• Review •

Aberrant expression of genes and proteins in pterygium and their implications in the pathogenesis

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Abstract

• Pterygium is a common ocular surface disease induced by a variety of factors. The exact pathogenesis of pterygium remains unclear. Numbers of genes and proteins are discovered in pterygium and they function differently in the occurrence and development of this disease. We searched the Web of Science and PubMed throughout history for literatures about the subject. The keywords we used contain pterygium, gene, protein, angiogenesis, fibrosis, proliferation, inflammation, pathogenesis and therapy. In this review, we summarize the aberrant expression of a range of genes and proteins in pterygium compared with normal conjunctiva or cornea, including growth factors, matrix metalloproteinases and tissue inhibitors of metalloproteinases, interleukins, tumor suppressor genes, proliferation related proteins, apoptosis related proteins, cell adhesion molecules, extracellular matrix proteins, heat shock proteins and tight junction proteins. We illustrate their possible mechanisms in the pathogenesis of pterygium as well as the related intervention based on them for pterygium therapy.

• **KEYWORDS:** pterygium; growth factors; matrix metalloproteinases; tissue inhibitors of metalloproteinases; interleukins; tumor suppressor genes; proliferation and apoptosis; cell adhesion molecules; extracellular matrix proteins
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INTRODUCTION

Pterygium, one of the most common ocular surface diseases, is characterized by the invasive growth of fibrovascular conjunctiva tissue extending on the corneal surface, which leads to the reduction of visual acuity[1]. Surgery is the traditional treatment for this disease. Despite pterygium has been extensively studied, the accurate pathogenesis remains a mystery. Epidemiological studies have found that the etiology of pterygium is relevant to chronic stimulations caused by ultraviolet and dust, *etc*[2]. Whereas numerous studies[3-5] provide the evidence that various molecules, such as growth factors, matrix metalloproteinases (MMPs) and interleukins (ILs), have close relation to angiogenesis, fibrosis, proliferation and inflammation, which constitute the pathology of pterygium.

We searched literatures concerning the keywords pterygium, gene, protein, angiogenesis, fibrosis, proliferation, inflammation, pathogenesis and therapy from the Web of Science and PubMed throughout history. In this review, we compare pterygium with normal ocular surface tissues and summarize the aberrant expression of some genes and proteins in pterygium (Table 1). In addition, we indicate the possible functions of these molecules involved in the pathogenesis of pterygium and demonstrate some therapeutic implications for pterygium according to these molecules.

Growth Factors Growth factors, a type of molecules that stimulate cell growth, have the ability to promote mitosis and proliferation in cell cycle. Numbers of growth factors, such as vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), nerve growth factor (NGF) and connective tissue growth factor (CTGF) have been discovered in pterygium[6].

Firstly, VEGF is one of the most important growth factors in ocular diseases. The VEGF family control pathological angiogenesis and increase vascular permeability in eye sicknesses[7]. Compared with normal conjunctiva, pterygium presented higher levels of VEGF and vascular endothelial growth factor receptor (VEGFR)-2, -3[8-9]. Gharaee *et al*[10] discovered VEGF mRNA expression was much higher in atopic pterygium patients than in non-atopic individuals. Upregulation of VEGF-C mRNA level probably leaded to lymphangiogenesis in pterygium, especially in recurrent

Table 1 Aberrant expression of some genes and proteins in pterygium

Genes/proteins	Upregulated	Downregulated	Invariant
Growth factors	VEGF, VEGFR-2, VEGFR-3, TGF-β, bFGF, IGFBP2, NGF, TrkA, CTGF	TGFR-β1, TGFR-β2, IGFBP3	
MMPs and TIMPs	MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-10, MMP-13, TIMP-1, TIMP-3		
ILs	IL-1, IL-4, IL-6, IL-8, IL-10, IL-17		
Tumor suppressor genes	P53, p63, p16	P27	
Proliferation related proteins	Ki-67, PCNA, cyclin D1		
Apoptosis related proteins	Survivin, Bcl-2, Bcl-w		Bax
CAMs	ICAM-1, VCAM-1, E-cadherin, integrin		
Extracellular matrix proteins	Keratin, tropoelastin, collagen type II		
HSPs	Hsp27, Hsp70, Hsp90		
Tight junction proteins		Claudin-1	

pterygium[11-12]. Lately, it was clarified TNF-α mediated the expression of VEGF-C[13]. Increased expression of VEGF leads to angiogenesis and lymphangiogenesis, which may influence the normal metabolism of conjunctiva cells and promote them to become pterygium cells. 5-fluorouracil, a new-trend treatment for preventing pterygium recurrence, was recently reported to be unable to affect VEGF expression in pterygium[14]. As we all know, anti-VEGF medicines like ranibizumab and bevacizumab have been extensively applied in healing ocular maladies. Nevertheless, current evidence didn't advocate the use of anti-VEGF drugs in pterygium surgery[15].

