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PTERYGIUM AND RELATED PROTEINS

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ABSTRACT: Pterygiums are benign growths that begin on the conjunctiva and can spread to the cornea, where they may cause visual impairments as they expand. It manifests as a raised, white, or pinkish lesion on the eye's surface. Proteins associated with inflammation, cell division, and extracellular matrix alterations have a role in pterygium formation. Prolonged exposure to UV light, dryness, wind, and dust are known factors that increase the risk of this condition. However, its exact etiology is yet unknown. Redness, discomfort, a grainy sensation, and infrequently blurred vision are signs that the cornea is impacted. Lubricating drops or ointments are usually used in the treatment of mild instances. If the pterygium causes discomfort, vision issues, or concerns about appearance, surgical removal—often combined with tissue grafting—is advised. Recurrence rates depend on surgical procedure and postoperative management; preventative tactics prioritize lubricating the eyes, protecting against UV rays, and avoiding windy or dusty surroundings. Understanding the molecular mechanisms of pterygium, including the many proteins involved, has been the main focus of research. This review focuses on pterygium protein-related mechanisms.

Keywords: pterygium, metalloproteinases, vascular endothelial growth factor, integrins.

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1. INTRODUCTION

A benign growth of the conjunctiva that may spread to the cornea is called a pterygium. Pterygium development and progression include several proteins, many of which are connected to inflammation, cell division, and extracellular matrix remodeling. Pterygium often appears as a raised, pinkish, or whitish growth on the eye's surface. It may gradually extend onto the cornea, potentially affecting vision if it grows large enough. Pterygium is linked to extended exposure to ultraviolet (UV) light, dry eyes, wind, dust, and other environmental conditions, yet its precise etiology is still unknown. Those who work outside a lot, like farmers and surfers, are more vulnerable. Typical symptoms include redness, discomfort, a grainy feeling, and even blurred vision if the pterygium presses against the cornea. Mild cases may be managed with lubricating eye drops or ointments. Surgical removal is typically recommended if the pterygium causes significant discomfort, affects vision, or is cosmetically bothersome. Surgical techniques include simple excision with or without grafting of healthy tissue onto the affected area. Pterygium can recur after surgical removal, primarily if the underlying risk factors (like UV exposure) are not addressed. The type of surgery done and the quality of the postoperative care affect the recurrence rate. Preventive strategies include wearing sunglasses that block UV rays, using lubricating eye drops in dry conditions, and preventing prolonged exposure to dusty or windy environments. Numerous facets of pterygium's pathophysiology have been studied, including the role of proteins and molecular pathways. A few proteins associated with pterygium are mentioned in Table 1.

Table 1: Proteins involved in pterygium

#	Protein	Description	References
1	Matrix Metalloproteinases (MMPs)	MMP-1, MMP-2, MMP-3, and MMP-9: These enzymes are involved in extracellular matrix degradation and tissue remodeling.	[1]
2	Vascular Endothelial Growth Factor (VEGF):	VEGF promotes angiogenesis and is often upregulated in pterygium.	[2]
3	Transforming Growth Factor-Beta (TGF-β):	TGF-β is implicated in fibrosis and extracellular matrix production in pterygium.	[3]
4	Interleukins (ILs):	IL-6 and IL-8: These cytokines are involved in the inflammatory response and can promote angiogenesis.	[4]
5	Fibronectin and Laminin:	These extracellular matrix proteins contribute to cell adhesion, migration, and differentiation.	[5]
6	Cyclooxygenase-2 (COX-2):	COX-2 is an enzyme associated with inflammation and angiogenesis in pterygium.	[6]

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7	Platelet-Derived Growth Factor (PDGF):	PDGF is involved in cell proliferation and migration in pterygium	[7]
8	Basic Fibroblast Growth Factor (bFGF):	bFGF promotes cell proliferation and angiogenesis in pterygium.	[8]
9	Epidermal Growth Factor (EGF):	EGF stimulates epithelial cell growth and proliferation in pterygium.	[9]
10	Tenascin-C:	Tenascin-C modulates cell adhesion and migration, found in areas of tissue remodeling	10]
11	Tumor Necrosis Factor-Alpha (TNF-α):	TNF-α is a pro-inflammatory cytokine that can contribute to inflammation and fibrosis in pterygium.	[11]
12	Cytokeratins (CKs)	Cytokeratins are a family of proteins involved in the structural integrity of epithelial cells and are often altered in pterygium tissue.	[12]
13	Integrins:	Integrins are cell surface receptors that mediate cell-extracellular matrix interactions and are involved in cell adhesion and migration.	[13]
14	Collagen:	Collagen, particularly types I and III, is a significant component of the extracellular matrix, and its altered expression is seen in pterygium.	[14]
15	Heat Shock Proteins (HSPs):	HSPs, such as HSP70, are involved in cellular stress responses and may play a role in the pathogenesis of pterygium.	[15]
16	E-cadherin:	E-cadherin is a cell adhesion molecule important for maintaining epithelial integrity, often downregulated in pterygium.	[16]
17	Toll-like Receptors (TLRs):	TLRs are involved in the innate immune response and may contribute to the inflammatory processes in pterygium.	[17]
18	Nuclear Factor Kappa B (NF-κB):	NF-κB is a transcription factor that regulates inflammation and immune responses and is potentially involved in pterygium pathogenesis.	[18]
19	Periostin:	Periostin is a matricellular protein involved in tissue repair and fibrosis, upregulated in pterygium.	[19]
20	Connective Tissue Growth Factor (CTGF):	CTGF is involved in fibroblast proliferation and extracellular matrix production, playing a role in pterygium fibrosis.	[20]

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The elements listed in Table 1 are discussed in depth below.

