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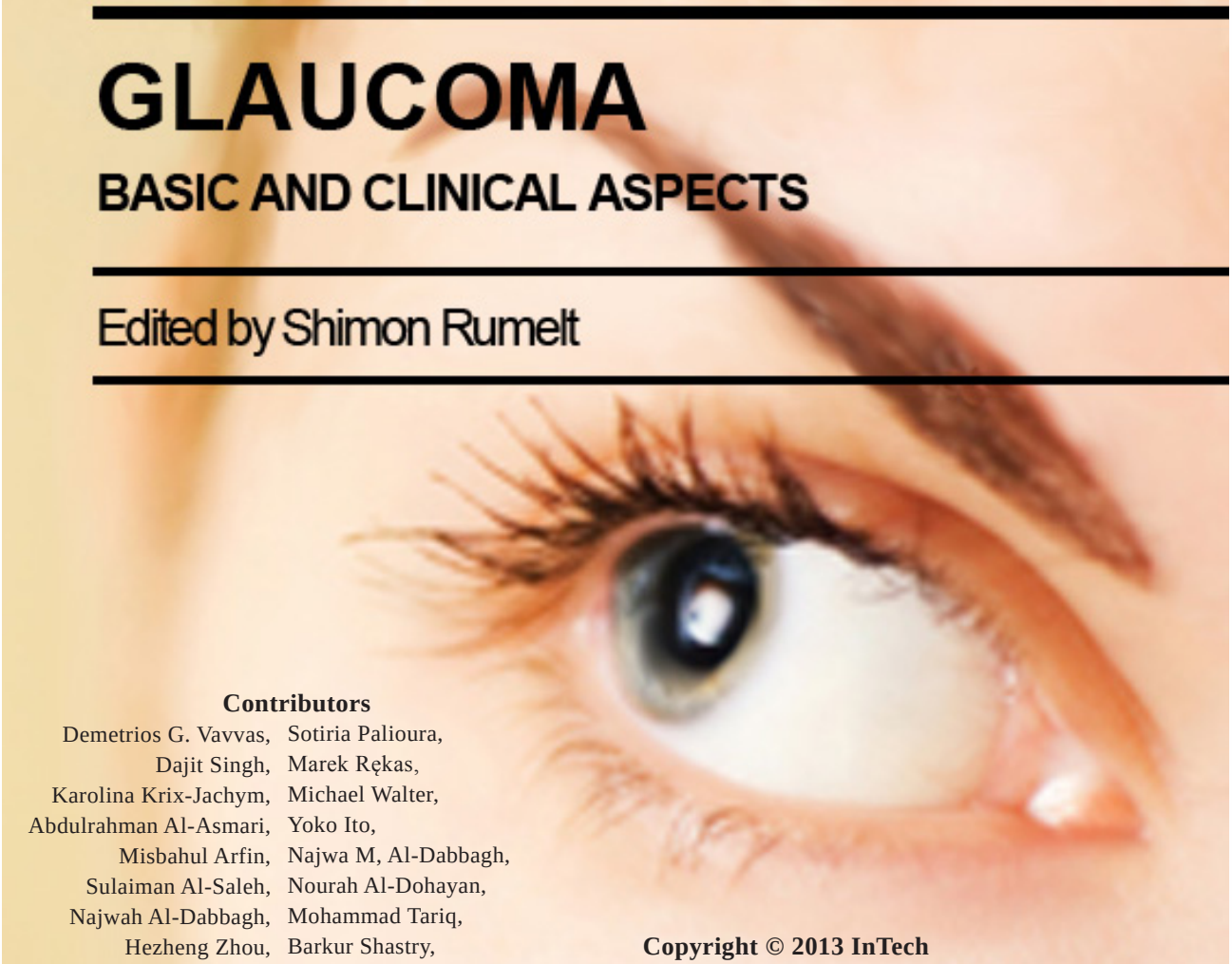
GLAUCOMA

BASIC AND CLINICAL ASPECTS

Edited by Shimon Rumelt



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The book is intended for the general ophthalmologists, glaucoma specialists, and researchers in the field, residents and fellows. It covers both basic and clinical concepts of glaucoma and each author incorporated his/ hers on perspectives on each topic adding his/ hers won theories, future trends and research. Therefore, the book should enable researches and clinicians to adopt new ideas for further basic and clinical research and implementation of the approaches for treating glaucomas.