Secondly, TGF-β regulates many of the processes common to both tissue repair and disease, including fibroblast proliferation, angiogenesis, controlled synthesis and degradation of matrix proteins like collagen and fibronectin[16]. With reverse transcription polymerase chain reaction (RT-PCR), Zhong *et al*[17] discovered TGF-β1 and TGF-β2 were upregulated while transforming growth factor-beta receptor 1, 2 (TGFR-β1, -β2) were downregulated in pterygium compared to normal bulbar conjunctival tissues. Bianchi *et al*[18] elucidated TGF-β was expressed moderately in the epithelial and stromal layers of pterygium, yet weakly in normal conjunctiva. In consistent with VEGF, the expression of TGF-β1 was obviously higher in atopic pterygium patients compared to non-atopic ones[19]. It was found by Tan *et al*[20] that Tafazzin (TAZ) protein adjusted conjunctiva epithelial cell propagation by suppressing TGF-β signaling. Pirfenidone and tranilast were newly reported to be effective in decreasing the expression of TGF-β in pterygium and might be safe adjuvants for pterygium surgery to avoid recurrence[21-22]. In addition, amniotic membrane grafting was shown to inhibit the signaling of TGF-β[23]. Thus, inhibiting the expression of TGF-β seems to be effective in preventing pterygium occurrence.

Thirdly, bFGF, also known as fibroblast growth factor 2 (FGF2), participates in angiogenesis, wound healing and various endocrine signaling pathways. The expression of bFGF was found to be increased in infiltrating mast cells, epithelium and blood vessels of pterygium, moreover, mast cells might serve as an additional source of bFGF[24-25]. Detorakis *et al*[26] measured the mRNA level of FGF2 in pterygium and normal conjunctiva with qRT-PCR, obtaining the result that higher FGF2 was expressed in pterygium. FGF2 was able to induce the expression of cyclooxygenase-2 (COX-2), which was absent in normal conjunctiva[27] but present in human pterygium fibroblasts[28]. COX-2 is the key enzyme for inflammatory cytokine-induced angiogenesis, thus FGF2 can induce inflammation and angiogenesis in pterygium. Recent study[29] found mycophenolic acid changed bFGF expression in pterygium and exhibited an inhibitory effect on fibroblasts proliferation.

Fourthly, IGF, capable of promoting cell mitosis, stimulating cell proliferation and inhibiting apoptosis, contributes to the growth of pterygium[30]. According to the study of Solomon *et al*[31], insulin-like growth factor binding protein-2 (IGFBP2) was found to be overexpressed in pterygium body fibroblasts. However, insulin-like growth factor binding protein-3 (IGFBP3) was notably decreased in pterygium compared to normal conjunctiva[32]. Downregulation of IGFBP3 is closely associated with the occurrence of cancer[33], in other words, low level of IGFBP3 may be relevant to the out of control cell proliferation, which means downregulation of IGFBP3 is linked to the continuing growth of pterygium possibly.

Fifthly, NGF, a neurotrophic factor, mainly regulates growth, proliferation and survival of certain cells. Expression of NGF was strong in epithelia, fibroblasts and vascular endothelial cells of pterygium, while weak in epithelia and fibroblasts of normal conjunctiva[34]. Ribatti *et al*[35] observed that endothelial cells in human pterygium were immunoreactive to both NGF and its receptor TrkA. These two molecules were related to microvascular density. Thus increased level of NGF and TrkA seem to accelerate vascularization in pterygium.

Last but not least, CTGF, which is involved in cell adhesion, migration and chemotaxis, belongs to the CCN family of proteins. The CCN family is a complicated family of multifunctional proteins including six members designated CCN1 to CCN6. The CCN abbreviation was introduced from the names of the first three members of the family to be discovered: cysteine-rich protein 61 (Cyr61), CTGF and nephroblastoma overexpressed gene (NOV)[36]. van Setten *et al*[37] illustrated that CTGF was present in the epithelium of pterygium, however, it appeared to be absent in normal conjunctiva. Therefore, it is possible that only pterygium can express CTGF, while normal conjunctiva can't.

Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases MMPs are a multigene family of over 25 secreted and cell surface enzymes that process or degrade lots of extracellular matrix[38], which can be divided into five subgroups based on substrate preference: collagenases (MMP-1, MMP-8, MMP-13), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10), membrane-associated MMPs (MT1-MMP, MT2-MMP) and others (*e.g.* MMP-12, MMP-19, MMP-20)[39]. Tissue inhibitors of metalloproteinases (TIMPs) bind to and deter the activities of most MMPs. The relationship between pterygium and these two groups of proteins has been a focus for exploring the pathogenesis of pterygium for a long time.

MMP-1, MMP-2, MMP-3, TIMP-1 and TIMP-3 were detected in increased amounts in pterygium tissues and cultured pterygium epithelial cells and fibroblasts compared with conjunctiva[40-41]. Siak *et al*[42] found TNF-α activated the nuclear factor kappa B (NF-κB) pathway in pterygium fibroblasts, thereby upregulated the expressions of MMP-1, MMP-2 and MMP-3. The extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase intracellular pathway was involved in the UVB induction of MMP-1 expression in pterygium[43]. Bevacizumab was lately demonstrated to reduce the level of MMP-1 in human Tenon's fibroblasts cultured from primary and recurrent pterygium[44]. Yao *et al*[45] indicated that higher MMP-3 and MMP-8 were expressed in pterygia than in normal tissues. MMP-3 and secreted protein acidic and rich in cysteine (SPARC) were reported to be upregulated and colocalized in the epithelium of pterygium, indicating they might collaborate to account for the diverse phenotypes of pterygium[46]. Recent study[47] shown cyclosporine A had the capability to lower MMP-3 and MMP-13 expression in cultured pterygium fibroblasts. Precursor and active forms of MMP-7 exist in epithelium and blood vessels of pterygium, but they are absent in conjunctival vessels[48]. Tsai *et al*[4] reported that the immune-positive rate for MMP-9, MMP-10 and TIMP-1 were 35.4%, 34.1% and 72.0% respectively among the 82 pterygium samples, and the invasion and migration ability of cells were increased in TIMPs knockdown pterygium epithelia. The results above came to a conclusion that MMP-9 and MMP-10 contributed to pterygium formation, whereas TIMPs inhibited pterygium invasion. Early study[49] suggested the expression of MMP-9 was similar in both pterygium and normal Tenon's capsule. However, further research conducted by Yang *et al*[50] pointed out MMP-9 and activated MMP-2 were not expressed in early-stage pterygium tissues and cultured fibroblasts until pterygium head passed the pupillary region. MMPs produced by pterygium cells had the ability of dissolving Bowman's layer, leading to the growth stimulation of stromal fibroblasts[51]. Moreover, MMPs seemed to be active in other ocular surface disorders, for example, MMP-1 and MMP-3 were overexpressed in cultured conjunctival fibroblasts and surgical samples from patients who suffered from superior limbic keratoconjunctivitis[52].

The expression of MMPs and TIMPs vary in different stages of pterygium. We consider the disruption of the balance between MMPs and TIMPs may be responsible for the progression or recurrence of pterygium.

Interleukins ILs are a group of secreted proteins and signal molecules that were first seen to be expressed by white blood cells[53]. White blood cells play vital roles in the process of inflammation, thus ILs ought to be closely related to pterygium.

In a previous study[54], the expression of IL-1α, IL-1β, IL-1β RA and IL-1β precursor proteins in primary pterygium and normal conjunctival epithelium were detected *via* immunofluorescence. It turned out that enhanced level of IL-1 family proteins were present only in pterygium. Likewise, Huang *et al*[55] found IL-1α was expressed higher not only in primary but also in recurrent pterygium. According to a research carried out by Kuo *et al*[56], IL-4 was transcriptionally elevated in recurrent pterygium tissues. Moreover, it was localized to perivascular tissues and endothelial cells in the stroma of the subconjunctiva of pterygium. As important proinflammatory cytokines, IL-6 and IL-8 proteins were strongly expressed in the epithelium of pterygium in comparison to normal cornea, conjunctiva and limbus. Besides, in contrast with nonirradiated pterygium, IL-6 and IL-8 proteins were significantly elevated in UVB-treated pterygium, suggesting UVB might induce the secretion of these two ILs[57]. IL-8 is able to induce vascularization of cornea directly[58]. A recent study[59] indicated that mitomycin C (MMC) increased the secretion of IL-8 concentration-dependently in human Tenon's capsule fibroblasts (HTFs), whereas dexamethasone reversed the HTFs proliferation through inhibiting the MMC-induced IL-8 secretion. It was reported that IL-10 and Foxp3 were expressed more abundantly in pterygium than in the normal conjunctiva[60]. The level of IL-17 was recently found to be upregulated in ocular surface inflammatory pathologies, such as pterygium, inflamed juvenile conjunctival nevus and