An extensive literature screening using Pub Med data was performed. Molecular biology data, trends, and novel therapies were all taken from published works and indexed in Pub Med. All the references used were appropriately cited. This review used a table summarizing protein involvement in pterygium and a figure illustrating the pterygium mechanism. MMPs, or matrix metalloproteinases, are essential in various processes. This is a synopsis of the roles played by particular MMPs in pterygium. MMP-1, also known as interstitial collagenase, is principally responsible for degrading collagen types I, II, and III, essential extracellular matrix constituents. MMP-1 expression has been found to be elevated in pterygium tissues, which may indicate that it plays a part in the fibrovascular tissue's invasion of the cornea and the disintegration of the corneal stroma. Gelatin, type IV collagen, which makes up a significant portion of basement membranes, and other ECM proteins are broken down by MMP-2 (Gelatinase A). MMP-2 is often overexpressed in pterygium, which facilitates the invasion and migration of fibrovascular tissue and aids in the breakdown of ECM and basement membranes. Numerous ECM constituents, including collagen types III, IV, and V, fibronectin, laminin, and proteoglycans, can be broken down by MMP-3 (Stromelysin-1). Tissue invasion and angiogenesis are aided by the substantial remodeling of the extracellular matrix (ECM) caused by elevated levels of MMP-3 in pterygium tissue. Gelatin, type IV and V collagens, and elastin are all broken down by MMP-9 (Gelatinase B). Pterygium-specific increases in MMP-9 expression are linked to the breakdown of ECM and basement membranes, encouraging angiogenesis and tissue remodeling. The crucial significance of these MMPs in the pathophysiology of the disease is highlighted by the overexpression of these proteins in the pterygium. These enzymes aid in infiltrating fibrovascular tissue into the cornea by breaking down different elements of the extracellular matrix (ECM) and basement membranes. This process is responsible for the distinctive development seen in pterygium.[21,22,23,24,25,26]. One of the most important factors in controlling angiogenesis—the process by which new blood vessels grow out of pre-existing ones—is vascular endothelial growth factor (VEGF). VEGF is important in the setting of pterygium because it stimulates the development of new blood vessels, which helps the fibrovascular tissue that is characteristic of this disorder expand and survive. Strong angiogenic factor VEGF promotes endothelial cell migration and proliferation, which develops new blood vessels. Elevated VEGF levels in pterygium are responsible for the lesion's considerable vascularization. Research has indicated that pterygium tissues have much greater levels of VEGF expression than normal conjunctival tissues. The development of pterygium is widely linked to several variables, including hypoxia, inflammation, and UV radiation, which are thought to be the driving forces behind this upregulation. The pterygium grows because of the enhanced angiogenesis that VEGF promotes, but it also plays a role in the invasive qualities of the growth. The proliferating fibrovascular tissue can expand onto the cornea because the new blood vessels give it the necessary nutrition and oxygen.

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Targeting VEGF or its signaling pathways offers a viable treatment approach because of the crucial role that VEGF plays in the etiology of pterygium. The effectiveness of anti-VEGF treatments, including bevacizumab, in preventing the growth and recurrence of pterygium by blocking angiogenesis has been studied[27,28]. Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that plays a crucial role in cellular processes such as proliferation, differentiation, and extracellular matrix (ECM) production. In the context of pterygium, TGF-β is particularly important due to its involvement in fibrosis and ECM production, contributing to the pathogenesis of this condition. TGF-β is a crucial mediator of fibrosis, stimulating the transformation of fibroblasts into myofibroblasts, which are cells responsible for the excessive production of ECM components such as collagen and fibronectin. In the pterygium, this fibrotic response leads to the lesion's thickening and scarring characteristics. TGF-β promotes the synthesis and deposition of ECM proteins, contributing to the structural alterations observed in pterygium. This increased ECM production supports the invasion and adherence of pterygium tissue onto the corneal surface. TGF-β can modulate the activity of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). By influencing the balance between MMPs and TIMPs, TGF-β controls ECM remodeling, further contributing to pterygium's invasive and recurrent nature. TGF-β is involved in the inflammatory response associated with pterygium. It can recruit and activate inflammatory cells, which release additional cytokines and growth factors, perpetuating a cycle of inflammation, fibrosis, and ECM remodeling. TGF-β can also promote angiogenesis, indirectly supporting the growth and vascularization of pterygium tissue. Combined with VEGF upregulation, this effect enhances the fibrovascular proliferation seen in pterygium[29,30]. Pro-inflammatory cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8) are critical players in the inflammatory response and can promote angiogenesis. Their involvement in pterygium contributes to the chronic inflammation and fibrovascular development that characterize this disease. A versatile cytokine, IL-6, is necessary for the acute inflammatory response stage. Pterygium has a significantly greater concentration of IL-6, which contributes to the chronic inflammatory environment. It prolongs the inflammatory cycle by promoting the creation of acute-phase proteins and attracting immune cells to the site of inflammation. IL-6 indirectly promotes angiogenesis by upregulating VEGF and other pro-angiogenic molecules. This facilitates the formation of new blood vessels within the pterygium tissue, stimulating its growth and invasion. IL-6 can stimulate fibroblasts, increasing the creation of extracellular matrix (ECM) components. This exacerbates the pterygium's fibrotic characteristics. IL-8 is an effective chemoattractant for neutrophils and immune cells. The high concentration of pterygium tissue at the location attracts these cells and amplifies the local inflammatory response. IL-8 stimulates and activates immune cells in pterygium, aiding in the maintenance of chronic inflammation. IL-8 directly promotes angiogenesis by promoting the migration and proliferation of endothelial cells. New blood vessels subsequently form, bringing oxygen and nutrients to the

