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Research Paper

Protein profile in pterygium tissue from patients with indoor activities

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ABSTRACT

Pterygium, commonly called "surfer's eye", is an ocular surface disease characterized by an abnormal wing-shaped growth of epithelial and fibro vascular tissue in the corneoscleral limbus that centripetally invades the cornea, significantly distorting the surface of the eye, and initiate astigmatism and blockage of the visual axis. It is usually manifested among populations with a high exposure to ultraviolet radiation (UVR). Given that pterygium also occurs in people with normal UVR contact, we performed this study in order to determine the differential proteomic profiling between advanced pterygium from patients with normal exposure to UVR and normal conjunctiva specimens using a mass spectrometry approach. We additionally discussed our results with previous report performed with pterygium specimens from patients with high exposure to UVR. Conjunctival tissues from pterygium and healthy conjunctiva were obtained by the same surgeon from patients with pterygium in an advanced stage that did not present any other surface eye disease. All patients performed indoor activities during most daylight hours in their entire lives. All procedures were in accordance with the tenets of the Declaration of Helsinki. Specimens were subjected to protein extraction followed by fractionation of proteins by "in solution" digestion, and proteomic mass spectrometry analysis was done using an Orbitrap Q-Exactive mass spectrometer. Bioinformatics analysis was performed using the Thermo Proteome Discoverer 2.2 software using appropriate databases. We obtained a protein profile from pterygium and normal conjunctival tissues. Comparative profiles between both kinds of specimens showed 41 common proteins. We found 32 unique proteins in pterygium and 17 unique proteins in normal conjunctival specimens. Among the unique species found in pterygium specimens, a number of proteins involved in immune response, unfolding protein response and oxidative .stress were found consistent with the nature of the disease. The unique proteins found in pterygium tissue support the concept that its genesis involves multifactorial mechanisms. The fact that the patients studied by us were not overexposed to UVR strengthened the idea that there could be pterygia with diverse genesis.

Key words: Ocular surface, environment, degenerative disease, etiology.

INTRODUCTION

Pterygium is a common ocular surface disorder characterized by an abnormal wing-shaped growth of epithelial and fibrovascular tissue in the corneoscleral limbus that centripetally invades the cornea, causing inflammation, discomfort, and in advance cases impair the vision (Cárdenas-Cantú et al., 2014; Bradley et al., 2010). Visual impairment can result from astigmatism and blockage of the visual axis induced by abnormal tissue migrating toward the central cornea (Marcovich et al., 2010). As the disease progresses and impairs the vision,

excision is necessary (Maheshwari, 2003). Although several surgical methodologies are available for the treatment of pterygium, recurrence rates are still elevated (Hovanesian et al., 2017).

Pterygium has a prevalence which varies geographically (Saw and Tan, 1999). In particular, this disease has higher rates in regions with hot, dusty and dry climate and more exposure to UV radiation, such as the countries between 37 degrees north and south of the Equator. Cameron named this region as "Pterygium belt" (Optometry MC-TAJ of, 1965).

The pathogenesis of primary pterygium is complex. Although it has been studied for many years, its pathogenesis still remains uncertain. It is thought to be an ophthalmoheliosis due to its possible relationship with high exposure to ultraviolet radiation (UVR) (di Girolamo et al., 2002; di Girolamo et al., 2006; Chui et al., 2008). A wide range of other pathogenic factors have been proposed, including epithelial-mesenchymal transition, deregulation of extracellular matrix (ECM) modulators and growth factors, viral infections, epigenetic aberrations, immunologic and anti-apoptotic mechanisms, angiogenic and lymphangiogenic stimulation, inflammation cascades, recruitment of bone-marrow-derived stem- and progenitor cells, and modifications in the cholesterol metabolism. Most of these factors are thought to be related to the development and maintenance of the disease than to its origin (Cárdenas-Cantú et al., 2014).

To determine a possible pathogenic mechanism, we have performed proteomic studies using LC-MS/MS techniques to compare advanced vs. normal conjunctiva specimens, to identify any possible differential composition between both, in patients that were not over exposed to UVR during most part of the day in their lifetime due to their activities.