The book is a result of multi-national glaucoma specialists from around the globe with a common characteristic of taking care of patients. Some of the authors are engaged for many years with this field, some are just at their beginning. Some authors are researches, other clinicians. Some are world leaders, others will be, I hope that the readers will be of wide verity as our authors.

The book is accessed online to allow a free access to as many readers worldwide as possible and is also available on print for those who do not have online access or are interested in having their own hard copy. This will definitely contribute to the distribution of the knowledge on glaucoma between researchers and clinicians.

The book is a welcome addition to the previous books on the subject published by InTech: "The mystery of glaucoma" edited by Tomaš Kubena, "Glaucoma – current clinical and research aspects" by Pinakin Gunvant and "Gaucoma – basic and clinical concepts" by Shimon Rumelt. It expands and updates previous topics and adds new ones.

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MODERN ASPECTS OF GLAUCOMA PATHOGENESIS LOCAL FACTORS FOR DEVELOPMENT OF PRIMARY OPEN-ANGLE GLAUCOMA ASSOCIATED WITH IMPAIRMENT OF SECRETORY FUNCTIONS OF THE EYE MEMBRANES

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Abstract

The research deals with one of the urgent problems of modern ophthalmology: revealing the mechanisms underlying induction of primary open-angle and pseudoexfoliative glaucoma. Till nowadays the problem remains rather actual, as the issue is open to discussion: what are the regional mechanisms underlying the disorders in functions of the trabecular apparatus of the anterior chamber angle of an eye and in the increase of intraocular pressure at the mentioned disease.

In line with the modern views, processes underlying the increased intraocular pressure originate in the eye structures as such: in connective-tissue, epithelial and endothelial cells of the ciliary body, cornea, retina, lens, trabecular apparatus of the anterior chamber angle of an eye. These cells possess selective secretory activity in the aspect of producing a number of biologically active substances exerting direct and/or indirect action to the processes regulating intraocular pressure.

Available literary data of the last 30 years – which discuss mediatory functions realized by cells of fibroblastic, epithelial and endothelial line in a ciliary body, cornea, retina, lens, a trabecular network – formed a basis for carrying out the research directed to clarify the role of in situ produced fibronectin, IGF-1, PgE_2 and cortisol at primary open-angle glaucoma.

High indices of fibronectin and IGF-1 found in aqueous humour of patients with primary open-angle glaucoma testify in favor of hypersecretion of mentioned cytokines by cells of the trabecular meshwork. The presence of fibronectin and insulin-like growth factor-1 high concentrations at the primary open-angle glaucoma, and also at pseudoexfoliative glaucoma, testifies to violation of drainage function of trabecular meshwork of the anterior chamber angle of an eye; this latter, to a certain extent, preconditions the high levels of intraocular pressure.

Keywords: *cataract, glaucoma, IGF-1, prolactin, cortisol, fibronectin, prostaglandins E_2, pathogenesis, eye immune privilege, lymphocytic indices.*

INTRODUCTION

The term "Glaucoma" integrates a wide range of eye diseases characterized by a diversity of clinical forms: mainly by the chronic course and rather unfavourable prognosis. Sufficient to mention that in developed countries the frequency of vision loss due to glaucoma is steadily at the level of 15-20% of the total number of all blind subjects [*Nesterov A.P., 2008*].

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It is considered long-established that among various clinical-and-anatomical manifestations of the glaucomatous process the anterior open-angle glaucoma is the most frequently diagnosed form.

The severity of course of anterior open-angle glaucoma and especially the unfavourable outcomes of the disease are mainly connected with those unsolvable problems faced by ophthalmologists at the study of pathogenesis of primary and secondary glaucomas. Precisely this circumstance is the "insurmountable" obstacle in pathogenetic therapy, thus limiting the entire complex of medical interventions within the early symptomatic therapy with

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underlying local application of hypotensive means aimed to decrease intraocular pressure.

To a known extent, the interpretation of aspects of pathogenesis in case of anterior open-angle glaucoma is connected to the fact that this type of glaucoma is rather frequently associated with the cataract and pseudoexfoliative syndrome.

At present the etiopathogenetic links engaged in induction and the course of anterior open-angle glaucoma are conditionally divided into general and local ones.