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growing pterygium tissue. IL-8 influences MMP expression and activity and plays a role in ECM remodeling. The modulation of MMP facilitates tissue invasion and intensifies the pterygium's structural changes.[31,32,33]. Extracellular matrix (ECM) proteins are essential for cell adhesion, migration, and differentiation mechanisms underpinning this illness's onset and course. Through interactions between different proteins, cell surface receptors, and other ECM components, the ECM gives tissues structural support and controls cellular processes. Tensile strength and structural integrity are provided by collagen, the main structural protein in the extracellular matrix (ECM). Cell adhesion uses collagen fibers as a substrate, which helps cells attach and create sturdy structures. Collagen fiber density and alignment affect cell migration paths, which makes it easier for fibrovascular tissue to invade the cornea. Collagen regulates cell differentiation processes essential for tissue remodeling through interactions with cell surface receptors (integrins, for example). A glycoprotein called fibronectin is involved in cell adhesion, growth, migration, and differentiation. Fibronectin facilitates cell adhesion and spreading by attaching to integrins on the cell surface. It creates fibrillar networks that direct migrating cells and facilitate the pterygium tissue's invasive expansion. How fibronectin interacts with cytokines and growth factors might affect how epithelial and stromal cells differentiate in pterygium. Laminin is an essential part of the basal lamina and plays a role in cell migration, differentiation, and adhesion. Laminin provides binding sites for integrins and other cell surface receptors, facilitating the attachment of epithelial cells. It supports directed cell migration, which is essential for the spread of pterygium cells over the cornea. Laminin interactions help maintain epithelial cell polarity and differentiation, contributing to tissue homeostasis and pathology in pterygium. Proteoglycans are ECM components that regulate matrix organization and cell signaling. Proteoglycans bind to collagen and other ECM proteins, enhancing cell adhesion and matrix stability. They modulate the activity of growth factors and cytokines, influencing cell migration and tissue remodeling. Proteoglycans participate in signaling pathways that regulate cell proliferation and differentiation, affecting the behavior of pterygium cells.[34,35,36]. An enzyme known as cyclooxygenase-2 (COX-2) is essential to the pathophysiology of pterygium, as it is involved in both angiogenesis and inflammation. This is a summary of the roles that COX-2 plays in the onset and development of pterygium. The inducible enzyme COX-2 converts arachidonic acid into prostaglandins, lipid molecules that control inflammatory reactions. Environmental variables such as UV radiation can cause COX-2 to become elevated in pterygium, leading to the induction of inflammatory signaling pathways. More prostaglandins that promote inflammation are produced as a result of this overexpression. Prolonged inflammation in the conjunctival and ocular tissues results from elevated prostaglandins, which also encourage cellular survival and proliferation and foster the establishment of pterygium. PGE2, one of the leading products of COX-2 action, exhibits potent angiogenic capabilities. Vascular endothelial growth factor (VEGF), essential for developing new blood vessels, is expressed more

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when PGE2 is present. COX-2 promotes angiogenesis, which is required to deliver nutrients and oxygen to the developing pterygium tissue, by upregulating VEGF. This neovascularization supports the fibrovascular growth that is characteristic of pterygium. In the pterygium, COX-2 and its byproducts can prevent fibroblasts and epithelial cells from going through programmed cell death, encouraging cell survival and proliferation. Additionally, COX-2 activity controls MMPs, which are enzymes that break down the extracellular matrix (ECM), allowing pterygium cells to invade and remodel tissue[37,38]. The growth and migration of cells, essential for developing and advancing pterygium, are facilitated by platelet-derived growth factor (PDGF). The mechanism of action of PDGF is through binding to its receptors, PDGFR-α and PDGFR-β, which are surface-expressed on fibroblasts, endothelial cells, and epithelial cells, among other cell types. One powerful mitogen that promotes fibroblast and epithelial cell proliferation in pterygium is called PDGF. This accelerated cell division facilitates the development of the fibrovascular tissue that is specific to pterygium. PDGF stimulates a number of downstream signaling pathways that are important in cell cycle regulation and proliferation upon binding to its receptors. These pathways include the MAPK, PI3K/AKT, and STAT pathways. Inducing fibroblasts and other cell types to migrate toward the site of inflammation or damage, PDGF acts as a chemoattractant. In the pterygium tissue, this causes fibroblasts and other cells to accumulate, which makes it easier for the tissue to extend over the cornea. Enzymes called matrix metalloproteinases (MMPs) break down extracellular matrix components. PDGF affects the expression and function of MMPs. This ECM remodeling produces a favorable environment for cell migration and tissue invasion. In order to create new blood vessels, PDGF also encourages the migration and proliferation of endothelial cells. These new arteries supply The developing pterygium tissue with the essential nutrients and oxygen. Pterygium is fibrovascular because PDGF acts with other growth factors, such as VEGF, to promote angiogenesis and tissue proliferation[39,40,41]. Basic Fibroblast Growth Factor (bFGF, sometimes called FGF-2) is a potent growth factor that plays a key role in angiogenesis and cell proliferation, two processes essential to forming and advancing pterygium. Fibroblasts, endothelial cells, and epithelial cells are just a few of the cell types that bFGF is known to stimulate in proliferative experiments. In pterygium context, bFGF stimulates these cells' proliferation inside the pterygium tissue. When bFGF interacts with its cell surface receptors, or FGFRs, it initiates downstream signaling pathways, including the PLCγ, PI3K/AKT, and MAPK pathways. Increased cell division and DNA synthesis are the results of these mechanisms. Because it promotes endothelial cell migration and proliferation, which results in the formation of new blood vessels, bFGF plays a crucial role in angiogenesis. This promotes vascularization in pterygium, bringing nutrients and oxygen to the developing tissue. In order to promote the growth of new blood vessels, bFGF frequently functions in concert with other angiogenic factors such as VEGF. This combined impact guarantees the pterygium tissue strong circulatory supply. Degrading ECM components, matrix metalloproteinases (MMPs) are enzymes