MATERIALS AND METHODS

Subjects

Conjunctival tissues were obtained from three patients with advanced stages of pterygium that underwent pterygium surgery. Individuals did not present any other surface eye disease. Samples of healthy conjunctiva from the same patients were used as controls. Patients work activities were: merchant, housewife, and public employee, implying that they all spend most daylight hours not directly exposed to UVR. All procedures were performed by the same surgeon and in accordance to the protocol approved by institutional review process and the tenets of the Declaration of Helsinki.

Protein extraction and digestion

Proteins were extracted from conjunctival and pterygium specimens using 125 mMTris-HCl (pH 7.0), 100 mMNaCl, 0.1% Triton X-100, 0.1% Genapol C-100, and 0.1% SDS. Insoluble materials were removed by centrifugation (10,000 g for 10 min at 4°C), and soluble proteins were quantified by the Bradford assay.

Proteins were precipitated from protein mixtures by adding 4 volumes of cold acetone (-20°C) per volume of sample and incubating on ice for 15 minutes. After precipitation, samples were centrifuged at 12,000 g for 10 min; supernatants were discarded, and pellets were resuspended in water for downstreaming further processing. Protein samples were reduced by adding dithiothreitol (DTT) during 30 min at room temperature, and subsequently alkylated during 30 minutes by adding fresh prepared iodoacetamide(IAA), in the dark. For enzymatic digestion, sequencing-grade modified trypsin (catalog no. V5113; Promega Corporation, Madison, WI; 0.1 µg/15 µl in 15 mM N-ethylmorpholine) was used overnight at 37°C. Samples were dried in a speed vac, and resuspended in 5% acetonitrile with 0.1% formic acid for mass spectrometric analysis.

Mass spectrometry

For sample resuspension, a 5% acetonitrile (Optima™ LC/MS Grade, Fisher Chemical) in 0.1% Formic acid (Optima™ LC/MS Grade, Fisher Chemical) solution was used, freshly prepared. Solvents A and B for high performance liquid chromatography (HPLC) were water and acetonitrile, respectively, sonicated before the experiment. HPLC was conducted in an Easy Nano LC 1000® instrument, from Thermo Fisher Scientific, Waltham MA, USA, connected online to a Q Exactive®Orbitrap mass spectrometer (Thermo Fisher Scientific, Pittsburgh PA, USA). The column of choice for reversed phase chromatography (RP) in this proteomics experiment was an Acclaim PepMap® 100, 75 um × 150 mm, with a particle size of 2 µm and 100 Å pore size.

Peptides were eluted from the Easy Nano LC1000 through the column into the Orbitrap instrument. The parameters were set to data-dependent mode, with an automatic gain control target (AGC) of 1.0E06 for full MS at 70,000@200 m/z resolution. For data dependent mode, dd-MS2, the resolution was set to 17,500@200 m/z. Isolation window was set to 1.3 m/z, normalized collision energy (NCE) set to 28eV, underfill ratio 1.0%, and dynamic exclusion 3.0.

For the proteomics bioinformatics analysis, Proteome Discoverer™ Software v. 2.2 from Thermo Fisher Scientific was used. The precursor tolerance was set to 10 ppm and the product to 0.02 Da. The most recent database for the organism of interest was downloaded from Uniprot (https://www.uniprot.org/) and incorporated in fasta format to the software. Sequest HT was chosen as the search engine, setting trypsin as the enzyme for digestion.