ocular demodicosis[61-62]. Subbarayal *et al*[63] suggested IL-17 promoted ocular surface autoimmunity partly *via* enhancing B cell proliferation, differentiation and plasma cell generation.

Tumor Suppressor Genes Tumor suppressor genes protect cells from converting to cancer cells and regulate the growth of cells along with the proto-oncogene. P53, one of the most common tumor suppressor genes, has been widely studied. Ueda *et al*[64] found mutant p53 existed in Japanese and Tunisian pterygium tissues. In addition, they suggested that damage caused by p53-dependent programmed cell death of pterygium cells may lead to mutations in other genes, which may allow the progressive multistep development of limbal tumors. Therefore mutant p53-positive pterygia can possibly develop into limbal tumors. Tsai *et al*[65] reviewed all immunohistochemical studies on pterygium from Medline and indicated over 20% of all pterygium samples in the literatures were positive for p53 expression. Weinstein *et al*[66] performed immunohistochemical staining on 13 pterygium specimens and 2 normal conjunctiva specimens, and the result showed that 54% of pterygia were positive for abnormal p53 expression, whereas no pathological staining was observed in conjunctiva. In the studies from other countries, p53 likewise had greater immunoreactivity in pterygium than conjunctiva[67-68]. Recently it was known that the p53 protein had positive correlation with Ki-67 protein, a marker of proliferative cellular activity, in pterygium[69]. Surprisingly, the increased expression of p53 in pterygium didn't block cell proliferation or cause apoptosis, implying these normal mechanisms of p53 were inactivated in pterygium[70]. According to Rodrigues *et al*[71], abnormal expression of p53, p53 codon 72 polymorphisms and human papillomavirus (HPV) DNA were necessary co-factors for the progression of pterygium. It was demonstrated HPV 16/18 E6 oncoprotein was involved in p53 inactivation in the pathogenesis of HPV-mediated pterygium[72]. It seems to us that the aberrant expression of p53 promotes cell proliferation and slows apoptosis in pterygium, thereby accelerates the development of this disease.

Besides p53, there are some homeotic tumor suppressor genes like p63, p16 and p27 functioning in pterygium as well. P63 expressed increasingly in the basal and parabasal layers of primary pterygium, and in the full thickness of the epithelium in recurrent pterygium. Increased expression of p16 protein was observed in pterygium. Yet p63 and p16 seemed to express rarely in normal conjunctiva[73]. Atkinson *et al*[74] also found p63 overexpressed in pterygium. To our astonishment, the p16 gene promoter was hypermethylated in pterygium, which might cause the suppression of p16 protein[75]. As a member of tumor suppressor genes, p27 was detected with low nuclear immunoreactivity in pterygium tissues, which differed from other tumor suppressor genes[76].

Proliferation Related Proteins Proliferation related proteins, such as Ki-67, proliferating cell nuclear antigen (PCNA) and cyclin D1, play important roles in the process of cell growth. One of the most significant characters of pterygium is proliferation, so proliferation related proteins ought to function actively in the progress of this disease.

The Ki-67 protein is known as a cellular marker for proliferation extensively[77]. Konuk *et al*[78] demonstrated that the expression of Ki-67 increased in both primary and recurrent pterygium, which supported the proliferative nature of pterygium. Ohara *et al*[79] suggested Ki-67 might be a sensitive marker for ocular malignant tumor. As we know, pterygium seems to have a few features similar to tumor, so Ki-67 may be a marker for pterygium likewise.