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whose expression and activity can be affected by bFGF. Pterygium's ability to support cell migration and tissue expansion depends on this ECM remodeling. The synthesis and deposition of ECM proteins like collagen and fibronectin are facilitated by bFGF's stimulation of fibroblasts, which supports the expansion and structural integrity of pterygium tissue. Because it stimulates angiogenesis, granulation tissue production, and re-epithelialization, bFGF is essential for wound healing and tissue repair. Pterygium hijacks these mechanisms, resulting in fibrosis and uncontrollably growing tissue[42,43]. A fibrovascular growth on the eyes' surface, pterygium, frequently spreads from the conjunctiva into the cornea. Growth factors that encourage angiogenesis, cell migration, and proliferation significantly impact its development. It is necessary to have epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF). For many different kinds of cells, including fibroblasts and endothelial cells, bFGF is an effective mitogen. In the pterygium, these cells proliferate in response to bFGF, promoting new tissue growth. The development and proliferation of the cell cycle depend on downstream signaling pathways that are started when bFGF binds to its receptors, or FGFRs. The pathways in question are PLCγ, PI3K/AKT, and MAPK. Endothelial cells proliferate and migrate in response to bFGF stimulation to produce new blood vessels. The developing pterygium tissue receives nutrition and oxygen from this neovascularization. Together with other angiogenic factors like VEGF, bFGF promotes the growth of new blood vessels. EGF promotes the main growth and proliferation of epithelial cells. EGF stimulates corneal and conjunctival epithelial cell growth in the pterygium. Increased cell proliferation results from signaling cascades such as the PI3K/AKT and MAPK pathways being activated when EGF binds to the Epidermal Growth Factor Receptor (EGFR) on cell surfaces[44]. Extracellular matrix (ECM) glycoprotein tenascin-C is essential for controlling cell adhesion and migration, particularly in tissue remodeling, inflammation, and healing areas. Its impact on these cellular functions makes its role in pterygium noteworthy. Depending on the cellular environment and the existence of additional ECM elements, tenascin-C can either stimulate or inhibit cell adhesion. It can change cell-ECM interactions to promote tissue growth at the leading edge of the invasive tissue in pterygium. Tenascin-C facilitates more effective cell detachment and migration by modifying adhesion. This is especially crucial in the pterygium because it requires migrating epithelial cells and fibroblasts over the corneal surface. Tumors and regions where significant tissue remodeling occurs have high tenascin-C expression levels. Its expression is elevated in the stroma and at the interface between the epithelium and the stroma in the pterygium, suggesting that remodeling activities are ongoing. Tenascin-C affects cellular behavior by interacting with different cytokines and growth factors. It can bind to and alter the function of molecules implicated in the pathophysiology of pterygium, such as transforming growth factor-beta (TGF-β) and fibroblast growth factors (FGFs). An increase in tenascin-C can occur in reaction to inflammatory stimuli. Chronic inflammation is a crucial characteristic of pterygium, and tenascin-C interacts with inflammatory cells and mediators to add

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to the inflammatory milieu[45,46]. A pro-inflammatory cytokine, tumor necrosis factor-alpha (TNF-α) is essential for both inflammation and fibrosis, two critical aspects of the pathophysiology of pterygium. TNF-α is a robust inflammatory inducer. It stimulates additional inflammatory cytokines and chemokines to be produced, which draws and activates inflammatory cells to the pterygium location, including neutrophils and macrophages. Long-term exposure to environmental elements such as ultraviolet (UV) radiation can cause pterygium to express TNF-α to rise, which helps maintain an inflammatory response. This ongoing inflammation accelerates the development of pterygium. Fibroblasts, the cells that make components of the extracellular matrix (ECM), including collagen, can be activated by TNF-α. This activation causes more extracellular matrix (ECM) to deposit, adding to pterygium's fibrotic characteristics. Together with other cytokines like TGF-β, TNF-α increases fibroblast activity and extracellular matrix formation, which leads to tissue remodeling and fibrosis. TNF-α can affect fibroblasts and epithelial cells, among other cell types within the pterygium, in terms of their survival and proliferation. The pterygium tissue grows and thickens as a result of this. TNF-α stimulates the pterygium to produce new blood vessels by expressing angiogenic factors like VEGF, which provides oxygen and nutrients to proliferating tissue [47]. A family of intermediate filament proteins called cytokeratins is essential for preserving the stability and structural integrity of epithelial cells. Pterygium tissue frequently exhibits alterations in these proteins, which are indicative of pathological abnormalities and epithelial cell differentiation. The cytoskeleton of epithelial cells contains cytokeratins, which support the structure of the cell and preserve its integrity. They are necessary for the surface-layer epithelial cells of the eye to endure mechanical stress. The pattern of cytokeratin expression is frequently changed in pterygium. Atypical epithelial cell differentiation and proliferation may be indicated by alterations in particular cytokeratins. For instance, pterygium commonly exhibits upregulation of cytokeratin 19 (CK19), which points to a transition towards a less differentiated and more proliferative state. Changes in cytokeratin expression are linked to epithelial-mesenchymal transition (EMT), in which cells become more migratory and invasive by acquiring mesenchymal traits. This change aids in the pterygium's invasive development onto the cornea. Certain cytokeratins can function as biomarkers for pterygium diagnosis and progression. Their expression levels could be correlated with the disease's severity and recurrence, which would be useful information for a clinical evaluation. Determining possible therapeutic targets can be aided by comprehending the variations in cytokeratin expression. Inhibiting the aberrant growth and invasion of pterygium may be possible by altering the expression or function of specific cytokeratins[48].