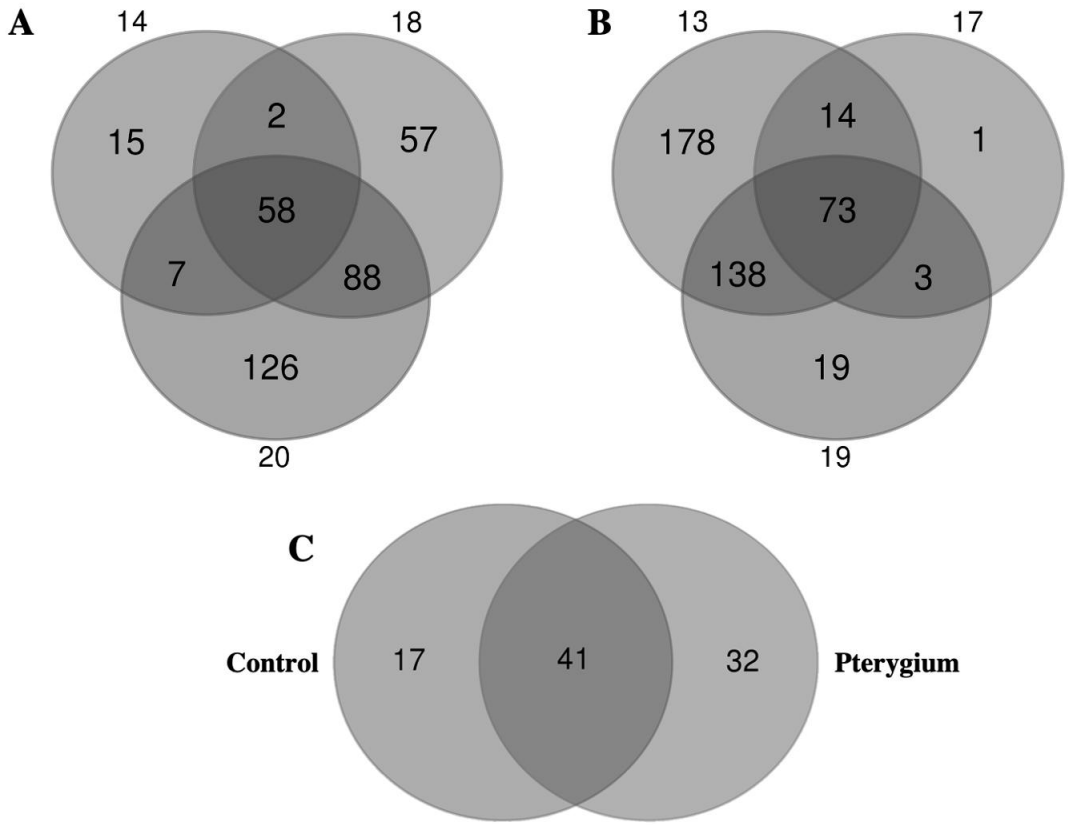

Figure 1: Venn diagrams showing **A)** number of proteins found in each control sample, **B)** number of proteins found in pterygium samples and **C)** number of unique proteins found in control or pterygium samples. In all cases, intersections represent the number of common proteins between groups. Numbers **14**, **18** and **20** outside Venn diagrams in **A** are coding numbers for control samples. Numbers **13**, **17** and **19** outside Venn diagrams in **B** are coding numbers for pterygium samples.

The false discovery rate (FDR) for relaxed and strict search were set to 0.05 and 0.01, respectively.

RESULTS

Protein identification with LC-MS/MS analysis

Proteins from normal conjunctiva and pterygium were reduced, alkylated and trypsin digested. Resultant peptides were subjected to sequence and protein identification by mass spectrometry using SEQUEST HT algorithm for UniProt database search. Using this approach, we obtained a protein profile from normal conjunctival and pterygium tissues, finding a total of 353 proteins in normal conjunctival specimens and 426 proteins in pterygium samples. Among the three control samples we found 58 common proteins. For pterygium specimens, 73 proteins were commonly found in all three samples (Figure 1A). Comparative profiles between both kinds of specimens showed 41 common proteins (Figure 1B). Furthermore, we found 17 unique proteins in normal conjunctival specimens and 32 unique proteins in pterygium tissues (Figure 1C). Unique proteins for control and for pterygium samples, as well as common proteins for both groups, are listed in Table 1.

Cellular protein components in control and pterygium samples were mainly from membrane, cytosol, cytoplasm, nucleus and extracellular proteins. The number of proteins associated to a particular cellular component is higher in pterygium versus control samples as shown in Figure 2.

The main protein molecular function found in both control and pterygium, was related to protein binding, followed by catalytic activity, RNA binding, metal ion binding and structural molecule activity, among others. The number of proteins associated to a particular function is higher in pterygium than in the control group as shown in Figure 3.

DISCUSSION

Although many studies have been conducted to elucidate the mechanisms involved in the pathogenic origin of pterygium, its etiology remains unclear. UVR can act on damaging cells and tissues through two general

Table 1: Description of common proteins and unique proteins found in control or pterygium samples.