Heredity, general type changes in specific integrative systems of the organism (CNS, endocrine, immune and cardiovascular) are among the general factors bringing forth disorders of the hematoophthalmic barrier and the increase of intraocular pressure.

Amongst the local factors relatively persistent elevation of intraocular pressure, primary dystrophic and atrophic changes, including age-related shifts in the cornea, ciliary body and the trabecular meshwork, which cause the infringement of hydrodynamic and hydrostatic properties of the aqueous humour, are considered. As mentioned by A.P. Nesterov (2008) chronologically occurring processes, which might be conditionally subdivided into 2 stages, are engaged in the pathogenesis of glaucomas in anterior and posterior chambers of an eye. At the first stage mechanisms bringing forth the increase of intraocular pressure are triggered in the anterior chamber of an eye. At the second stage mechanisms localized in the posterior part of the eye chamber are initiated and in the long run become the cause of atrophy of the visual nerve. At that, the "glaucomatous process" firstly originates in the anterior chamber of an eye, while the dystrophic and atrophic processes in the visual nerve are resulting from the exposure to high intraocular pressure.

During the last years, rather informative evidences were obtained to discuss the role of biologically active substances produced *in situ*, i.e. in specific eye membranes, in mechanisms of anterior open-angle glaucoma origination using the clinical and experimental material.

We did not set the problem to analyze the current state of the art on the role of general pathogenetic factors engaged in induction and the course of anterior open-angle glaucoma.

The currently available data of scientific publications and results of our own investigations devoted to the role of *in situ* produced biologically active substances of cytokine, mediatory and hormonal origin in mechanisms of a stable increase of the intraocular pressure in case of anterior open-angle glaucoma will be analyzed in this work.

2. SECRETORY-MEDIATORY HORMONE-DEPENDENT FUNCTIONS OF EYE MEMBRANES IN THE MECHANISMS OF GLAUCOMA DEVELOPMENT

2.1. The role of transforming growth factor β-2, insulin-like growth Factor-1 and E_2 prostaglandins in pathogenesis of primary open-angle glaucoma

Nowadays the role of TGF_{β} produced in post-barrier membranes of an eye is considered to be of no less importance for realization of processes ensuring the drainage function of the eye anterior chamber-associated immune deviation (ACAID) [*Mansfield K. et al., 2004; Banh A. et al., 2006; Kim Y.S. et al., 2008; Dawes L.J. et al., 2009*]. According to scientific publications. $TGF_{\beta\text{-}2}$ produced in the post-barrier membrane of an eye (in cornea, ciliary body, retina) at some eye diseases takes an active part in the increase of intraocular pressure [*de Iongh R.U. et al., 2005; Stefan C. et al., 2008; Dawes L.J. et al., 2009; Hindman H.B. et al., 2010; Pattabiraman P.P. Rao P.V., 2010*].

To our mind, during the last years rather informative data signifying in favour of pleotropic potencies of $TGF_{\beta\text{-}2}$ produced in post-barrier membranes of the eye.

In particular, in a post-surgery period in patients operated for complicated and senile cataracts *in situ* produced $TGF_{\beta\text{-}2}$ induces trans-differentiation of epithelial cells of crystalline lens capsule into fibroblasts; this latter was manifested as opacity of lens with all the subsequent after-effects [*Dawes L.J. et al., 2009*]. The modulatory effect of $TGF_{\beta\text{-}1}$ towards the processes of activation of cells of fibroblastic line in the cornea was also established. Thus, the authors [*Karamichos D. et al., 2010*] under conditions of cultivating cells of cornea using $TGF_{\beta\text{-}1}$ dose-dependent mode activated *in situ* synthetic processes in fibroblasts, thus bringing forth intensification of collagen(ous) fibrilles synthesis and eventually to regional overgrowth of immature connective tissue with the resulting fibrosis.

$TGF_{\beta-2}$ high level was also revealed in cells of the trabecular meshwork of patients with open-angle glaucoma [*Stefan C. et al., 2008*]. The authors consider that at the mentioned disease $TGF_{\beta-2}$ stimulates fibronectin synthesis in trabecular cells, thus predefining "profibrotic" effects of $TGF_{\beta-2}$ in post-barrier membranes of the eye.