Integrins are major cell surface receptors that play key roles in cell adhesion, migration, and signaling by mediating interactions between cells and the extracellular matrix (ECM). Integrins play a major role in the pathogenic mechanisms that underlie the development and progression of pterygium. Integrins link the cell cytoskeleton, collagen, fibronectin, and laminin, among other

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ECM constituents. Integrins in the pterygium help epithelial and fibroblast cells adhere to the extracellular matrix (ECM), which permits the cells to migrate and invade the corneal surface. Integrins bind to ligands to start intracellular signaling cascades and to offer mechanical support through adhesion. The cellular processes of proliferation, survival, and differentiation that are dysregulated in pterygium are regulated by these signaling pathways. As a characteristic of pterygium, angiogenesis—the formation of new blood vessels—is facilitated by integrins. Within the pterygium tissue, they facilitate endothelial cell adhesion and migration during vessel sprouting and enlargement. By controlling fibroblast activation and differentiation, integrins contribute to fibrosis by increasing the synthesis and deposition of extracellular matrix (ECM) proteins including collagen. This adds to the fibrotic characteristics of the tissue in pterygium. Therapeutic therapies targeting integrins may be effective in controlling the growth and recurrence of pterygium. It may be possible to prevent angiogenesis, migration, and pterygium cell attachment by altering integrin expression or activity. Treatment options for pterygium patients could be customized with the help of changes in integrin expression profiles, which could act as prognostic markers for disease progression and recurrence risk[49]. Collagen, particularly types I and III, plays a crucial role in the structure and function of the extracellular matrix (ECM) in ocular tissues. In the context of pterygium, the expression and organization of these collagen types are notably altered, contributing to the pathogenesis of the condition. Type I collagen is the most abundant collagen in the human body and provides tensile strength to the ECM. In pterygium, there is often an overproduction of type I collagen, which can lead to fibrosis and thickening of the tissue. This excessive collagen deposition contributes to the growth and persistence of the pterygium. Type III collagen is typically found in tissues that require flexibility and is usually co-expressed with type I collagen. Similar to type I, type III collagen is also upregulated in pterygium. The imbalance in the collagen ratio (increased type III relative to type I) may affect the tissue's mechanical properties and contribute to the abnormal structure and behavior of the pterygium. The altered expression of collagens I and III in pterygium suggests a disrupted balance in ECM remodeling processes. Several factors contribute to this phenomenon: UV exposure can stimulate fibroblasts and other cells in the conjunctiva to produce more collagen, particularly types I and III, leading to tissue overgrowth and fibrosis. Chronic inflammation, often seen in pterygium, can further exacerbate collagen production and deposition. Growth factors such as transforming growth factor-beta (TGF-β) are known to regulate collagen synthesis and are often upregulated in pterygium tissue. Immunohistochemical staining for types I and III collagen can help diagnose and understand the extent of pterygium. Treatments targeting collagen synthesis and deposition may be beneficial. For instance, collagen synthesis inhibitors or agents promoting balanced ECM remodeling could be potential therapeutic strategies. Understanding the roles of collagens I and III in pterygium provides valuable insights into its pathogenesis and possible avenues for treatment, emphasizing the need for targeted approaches to

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manage this condition effectively[50]. Heat Shock Proteins (HSPs), including HSP70, are a family of proteins that play a crucial role in the cellular stress response by acting as molecular chaperones. They help properly fold proteins, protect against stress-induced damage, and repair damaged proteins. In the context of pterygium, HSPs, particularly HSP70, are implicated in the pathogenesis of the condition due to their involvement in cellular responses to stress, inflammation, and apoptosis. HSP70 helps protect cells from stress-induced damage by preventing protein aggregation and assisting in protein refolding. It is upregulated in response to various stressors, including UV radiation and oxidative stress. In pterygium, HSP70 expression is often increased, reflecting the tissue's response to chronic stress and inflammation. This upregulation may contribute to the survival and proliferation of abnormal cells in pterygium. Pterygium is commonly associated with chronic UV exposure. HSP70 is upregulated in response to UV-induced stress, helping to mitigate DNA damage and protein misfolding. Chronic inflammation is a hallmark of pterygium. HSP70 can modulate inflammatory responses by interacting with immune cells and cytokines, potentially contributing to the persistent inflammatory environment in pterygium. HSP70 has anti-apoptotic properties, which may help pterygium cells evade programmed cell death, leading to uncontrolled cell proliferation and tissue growth. Continuous exposure to UV light and oxidative stress induces a sustained upregulation of HSP70, which helps cells survive under adverse conditions. HSP70 interacts with various immune system components, potentially exacerbating the inflammatory milieu seen in pterygium. By inhibiting apoptosis, HSP70 may facilitate the abnormal proliferation of fibrovascular tissue characteristic of pterygium. Immunohistochemical detection of HSP70 can be used to identify and understand the extent of cellular stress and damage in pterygium tissue. Targeting HSP70 and its regulatory pathways may offer new therapeutic strategies. For example, HSP70 inhibitors or modulators could help reduce cell survival and proliferation in pterygium, potentially limiting its growth and recurrence[51]. E-cadherin is a crucial cell adhesion molecule that maintains epithelial cell integrity and tissue architecture by mediating cell-cell adhesion. In pterygium, E-cadherin expression is often downregulated, contributing to the affected cells' disrupted cellular organization and increased migratory potential. E-cadherin is a transmembrane protein that facilitates calcium-dependent cell-cell adhesion, playing a critical role in maintaining epithelial tissues' structural integrity and polarity. Proper E-cadherin function is essential for tissue homeostasis, inhibiting cell migration and proliferation by maintaining stable cell contacts. In pterygium, E-cadherin expression is frequently reduced. This downregulation is associated with the loss of epithelial integrity, increased cell detachment, and enhanced migratory and invasive capabilities of epithelial cells. The decreased expression of E-cadherin facilitates the epithelial-mesenchymal transition (EMT))---like changes in pterygium cells, contributing to this condition's fibrovascular proliferation characteristic. Several mechanisms can lead to the downregulation of E-cadherin. Chronic exposure to UV light, a significant risk factor for pterygium, can induce changes