Group	Number of proteins	Protein Description
Common	**41**	Isoform 2 of Annexin A2 OS=Homo sapiens GN=ANXA2
		Immunoglobulin heavy constant alpha 1 OS=Homo sapiens GN=IGHA1 PE=1 SV=2
		Keratin, type I cytoskeletal 19 OS=Homo sapiens GN=KRT19 PE=1 SV=4
		Protein disulfide-isomerase A3 OS=Homo sapiens GN=PDIA3 PE=1 SV=4
		Isoform 2 of Histone H2B type 2-F OS=Homo sapiens GN=HIST2H2BF
		Catalase OS=Homo sapiens GN=CAT PE=1 SV=3
		Annexin A1 OS=Homo sapiens GN=ANXA1 PE=1 SV=2
		Keratin, type I cytoskeletal 13 OS=Homo sapiens GN=KRT13 PE=1 SV=4
		Apolipoprotein A-I OS=Homo sapiens GN=APOA1 PE=1 SV=1
		Hermansky-Pudlaksyndrome 1 protein OS=Homo sapiens GN=HPS1 PE=1 SV=2
		Hemoglobinsubunit delta OS=Homo sapiens GN=HBD PE=1 SV=2
		Serumalbumin OS=Homo sapiens GN=ALB PE=1 SV=2
		Isoform 2 of Clusterin OS=Homo sapiens GN=CLU
		Fibrinogen beta chain OS=Homo sapiens GN=FGB PE=1 SV=2
		Hemoglobinsubunit beta OS=Homo sapiens GN=HBB PE=1 SV=2
		Fibrinogen gamma chain OS=Homo sapiens GN=FGG PE=1 SV=3
		Filamin-A OS=Homo sapiens GN=FLNA PE=1 SV=4
		Glyceraldehyde-3-phosphate dehydrogenase OS=Homo sapiens GN=GAPDH PE=1 SV=3
		Immunoglobulin gamma-1 heavy chain OS=Homo sapiens PE=1 SV=1
		Carbonic anhydrase 2 OS=Homo sapiens GN=CA2 PE=1 SV=2
		Peptidyl-prolylcis-transisomerase A OS=Homo sapiens GN=PPIA PE=1 SV=2
		Prelamin-A/C OS=Homo sapiens GN=LMNA PE=1 SV=1
		Plectin OS=Homo sapiens GN=PLEC PE=1 SV=3
		Histone H4 OS=Homo sapiens GN=HIST1H4A PE=1 SV=2
		Fibrinogen alphachain OS=Homo sapiens GN=FGA PE=1 SV=2
		Hemoglobinsubunitalpha OS=Homo sapiens GN=HBA1 PE=1 SV=2
		Peroxiredoxin-2 OS=Homo sapiens GN=PRDX2 PE=1 SV=5
		Immunoglobulin heavy constant gamma 2 OS=Homo sapiens GN=IGHG2 PE=1 SV=2
		Protein S100-A4 OS=Homo sapiens GN=S100A4 PE=1 SV=1
		Isoform 2 of Transketolase OS=Homo sapiens GN=TKT
		Band 3 anion transport protein OS=Homo sapiens GN=SLC4A1 PE=1 SV=3
		Vimentin OS=Homo sapiens GN=VIM PE=1 SV=4
		Alpha-1-antitrypsin OS=Homo sapiens GN=SERPINA1 PE=1 SV=3
		Complement C3 OS=Homo sapiens GN=C3 PE=1 SV=2
		Immunoglobulin kappa constant OS=Homo sapiens GN=IGKC PE=1 SV=2
		Haptoglobin OS=Homo sapiens GN=HP PE=1 SV=1
		Carbonicanhydrase 1 OS=Homo sapiens GN=CA1 PE=1 SV=2
		Keratin, type II cytoskeletal 5 OS=Homo sapiens GN=KRT5 PE=1 SV=3
		Phosphoglycerate kinase 1 OS=Homo sapiens GN=PGK1 PE=1 SV=3
		Actin, cytoplasmic 1 OS=Homo sapiens GN=ACTB PE=1 SV=1
		Serotransferrin OS=Homo sapiens GN=TF PE=1 SV=3
Control Unique	**17**	Keratin, type I cytoskeletal 10 OS=Homo sapiens GN=KRT10 PE=1 SV=6
		Keratin, type II cytoskeletal 1 OS=Homo sapiens GN=KRT1 PE=1 SV=6
		Keratin, type II cytoskeletal 4 OS=Homo sapiens GN=KRT4 PE=1 SV=4
		Alpha-1-acid glycoprotein 1 OS=Homo sapiens GN=ORM1 PE=1 SV=1
		Isoform 3 of Vitamin D-binding protein OS=Homo sapiens GN=GC
		Isoform 2 of Immunoglobulin heavy constant mu OS=Homo sapiens GN=IGHM
		Isoform 2 of Heat shock protein HSP 90-alpha OS=Homo sapiens GN=HSP90AA1
		Gelsolin OS=Homo sapiens GN=GSN PE=1 SV=1