PCNA is a DNA clamp and achieves its processivity by encircling the DNA, where it acts as a scaffold to recruit proteins involved in DNA replication, DNA repair, chromatin remodeling and epigenetics[80]. It was reported that the expression of PCNA and Ki-67 was significantly higher in pterygium than normal conjunctiva[81]. It seems to us that the synergy of PCNA and Ki-67 may consolidate the cell proliferation in pterygium pathogenesis.

Cyclin D1 is a protein required for progression through the G1 phase of the cell cycle[82]. Recent study[83] found PCNA and cyclin D1 were overexpressed in limbal part of pterygium epithelial cells compared with normal conjunctivas, which might lead to the limbal micro-environmental anomaly such as hyper-proliferation of resident epithelial cells. This may explain how these two proteins promote the initiation of this disease. Tung *et al*[84] indicated β-catenin expressed in nuclei/cytoplasm could increase cyclin D1 protein expression, which contributed to proliferation of pterygium cells. In addition, PCNA was overexpressed in cultured human pterygium fibroblasts *in vitro* and ahylysantinfarctase could inhibit its expression at a dose-dependent manner[85]. Moreover, DK2, a peroxisome proliferator-activated receptor γ agonist, was found to be capable of inducing the apoptosis and suppressing the expression of PCNA mRNA and protein in human pterygium fibroblasts[86].

Apoptosis Related Proteins Apoptosis related proteins, such as survivin, Bcl-2, Bax and Bcl-w, are suggested to be involved in the regulation of cell apoptosis.

Survivin, an important member of the apoptosis inhibitors family, is capable of inhibiting caspases activation, leading to negative regulation of apoptosis. Xu *et al*[87] revealed that survivin was strongly expressed in pterygium tissues and located in both nucleus and cytoplasm of epithelial cells, however, it was only weakly expressed in the cytosol of normal conjunctival epithelium. Furthermore, knockdown of survivin suppressed propagation of pterygium epithelial cells, along with downregulation of p63 and upregulation of

p57 and p21 expressions. It was demonstrated that oxidative stress could cause activation of survivin expression, inducing a hyperproliferative condition, which might be a crucial event in the growth of pterygium[88]. Survivin had an essential connection with COX-2 in primary pterygium, suggesting that pterygium might originate *via* an anti-apoptotic mechanism[89]. Bcl-2, a protein encoded in humans by the Bcl-2 gene, is the founding member of the Bcl-2 family that controls apoptosis by either inducing or inhibiting apoptosis[90-91]. Bax, known as an apoptotic activator protein, comes from the Bcl-2 gene family as well. Apparent expression of Bcl-2 was observed in the basal epithelial layer of all pterygium epithelial cells, while normal conjunctiva showed no evidence of Bcl-2. Bax came from the same family as Bcl-2, so the expression of Bax might be upregulated in theory. But the truth was that its expression seemed to be similar in both pterygium and normal conjunctiva[92]. Zheng *et al*[93] got the same results as the previous study concerning these two proteins. Ahylysantinfarctase was shown to inhibit the Bcl-2 expression in cultured human pterygium fibroblasts[85]. Bcl-w, a member of Bcl-2 family, protects cell from apoptosis[94]. Recently it was reported that Bcl-w was overexpressed in pterygium and the decrease of miR-122 could result in abnormal apoptosis in pterygium *via* its regulation of the Bcl-w expression[95].

Cell Adhesion Molecules Cell adhesion molecules (CAMs) are proteins located on the cell surface and involved in binding with other cells or with the extracellular matrix in the process called cell adhesion, including selectin, syndecan, cadherin and integrin[96].

Beden *et al*[97] found the expression of intercellular adhesion molecule-1 (ICAM-1) was present in pterygium, while absent in normal conjunctival epithelium. van de Stolpe and van der Saag[98] indicated that ICAM-1 stimulated antigen-presenting cells to activate MHC class II restricted T-cells, and other cell types in association with MHC class I to activate cytotoxic T-cells. And ICAM-1 was able to promote migration of leukocytes to sites of inflammation. Thus, pterygium epithelial cells participated in the inflammatory process by expressing ICAM-1. Tekelioglu *et al*[99] demonstrated ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) was upregulated in pterygium compared with normal conjunctival tissue, along with higher levels of CD4 and CD8 lymphocytes. This means ICAM-1 and VCAM-1 may elevate the levels of T-lymphocyte infiltration, thereby promote the pathogenesis of pterygium.