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in gene expression, including the suppression of E-cadherin. Chronic inflammation in pterygium is marked by elevated levels of cytokines such as TGF-β, which can downregulate E-cadherin expression and promote EMT. DNA methylation and histone modifications can lead to silencing the E-cadherin gene (CDH1), contributing to its reduced expression in pterygium. The downregulation of E-cadherin in pterygium has several pathophysiological implications. Reduced E-cadherin weakens cell-cell adhesion, disorganizing the epithelial layer and facilitating abnormal tissue growth. Lower levels of E-cadherin enhance the migratory potential of epithelial cells, promoting the extension of pterygium tissue onto the cornea. The loss of E-cadherin supports EMT-like changes, contributing to the fibrovascular proliferation observed in pterygium. Immunohistochemical staining for E-cadherin can help assess the degree of its expression and the extent of epithelial disruption in pterygium tissue. Strategies to upregulate or restore E-cadherin expression may help inhibit pterygium progression. Potential approaches include targeting the pathways that lead to its downregulation, such as using inhibitors of TGF-β signaling or agents that reverse epigenetic modifications[52]. An essential part of the innate immune system, toll-like receptors (TLRs) are involved in the identification of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). They trigger signaling pathways that produce antimicrobial peptides and pro-inflammatory cytokines, vital for the host's defense against infections. TLRs, specifically TLR2, TLR4, and TLR9, are associated with pterygium and play a role in the inflammatory pathways that underlie the development of this eye ailment. TLRs recognize and attach to particular patterns on pathogens (PAMPs) and chemicals secreted by injured cells (DAMPs), which sets off a series of immunological reactions. Both endogenous and external stimuli, including UV light, oxidative stress, and microbiological elements, are believed to activate TLRs in pterygium and cause an inflammatory response. Identifies extracellular matrix elements and bacterial lipoproteins. TLR2 is frequently overexpressed in pterygium, which adds to the inflammatory environment. Reacts to several stress signals, including lipopolysaccharides (LPS) produced by Gram-negative bacteria. Increased TLR4 expression in pterygium indicates that it plays a part in promoting tissue remodeling and inflammation. Finds CpG motifs that are not methylated in viral and bacterial DNA. TLR9 may trigger an inflammatory response by identifying endogenous or microbiological DNA released from pterygium's injured cells. Activation of TLRs leads to the upregulation of cytokines such as TNF-α, IL-1β, IL-6, and IL-8, which exacerbate inflammation and recruit immune cells to the site of infection or tissue damage TLR activation triggers the NF-κB signaling pathway, a central regulator of inflammation. This pathway promotes the transcription of genes encoding inflammatory cytokines, adhesion molecules, and enzymes involved in matrix degradation. TLR signaling in pterygium may intersect with other signaling pathways, such as those mediated by cytokines like TGF-β and IL-17, further amplifying the inflammatory response and promoting fibrovascular proliferation. The persistent activation of TLRs and the resultant

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inflammatory response contribute to the chronic inflammation seen in pterygium, leading to tissue damage and fibrosis. TLR-mediated signaling promotes the expression of matrix metalloproteinases (MMPs) and other ECM-degrading enzymes, facilitating the remodeling of the extracellular matrix and the growth of fibrovascular tissue. Pro-inflammatory cytokines and chemokines release- attract immune cells, such as macrophages, neutrophils, and T cells, to the pterygium tissue, sustaining the inflammatory environment. Immunohistochemical staining and molecular techniques can be used to assess the expression levels of TLRs and associated cytokines in pterygium tissues, aiding in diagnosing and understanding the inflammatory profile. Targeting TLR signaling pathways presents a potential therapeutic strategy for managing pterygium. Possible approaches include: a. Use of small molecules or biologics that inhibit TLR signaling to reduce inflammation and prevent tissue remodeling. b. Development of drugs specifically targeting the downstream effects of TLR activation, such as cytokine inhibitors or modulators of the NF-κB pathway[53]. NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a crucial transcription factor in regulating the immune response, inflammation, cell proliferation, and survival. In the context of pterygium, NF-κB is thought to be significantly involved in the pathogenesis of the condition by mediating inflammatory and immune responses and promoting cellular changes associated with disease progression. NF-κB controls the transcription of various genes involved in immune and inflammatory responses, including cytokines, chemokines, adhesion molecules, and enzymes that degrade the extracellular matrix. NF-κB is typically activated in response to stimuli such as cytokines, UV radiation, oxidative stress, and microbial components, all relevant to pterygium development. This pathway involves the activation of NF-κB through the degradation of its inhibitor, IκB, which allows NF-κB to translocate to the nucleus and initiate gene transcription. It consists of the processing of NF-κB2/p100 to p52, which pairs with RelB to form active transcription complexes. Chronic exposure to UV light can activate NF-κB, increasing pro-inflammatory cytokine expression and growth factors promoting pterygium growth. Elevated levels of cytokines such as TNF-α and IL-1β in pterygium tissues can activate NF-κB, perpetuating a cycle of inflammation and tissue remodeling. Reactive oxygen species (ROS) generated by UV exposure and inflammation can activate NF-κB, contributing to the oxidative damage observed in pterygium. NF-κB activation leads to the transcription of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-8), which sustain the chronic inflammatory environment in pterygium. Chemokines induced by NF-κB attract immune cells such as macrophages and neutrophils, exacerbating inflammation. NF-κB regulates the expression of MMPs, which degrade the extracellular matrix and facilitate the fibrovascular proliferation characteristic of pterygium. NF-κB induces the expression of growth factors (e.g., VEGF), promoting angiogenesis and tissue growth. NF-κB upregulates anti-apoptotic proteins (e.g., Bcl-2, Bcl-xL), enhancing the survival and proliferation of pterygium cells. NF-κB influences cell cycle regulators, supporting the uncontrolled cell proliferation seen in pterygium.