Table 1: Continued.

		Alpha-2-macroglobulin OS=Homo sapiens GN=A2M PE=1 SV=3 Keratin, type I cytoskeletal 14 OS=Homo sapiens GN=KRT14 PE=1 SV=4 Histone H2A type 1-B/E OS=Homo sapiens GN=HIST1H2AB PE=1 SV=2 Alpha-1-acid glycoprotein 2 OS=Homo sapiens GN=ORM2 PE=1 SV=2 Heat shock 70 kDa protein 1B OS=Homo sapiens GN=HSPA1B PE=1 SV=1 Mimecan OS=Homo sapiens GN=OGN PE=1 SV=1 Talin-1 OS=Homo sapiens GN=TLN1 PE=1 SV=3 Flavinreductase (NADPH) OS=Homo sapiens GN=BLVRB PE=1 SV=3 14-3-3 protein zeta/delta OS=Homo sapiens GN=YWHAZ PE=1 SV=1
Pterygium Unique	**32**	Immunoglobulin J chain OS=Homo sapiens GN=JCHAIN PE=1 SV=4 Hemopexin OS=Homo sapiens GN=HPX PE=1 SV=2 Macrophage-capping protein OS=Homo sapiens GN=CAPG PE=1 SV=2 Alpha-enolase OS=Homo sapiens GN=ENO1 PE=1 SV=2 Protein S100-A6 OS=Homo sapiens GN=S100A6 PE=1 SV=1 L-lactate dehydrogenase B chain OS=Homo sapiens GN=LDHB PE=1 SV=2 Heat shock protein beta-1 OS=Homo sapiens GN=HSPB1 PE=1 SV=2 ATP synthase subunit alpha, mitochondrial OS=Homo sapiens GN=ATP5A1 PE=1 SV=1 Leucine-rich alpha-2-glycoprotein OS=Homo sapiens GN=LRG1 PE=1 SV=2 Histone H3.1 OS=Homo sapiens GN=HIST1H3A PE=1 SV=2 Lumican OS=Homo sapiens GN=LUM PE=1 SV=2 Phosphatidylethanolamine-binding protein 1 OS=Homo sapiens GN=PEBP1 PE=1 SV=3 Serum amyloid P-component OS=Homo sapiens GN=APCS PE=1 SV=2 Alpha-1B-glycoprotein OS=Homo sapiens GN=A1BG PE=1 SV=4 10 kDa heat shock protein, mitochondrial OS=Homo sapiens GN=HSPE1 PE=1 SV=2 Glucosidase 2 subunit beta OS=Homo sapiens GN=PRKCSH PE=1 SV=2 Triosephosphateisomerase OS=Homo sapiens GN=TPI1 PE=1 SV=3 78 kDaglucose-regulatedprotein OS=Homo sapiens GN=HSPA5 PE=1 SV=2 NACHT, LRR and PYD domains-containing protein 2 OS=Homo sapiens GN=NLRP2 PE=1 SV=1 Core histone macro-H2A.1 OS=Homo sapiens GN=H2AFY PE=1 SV=4 Tropomyosin alpha-4 chain OS=Homo sapiens GN=TPM4 PE=1 SV=3 Retinaldehydrogenase 1 OS=Homo sapiens GN=ALDH1A1 PE=1 SV=2 Glutathione S-transferase P OS=Homo sapiens GN=GSTP1 PE=1 SV=2 Isoform 2 of Fructose-bisphosphate aldolase A OS=Homo sapiens GN=ALDOA Endoplasmin OS=Homo sapiens GN=HSP90B1 PE=1 SV=1 Neuroblast differentiation-associated protein AHNAK OS=Homo sapiens GN=AHNAK PE=1 SV=2 Apolipoprotein A-II OS=Homo sapiens GN=APOA2 PE=1 SV=1 Isoform 2 of Spectrin beta chain, erythrocytic OS=Homo sapiens GN=SPTB Peroxiredoxin-1 OS=Homo sapiens GN=PRDX1 PE=1 SV=1 Isoform 2 of Tropomyosin alpha-3 chain OS=Homo sapiens GN=TPM3 Spectrin alpha chain, erythrocytic 1 OS=Homo sapiens GN=SPTA1 PE=1 SV=5 Histone H2A.Z OS=Homo sapiens GN=H2AFZ PE=1 SV=2

