym* 2015;**121**:328–35
32. Yin X, Liang Z, Yun Y, Pei L. Intravenous transplantation of BMP2-transduced endothelial progenitor cells attenuates lipopolysaccharide-Induced acute lung injury in rats. *Cell Physiol Biochem* 2015;**35**:2149–58
33. Moura J, da Silva L, Cruz MT, Carvalho E. Molecular and cellular mechanisms of bone morphogenetic proteins and activins in the skin: potential benefits for wound healing. *Arch Dermatol Res* 2013;**305**:557–69
34. van Eijl RAPM, van Buggenum JAGL, Tanis SEJ, Hendriks J, Mulder KW. Single-cell ID-seq reveals dynamic BMP pathway activation upstream of the MAF/MAFB-Program in epidermal differentiation. *iScience* 2018;**9**:412–22
35. Chung M-I, Bujnis M, Barkauskas CE, Kobayashi Y, Hogan BLM. Niche-mediated BMP/SMAD signaling regulates lung alveolar stem cell proliferation and differentiation. *Development* 2018;**145**:dev163014
36. Tadokoro T, Gao X, Hong CC, Hotten D, Hogan BL. BMP signaling and cellular dynamics during regeneration of airway epithelium from basal progenitors. *Development* 2016;**143**:764–73
37. Wang C, Ross WT, Mysorekar IU. Urothelial generation and regeneration in development, injury, and cancer. *Dev Dyn* 2017;**246**:336–43
38. Wertheimer T, Velardi E, Tsai J, Cooper K, Xiao S, Kloss CC, Ottmuller KJ, Mokhtari Z, Brede C, deRoos P, Kinsella S, Palikuqi B, Ginsberg M, Young LF, Kreines F, Lieberman SR, Lazrak A, Guo P, Malard F, Smith OM, Shono Y, Jenq RR, Hanash AM, Nolan DJ, Butler JM, Beilhack A, Manley NR, Rafii S, Dudakov JA, van den Brink MRM. Production of BMP4 by endothelial cells is crucial for endogenous thymic regeneration. *Sci Immunol* 2018;**3**:eaal2736
39. Rider CC, Mulloy B. Heparin heparan sulphate and the TGF-beta cytokine superfamily. *Molecules* 2017;**22**:713
40. Tatsinkam AJ, Rune N, Smith J, Norman JT, Mulloy B, Rider CC. The binding of the bone morphogenetic protein antagonist gremlin to kidney heparan sulfate: such binding is not essential for BMP antagonism. *Int J Biochem Cell Biol* 2017;**83**:39–46
41. Chen Q, Liu Y, Jeong H-W, Stehling M, Dinh VV, Zhou B, Adams RH. Apelin endothelial niche cells control hematopoiesis and mediate vascular regeneration after myeloablative injury. *Cell Stem Cell* 2019;**25**:768–83
42. Guyot B, Maguer-Satta V. Blocking TGF-β and BMP SMAD-dependent cell differentiation is a master key to expand all kinds of epithelial stem cells. *Stem Cell Investig* 2016;**3**:88–88
43. Heber-Katz E, Chen P, Clark L, Zhang XM, Troutman S, Blankenhorn EP. Regeneration in MRL mice: further genetic loci controlling the ear hole closure trait using MRL and M.m. Castaneus mice. *Wound Repair Regen* 2004;**12**:384–92
44. Kangsamaksin T, Morris RJ. Bone morphogenetic protein 5 regulates the number of keratinocyte stem cells from the skin of mice. *J Invest Dermatol* 2011;**131**:580–5

45. Masinde GL, Li X, Gu W, Davidson H, Mohan S, Baylink DJ. Identification of wound healing/regeneration quantitative trait loci (QTL) at multiple time points that explain seventy percent of variance in (MRL/MpJ and SJL/J) mice F2 population. *Genome Res* 2001;**11**:2027–33
46. Popova NV, Suleimanian NE, Stepanova EA, Teti KA, Wu KQ, Morris RJ. Independent inheritance of genes regulating two subpopulations of mouse clonogenic keratinocyte stem cells. *J Investig Dermatol Symp Proc* 2004;**9**:253–60
47. Garcia EV, Valdecantos PA, Barrera D, Roldan-Olarte M, Miceli DC. Bone morphogenetic proteins in the bovine oviduct: differential expression of BMP-5 in the isthmus during the estrous cycle. *Theriogenology* 2014;**81**:1032–41
48. Valdecantos PA, Bravo Miana RDC, Garcia EV, Garcia DC, Roldan-Olarte M, Miceli DC. Expression of bone morphogenetic protein receptors in bovine oviductal epithelial cells: evidence of autocrine BMP signaling. *Anim Reprod Sci* 2017;**185**:89–96
49. Guenther CA, Wang Z, Li E, Tran MC, Logan CY, Nusse R, Pantalena-Filho L, Yang GP, Kingsley DM. A distinct regulatory region of the Bmp5 locus activates gene expression following adult bone fracture or soft tissue injury. *Bone* 2015;**77**:31–41