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Staining for NF-κB and its target genes can help assess the extent of its activation in pterygium tissues. Techniques such as qPCR and Western blotting can quantify NF-κB activity and expression of its downstream targets. Small molecules or biological agents that inhibit NF-κB activation could reduce inflammation and tissue remodeling in pterygium. Drugs targeting the cytokines and pathways activated by NF-κB (e.g., TNF-α inhibitors) may help manage pterygium progression. Agents that reduce oxidative stress might indirectly inhibit NF-κB activation, providing therapeutic benefits[54]. Periostin is a matricellular protein crucial in tissue repair, remodeling, and fibrosis. It interacts with other extracellular matrix (ECM) components to influence cell adhesion, migration, and proliferation. In pterygium, periostin is often upregulated, contributing to the pathological changes seen in this condition. Periostin is involved in the organization and remodeling of the extracellular matrix by binding to other ECM proteins such as collagen and fibronectin. It promotes cell adhesion, migration, and proliferation, essential for wound healing and tissue repair. Periostin expression is significantly increased in pterygium tissues compared to normal conjunctival tissues. The upregulation of periostin in the pterygium suggests its involvement in the excessive ECM remodeling, fibrosis, and cellular proliferation that characterize this condition. Chronic exposure to ultraviolet (UV) light is a significant risk factor for pterygium. UV radiation can induce periostin expression by activating various signaling pathways, including those mediated by growth factors and cytokines. Pro-inflammatory cytokines such as TGF-β (Transforming Growth Factor beta) are elevated in the pterygium and can stimulate periostin production, promoting fibroblast activation and fibrosis. Reactive oxygen species (ROS) generated by UV radiation and inflammation can also contribute to the upregulation of periostin, further enhancing tissue remodeling and fibrotic processes. Periostin promotes the deposition and organization of collagen and other ECM components, leading to the thickened and fibrotic tissue observed in the pterygium. It stimulates fibroblasts to produce more ECM proteins, enhancing fibrosis and tissue stiffness. By interacting with integrins and other cell surface receptors, periostin facilitates the migration of fibroblasts and epithelial cells, contributing to the invasive growth of the pterygium. Periostin promotes the proliferation of fibroblasts and other cell types, supporting the expansion of fibrovascular tissue in the pterygium. Periostin can also act as a pro-inflammatory mediator, recruiting immune cells to the site of tissue injury and contributing to the chronic inflammation seen in the pterygium. Detecting periostin in tissue samples using immunohistochemistry can help identify its expression levels and distribution in pterygium tissues. Quantitative PCR and Western blotting can measure periostin mRNA and protein levels, providing insights into its role in pterygium. Targeting periostin or its signaling pathways could help reduce fibrosis and ECM remodeling in pterygium. Potential approaches include using antibodies or small molecules that inhibit periostin function. Reducing inflammation with corticosteroids or other anti-inflammatory agents may decrease periostin expression and its pro-fibrotic effects. Preventative measures such as wearing UV-blocking