mechanisms: direct phototoxic effects on DNA, and generation of reactive oxygen species (ROS), which can also damage cellular DNA, proteins, and lipids (Marchetti et al., 2011; Kau et al., 2006; Marchitti et al., 2011). It is well known that there is an association between UVR and the development of many ocular diseases, among them, pterygium (Lim et al., 1998; Clear et al., 1979 di Girolamo, 2010; Suárez et al., 2015). Despite this fact, the precise mechanism through which UVR participates in pterygium development is unknown. Chui et al. (2008) postulated that focal UVR could damage the limbal stem cells repository, which acts as a barrier between cornea and conjunctiva, allowing the latest to invade the cornea, leading to pterygium formation (Chui et al., 2008).

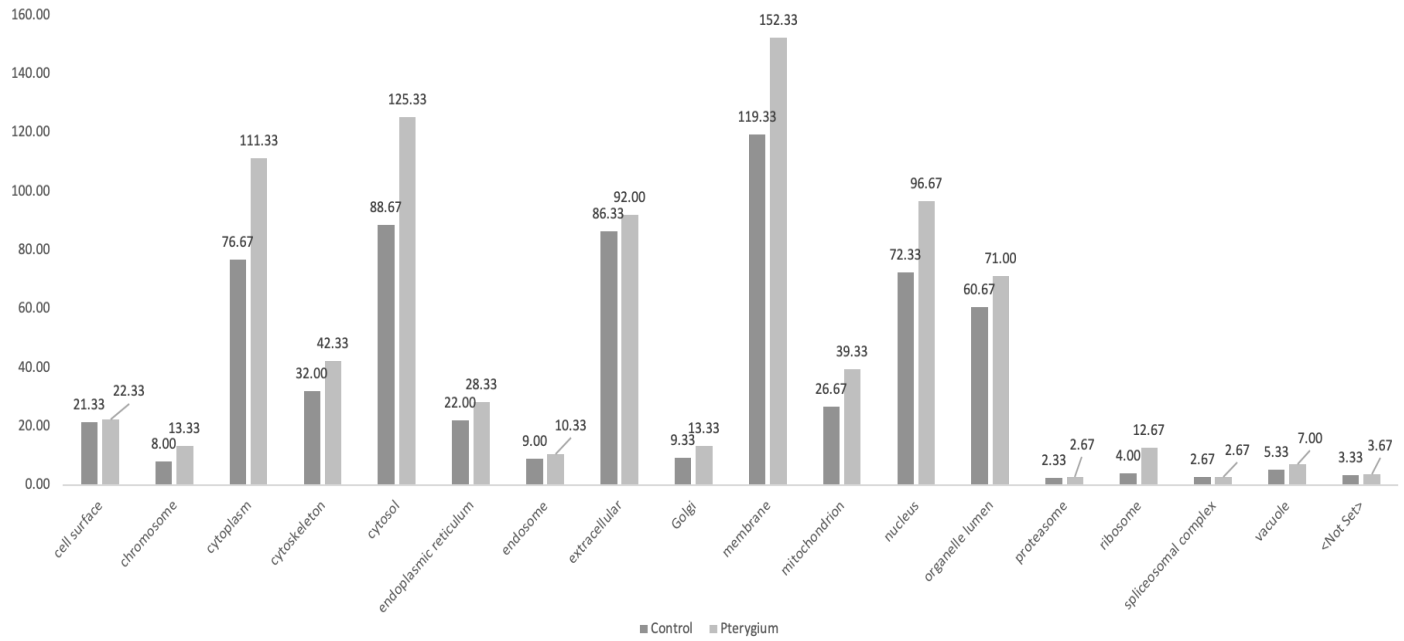

Figure 2: Cellular component for control (dark grey) and pterygium (light grey) samples. Numbers on each bar represents the mean of protein numbers found in the three specimens (control or pterygium) for each cellular component.