50. Kowtharapu BS, Prakasam RK, Murin R, Koczan D, Stahnke T, Wree A, Junemann AGM, Stachs O. Role of bone morphogenetic protein 7 (BMP7) in the modulation of corneal stromal and epithelial cell functions. *IJMS* 2018;**19**:1415
51. Pellegrini G, Rasperini G, Pagni G, Giannobile WV, Milani S, Musto F, Dellavia C. Local wound healing biomarkers for real-time assessment of periodontal regeneration: pilot study. *J Periodontal Res* 2017;**52**:388–96
52. Liang D, Wang Y, Zhu Z, Yang G, An G, Li X, Niu P, Chen L, Tian L. BMP-7 attenuated silica-induced pulmonary fibrosis through modulation of the balance between TGF-beta/Smad and BMP-7/Smad signaling pathway. *Chem Biol Interact* 2016;**243**:72–81
53. Ying X, Sun Y, He P. Bone morphogenetic protein-7 inhibits EMT-associated genes in breast cancer. *Cell Physiol Biochem* 2015; **37**:1271–8
54. Brody SL, Kaiko GE. Harnessing TGF-β and BMP signaling for expansion of p63-positive epithelial stem cells. *Stem Cell Investig* 2016;**3**:82
55. Chen X, Orriols M, Walther FJ, Laghmani EH, Hoogeboom AM, Hogen-Esch ACB, Hiemstra PS, Folkerts G, Goumans M-J, T, Dijke P, Morrell NW, Wagenaar GTM. Bone morphogenetic protein 9 protects against neonatal hyperoxia-induced impairment of alveolarization and pulmonary inflammation. *Front Physiol* 2017;**8**:486
56. Herrera B, Dooley S, Breitkopf-Heinlein K. Potential roles of bone morphogenetic protein (BMP)-9 in human liver diseases. *Int J Mol Sci* 2014;**15**:5199–220
57. Noh B-J, Kim YW, Park Y-K. A rare Colon cancer with ossification: pathogenetic analysis of bone formation. *Ann Clin Lab Sci* 2016;**46**:428–32
58. Brand V, Lehmann C, Umkehrer C, Bissinger S, Thier M, de Wouters M, Raemsch R, Jucknischke U, Haas A, Breuer S, Birzele F, Racek T, Reis M, Lorenzon E, Herting F, Stürzl M, Lorenz S, Kienast Y. Impact of selective anti-BMP9 treatment on tumor cells and tumor angiogenesis. *Mol Oncol* 2016;**10**:1603–20
59. Wang Y, Yang B, Zhao J, Yu X, Liu X, Zhang L, Zhang Y, Li X, Zhai Z. Epithelial–mesenchymal transition induced by bone morphogenetic protein 9 hinders cisplatin efficacy in ovarian cancer cells. *Mol Med Rep* 2019;**19**:1501–08
60. Li Q, Gu X, Weng H, Ghafoory S, Liu Y, Feng T, Dzieran J, Li L, Ilkavets I, Kruithof-de Julio M, Munker S, Marx A, Piiper A, Augusto Alonso E, Gretz N, Gao C, Wölfl S, Dooley S, Breitkopf-Heinlein K. Bone morphogenetic protein-9 induces epithelial to mesenchymal transition in hepatocellular carcinoma cells. *Cancer Sci* 2013;**104**:398–408
61. García-Álvaro M, Addante A, Roncero C, Fernández M, Fabregat I, Sánchez A, Herrera B. BMP9-induced survival effect in liver tumor cells requires p38MAPK activation. *Int J Mol Sci* 2015;**16**:20431–48
62. Varadaraj A, Patel P, Serrao A, Bandyopadhay T, Lee NY, Jazaeri AA, Huang Z, Murphy SK, Mythreye K. Epigenetic regulation of GDF2 suppresses anoikis in ovarian and breast epithelia. *Neoplasia* 2015;**17**:826–38
63. Settle S, Marker P, Gurley K, Sinha A, Thacker A, Wang Y, Higgins K, Cunha G, Kingsley DM. The BMP family member GDF7 is required for seminal vesicle growth, branching morphogenesis, and cytodifferentiation. *Dev Biol* 2001;**234**:138–50
64. Croze RH, Buchholz DE, Radeke MJ, Thi WJ, Hu Q, Coffey PJ, Clegg DO. ROCK inhibition extends passage of pluripotent stem cell-derived retinal pigmented epithelium. *Stem Cells Transl Med* 2014;**3**:1066–78
65. Radeke MJ, Radeke CM, Shih Y-H, Hu J, Bok D, Johnson LV, Coffey PJ. Restoration of mesenchymal retinal pigmented epithelial cells by TGFβ pathway inhibitors: implications for age-related macular degeneration. *Genome Med* 2015;**7**:58
66. You L, Kruse FE, Pohl J, Völcker HE. Bone morphogenetic proteins and growth and differentiation factors in the human cornea. *Invest Ophthalmol Vis Sci* 1999;**40**:296–311
67. Enescu AS, Mărgăritescu CL, Crăiţoiu Mm Enescu A, Crăiţoiu Ş. The involvement of growth differentiation factor 5 (GDF5) and aggrecan in the epithelial-mesenchymal transition of salivary gland pleomorphic adenoma. *Rom J Morphol Embryol* 2013;**54**:969–76