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sunglasses can reduce UV-induced periostin expression and the risk of pterygium development[55]. Connective Tissue Growth Factor (CTGF), or CCN2, is a matricellular protein involved in various cellular processes, including cell adhesion, migration, proliferation, and extracellular matrix (ECM) production. CTGF plays a significant role in tissue repair and fibrosis. In pterygium, CTGF is upregulated and contributes to fibroblast proliferation and ECM production, leading to the fibrotic changes characteristic of this condition. CTGF promotes the proliferation and differentiation of fibroblasts, which are critical for tissue repair and fibrosis. It stimulates the production of ECM components, including collagen, fibronectin, and proteoglycans, contributing to tissue remodeling and fibrosis. CTGF is significantly upregulated in pterygium tissues compared to normal conjunctival tissues. The increased expression of CTGF in pterygium suggests its involvement in the fibrotic processes and abnormal tissue growth observed in this condition. Transforming Growth Factor-beta (TGF-β) is a significant regulator of CTGF expression. Elevated levels of TGF-β in pterygium can induce CTGF production, promoting fibroblast activation and fibrosis. Mechanical factors, such as the movement of the eyelid over the pterygium tissue, can upregulate CTGF, contributing to the fibrotic response. Reactive oxygen species (ROS) generated by UV radiation and inflammation can enhance CTGF expression, promoting ECM production and fibrosis. CTGF encourages the proliferation of fibroblasts, increasing the population of cells involved in ECM production and fibrosis. It induces fibroblasts to adopt a myofibroblast phenotype, characterized by increased contractile activity and ECM synthesis, contributing to tissue stiffness and fibrosis. CTGF stimulates collagen production and other ECM proteins, leading to the thickened and fibrotic tissue observed in pterygium. The increased ECM production and remodeling driven by CTGF contribute to pterygium's progressive growth and fibrotic nature. CTGF can act synergistically with inflammatory cytokines to sustain a chronic inflammatory environment, further promoting fibrosis and tissue remodeling. Detection of CTGF in tissue samples using immunohistochemistry can help identify its expression levels and distribution in pterygium tissues. Quantitative PCR and Western blotting can measure CTGF mRNA and protein levels, providing insights into its role in pterygium. Targeting CTGF or its signaling pathways could help reduce fibrosis and ECM remodeling in pterygium. Potential approaches include using antibodies or small molecules that inhibit CTGF function. Since TGF-β is a significant inducer of CTGF, targeting TGF-β signaling may also reduce CTGF expression and its fibrotic effects. Reducing oxidative stress with antioxidants might indirectly inhibit CTGF upregulation, providing therapeutic benefits[56].

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The pterygium protein-related mechanism is represented in the figure below (Figure 1).

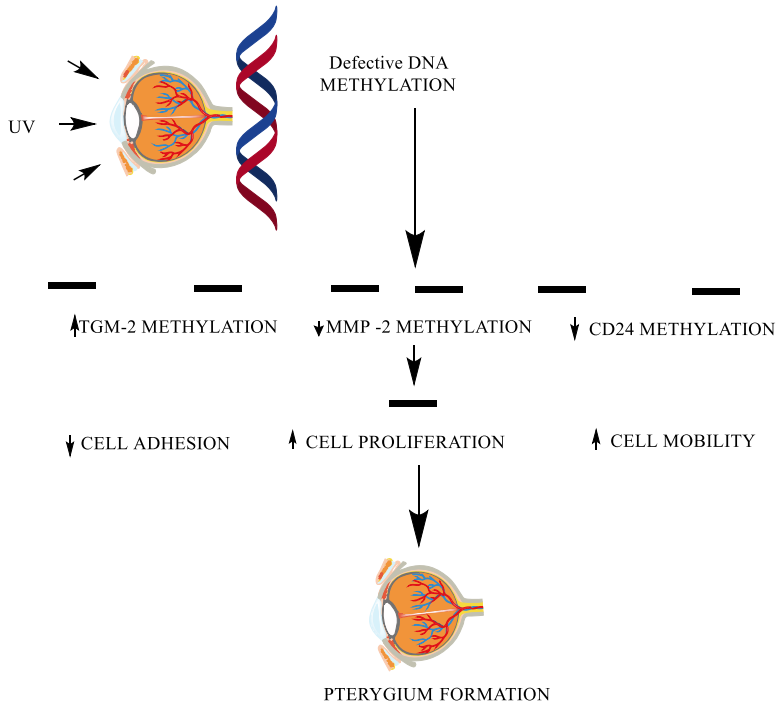

Figure 1: Pterygium formation is a UV (ultraviolet light) related mechanism.

Recent developments in the treatment of pterygium focus on enhancing surgical techniques, minimizing recurrence rates, and improving patient recovery. The primary advancements include using conjunctival autografts, introducing fibrin glue, and innovative laser treatments. This technique remains a gold standard in pterygium surgery due to its low recurrence rates and better healing outcomes. The price because of its superior healing results and low recurrence rates, this procedure is still considered the gold standard in pterygium surgery. The pterygium is removed during the surgery, and the afflicted area is covered with healthy conjunctival tissue from a different area of the patient's eye. This approach is substantially more successful than the bare sclera treatment, with a recurrence rate of less than 5%.dure involves removing the pterygium and covering the affected area with healthy conjunctival tissue from another part of the patient's eye. This method has a recurrence rate of less than 5%, making it significantly more effective than the bare sclera technique[57]. The use of fibrin glue in place of traditional sutures has been a notable advancement. It reduces surgery time, decreases postoperative inflammation, and enhances patient comfort. Fibrin glue also minimizes the risk of recurrence compared to sutures, which can cause irritation and prolonged healing times[58] Although this technique has higher recurrence rates than conjunctival autografts, it is still used in specific cases to promote healing and reduce inflammation. However, it is generally not preferred due to its comparatively higher recurrence rate[59]. Pterygium laser treatment, also known as pterygium excision with amniotic membrane transplantation (PEAT), is a minimally invasive option that offers precise removal of the pterygium and promotes healing with

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the help of an amniotic membrane graft. This method has shown promising results in reducing recurrence and shortening recovery times[60]. In addition to these surgical advancements, non-surgical treatments such as lubricating and steroid eye drops continue to play a role in managing symptoms and inflammation associated with pterygium. However, these treatments do not address the underlying growth and are typically used in conjunction with or as a precursor to surgical interventions. These advancements collectively aim to provide more effective and long-lasting solutions for individuals affected by pterygium, improving surgical outcomes and overall patient experience.

4. CONCLUSION

The latest updates in pterygium protein research primarily focused on understanding its causes, improving surgical techniques, and exploring non-surgical treatment options. Biomolecular mechanisms remain a keystone in developing pterygium-efficient therapies.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals or humans were used for the studies that are based on this research.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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