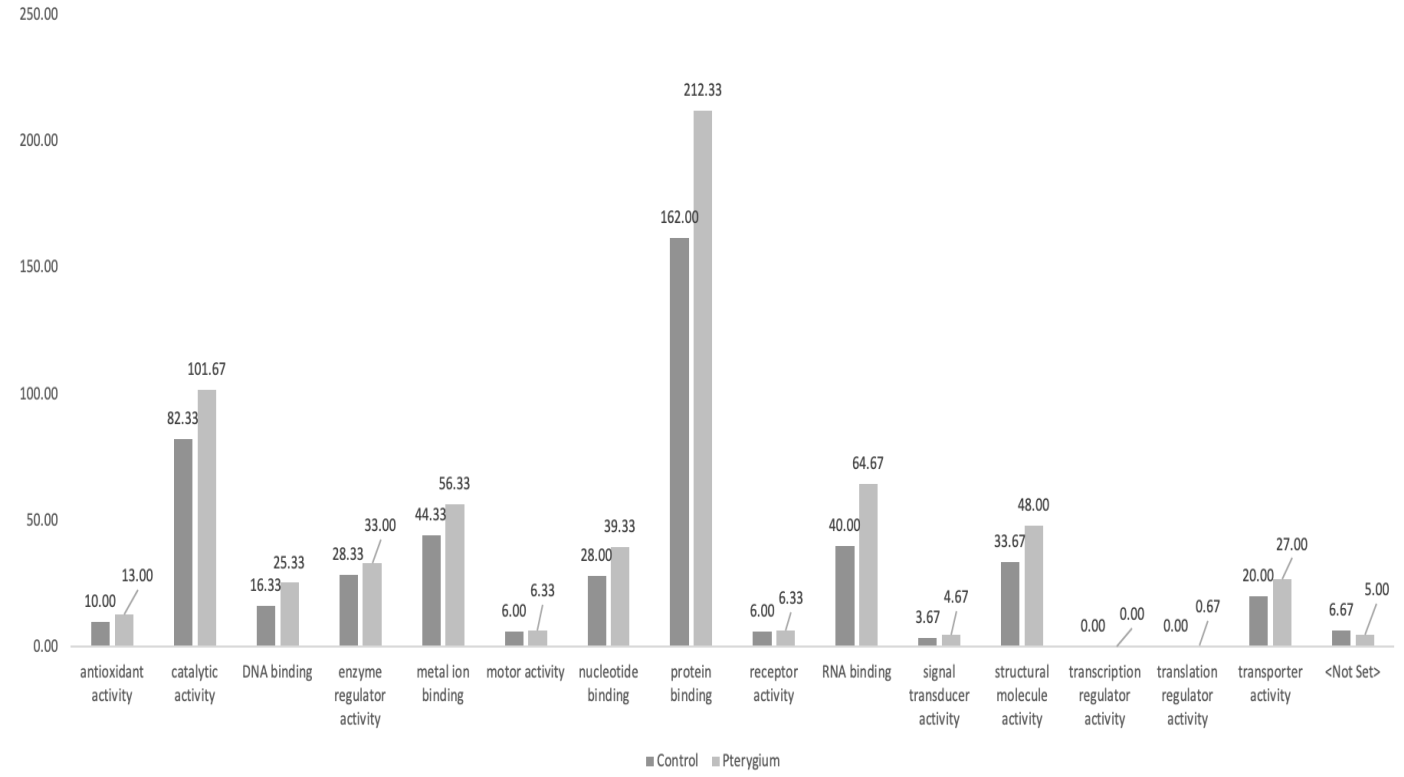

Figure 3: Molecular function for proteins found in control (dark grey) and pterygium (light grey) samples. Numbers on each bar represents the mean of the protein numbers found in the three specimens (control or pterygium) for each molecular function.