Selectin and syndecan are less investigated for their involvement in pterygium, thus we pay more attention to cadherin and integrin. Kase *et al*[100] indicated E-cadherin was present in diverse epithelial cells in pterygium, but deficient in normal cornea and conjunctiva. E-cadherin, a transmembrane glycoprotein mediates cell-to-cell adhesion[101], may advance the adhesion of epithelial and vascular cells in pterygium and accelerate the pathogenesis. Integrin functions interactions between cells and the extracellular matrix and hence promote cell migration, tissue stability and a stable cellular environment for stem cells[102]. In our opinion, increased integrin may disturb the steady status of limbal cells, influence the adhesion and migration of conjunctiva cells, which would cause the occurrence and recurrence of pterygium. Recent study[103] revealed that doxycycline treatment could evidently reduce the expression of integrin in pterygium.

Extracellular Matrix Proteins Extracellular matrix proteins contain keratin, elastin, collagen, fibroin and so on. Some keratins (K8, K16, K14 and AE3) are found to be present in the full thickness in pterygium epithelium, but not in normal conjunctiva[104]. Perez-Rico *et al*[105] indicated that pterygium shown higher mRNA level and expression of tropoelastin than conjunctival tissue. The expression of tropoelastin in pinguecular part of pterygium is increased because of the posttranscriptional modification[106]. Lately, it was found that several extracellular matrix constituents, such as LOXs, FBN1 and FBLN5, involved in the development of elastin were overexpressed in pterygium[107], which meant elastin might be overexpressed likewise. Collagen types I, III and IV were detected in both pterygium and normal conjunctiva, but collagen type II only existed in pterygium[108]. Recently it was reported the use of biodegradable collagen matrix implants following pterygium excision seemed to lower the risk of pterygium recurrence[109]. Since pterygium is fibrovascular tissue characterized by excessive extracellular matrix deposition and vascular ingrowth, the aberrant expression of extracellular matrix proteins seems to be directly associated with the growth of pterygium.

Heat Shock Proteins Heat shock proteins (HSPs) are a family of proteins that are produced by cells in response to exposure to stressful conditions. Pharmakakis and Assimakopoulou[110] indicated the expression of Hsp27 was detected in the epithelial cells, endothelial cells and vascular smooth muscle cells of pterygium while only in the epithelium of normal conjunctiva. In 10 normal conjunctiva and 15 pterygium samples, Sebastia *et al*[111] found pterygium epithelium expressed more Hsp90 than normal conjunctiva epithelium. Recently it was shown the expressions of HSPs (Hsp27, Hsp70 and Hsp90) and hypoxia-inducible factor-1α (HIF-1α) were noticeably increased in pterygium[112]. Hsp90 cooperated with HIF-1α in regulating the transcription of abundant target genes involved in vascularization, energy metabolism and apoptosis[113]. In addition, some members of HSPs were found to be overexpressed in other ocular surface disease like keratoconjunctivitis[114]. In our opinion, chronic stimulations caused by UV radiation or dust might lead to the occurrence of pterygium *via* elevating the expression of HSPs.

Tight Junction Proteins Tight junctions are the intimately associated areas of two cells whose membranes join together forming an impermeable barrier to fluid. Claudins are indispensable proteins for the formation and maintenance of tight junctions. Dogan *et al*[115] used immunohistochemical evaluation and McNemar test to investigate the tight junction protein claudin-1 expressions in pterygium with respect to normal conjunctiva. They found the expression of claudin-1 decreased significantly in pterygium, which meant the loss of claudin-1 probably contributed to the pathogenesis of pterygium.

CONCLUSION AND PERSPECTIVES

With histology and molecular biology technique, the genes and proteins expression profile of pterygium was found to be greatly different from normal conjunctiva or cornea. Moreover, the expression profile also varies with the clinical stage or onset (primary or recurrent). These genes and proteins can be classified into different groups according to their major function, and they may play a role in the diverse biological process and contribute to the initiation and development of pterygium with interaction. Many proteins that are found to aberrantly expressed in pterygium need to be studied by further investigation, such as human cystatin C[116] and COX-2[117], *etc*. It is also possible that many important genes and proteins in pterygium pathogenesis still remain unknown. Further studies should be performed to understand the mechanisms by which these genes and proteins are involved in pterygium. Pharmaceutical intervention targeting these molecules that are proved to be critical in pterygium development might be a promising therapy for pterygium besides surgical treatment.

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