Among the unique proteins found in pterygium specimens we can highlight many serumproteins involved in immune responses; chaperones such as HSPB1 (or Hsp27), HSPE1 (or Hsp10), endoplasmin (HSP90B1) and GRP78/BiP (HSP5A); protein S100-A6; peroxiredoxin 1; and structural proteins.

Many authors have described the increased expression of heat shock proteins such as Hsp27, Hsp70, Hsp90, not only in pterygium, but also in other ocular surface diseases, such as keratoconjunctivitis (Leonardi et al., 2016; Pagoulatos et al.,2014; Sebastiá et al., 2013; Pharmakakis and Assimakopoulou, 2001). Feng et al. (2017) have postulated that chronic exposure to UVR or dust could lead to the development of pterygium through overexpression of HSPs (Feng et al., 2017). In this study, we reported the presence of HSPB1 (or Hsp27), HSPE1 (or Hsp10), endoplasmin (HSP90B1) as unique proteins in pterygium tissue. Hsp 70 and Hsp 90 were only found among unique proteins in control specimens.

Proteins S100 are a family of small calcium-binding dimeric proteins (Leonardi et al.,2016) that have been involved in many diseases(Gonzalez et al.,2020; Sreejit et al., 2020; Yammani, 2012; Manolakis et al., 2011; Lukanidin and Sleeman, 2012; Tong et al., 2014; Sheng, 1994; Cross et al., 2005), among them is pterygium (Tong et al., 2014; Riau et al., 2009; Hou et al., 2014). Riau et al. (2009) in their study, found that higher levels of S100A6, S100A8, and S100A9 expressions are found in pterygium tissue respect to normal conjunctiva. In addition, they described an alteration of S100A11 expression localization in pterygium epithelium compared to the conjunctiva (Riau et al., 2009). It is known that expression of some S100 proteins are induced by UVR (Grimbaldeston et al., 2003) and other stresses such as oxidative stress (Marionnet et al., 2003; Eckert et al., 2004). We have described in this study the presence of S100A6 protein in pterygium tissue from patients that spent most of the day performing indoor activities.

Peroxiredoxins are key proteins that are known to act as scavengers of hydrogen peroxide and other peroxides, controlling cellular redox homeostasis (Pastor-Flores et al., 2020; Perkins et al., 2015). It was found that peroxiredoxin 2 is overexpressed in pterygium compared to normal conjunctiva but its functional role is still unclear (Bautista-de Lucio et al., 2013). Among common proteins between pterygium and control tissue, we found peroxiredoxin 2. Taking into account that our study is descriptive, and the mean number of proteins for each cellular component is always greater in pterygium than in control specimens (Figure 2); we can infer that this protein could be upregulated in pterygium tissue. Also, our study has shown expression of peroxiredoxin 1 only in pterygium samples, suggesting the presence of other enzyme family member in this type of pterygium.

GRP78 is a major ER chaperone that usually binds to the three unfolding protein response (UPR) sensors (ATF6, PERK and IRE1), when the ER is under homeostasis conditions. Upon the presence of misfolded or unfolded proteins, GRP78 is released leading to the activation of the UPR (Yoshida, 2007; Sano, 2013; Schröder and Kaufman, 2005). GRP78, as well as other UPR proteins were found overexpressed in pterygium tissues, suggesting that all three UPR branches are activated and ER stress is playing a role in the etiopathogenesis of this disease (Zhou, 2019). We have only found the presence of GRP78 in our pterygium specimens, showing the activation of the UPR.

The unique proteins found in pterygium specimens in this study sustain the concept that its genesis involves multifactorial mechanisms such as: oxidative stress, ER stress and immune-mediated inflammatory processes. It is worthy to mention the fact that most of the publications do not clarify if pterygium specimens are from patients overexposed to UVR or another extreme environmental condition. The fact that our patients have not experienced lengthy exposure to UVR due to their indoor work activities opens the question to the role of UVR in some particular pterygium cases. Since there are some discrepancies among the involvement of diverse factors, it is possible that there could be different pterygia with various genesis (Serra et al., 2018). Further studies need to be done to resolve these dissimilarities.

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