Literature data is available [*Ochiai Y., Ochiai H., 2002*], according to which in patients with anterior open-angle glaucoma, diabetes complicated by anterior open-angle glaucoma the level of $TGF_{\beta-2}$ in aqueous / intraocular humor is markedly increased. As a control, the authors studied aqueous humour of patients with cataracts.

Processes reflecting the specific precise stages of $TGF_{\beta-2}$ and IGF-1 activity in post-barrier membranes of the eye are the subject of a wide discussion. Furthermore, the study on mechanisms of their direct and/or mediated interaction in processes ensuring the drainage function of an eye is mainly emphasized.

In the organism of mammals, the post-barrier membranes of an eye also serve as a source of both cytocines, IGF-1 and its receptors, IGF-IR, were found in epitheliocytes of lens and cornea, epitheliocytes of retina meshwork, Muller's cells [*Shaw L.C. et al., 2006; Ko J.A. et al., 2009*]. $TGF_{\beta-2}$ is produced in post-barrier membranes of an eye and, first of all, in fibroblasts of cornea [*Streilein J. et al., 1992; Wilkbanks G. et al., 1992; Hollborn M. et al., 2000; Fleenor D. et al., 2006*].

According to C. Stefan et al. (2008), cells of the trabecular meshwork of the anterior angle of the eye chamber might serve as the source of $TGF_{\beta-2}$ synthesis.

S.H. Chung and associates used human lens epithelial cells (HLE B-3) to reveal the role of IGF-1 in processes of $TGF_{\beta-2}$ mediated fibronectin accumulation in lens cells [*Chung S.H. et al., 2007*]. Based on analysis performed by the authors (reverse polymerase transcriptase chain reaction, immune-fluorescent studies) mentioned researchers draw a conclusion that IGF-1 counteracts $TGF_{\beta-2}$ induced fibronectin accumulation in lens epitheliocytes.

J.A. Ko et al. (2009) studied the role of IGF-1 in intrercellular regulation in cultured fibroblasts and human corneal epitheliocytes. According to authors, the presence of epitheliocytes in the culture medium enhanced N-cadherin expression in fibroblasts. Similar effect of corneal epitheliocytes was also simulated by IGF-1, but not fibroblasts growth factor or epidermal growth factor. The authors conclude that IGF-1 produced in epitheliocytes regulates N-cadherin positive expression in corneal fibroblasts.

There is an opinion that IGF-1 and IGF-2 regulate the processes of proliferation and apoptosis in corneal epitheliocytes [*Yanai R. et al., 2006*]. According to K. Izumi and co-workers (2006). TGF_{β} produces an influence to corneal fibroblasts differentiation into myofibroblasts. Moreover, IGF-1 is engaged in this mechanism. Thus, treatment with $TGF_{\beta-2}$ caused expression of IGF-1, mRNA. IGF BP-3 and IGF BR-3 protein in human corneal. According to N. Yamada et al. (2005), IGF-1, alongside with fibronectin, IL-6 and substance P, actively participate in stimulation of fibroblastic processes in cornea.

The analysis of above mentioned scientific publications signifies to the important role of *in situ* produced $TGF_{\beta-2}$ and IGF-1 in mechanisms of fibroblastic processes formation and their cellular metaplasia in specific eye membranes: in post-barrier eye membranes in ACAID mechanisms and withdrawal. One cannot exclude that locally produced cytokines possess short-distant range of activity; moreover, their realization might occur according to either the principles of intercellular interaction, i.e. through the paracrine mechanism, or on the basis of intercellular autocrine regulation. Apparently, both mechanisms have an important part in infringement of drainage function of an eye at different types of glaucoma.

As known, prostaglandins play an important role in integrative activity of the mammalian organism, in particular, in regulation of immunogenesis, hemostasis, non-specific resistance at the organism level [*Kuznik B. et al., 1989*].

However, until present the probability of prostaglandins synthesis in post-barrier membranes of an eye seems still disputable.

There are only sporadic communications related to the mentioned aspect; an attempt was made to reveal E_1, E_2 and $F_{2\alpha}$ prostaglandins in post-barrier membranes of an eye and in the aqueous humour.

It is considered established that prostaglandins increase intraocular pressure and infringe the function of hematoophthalmic barrier [*Podos S.M. et al., 1972 a; b; Podos S.M., 1976 a; b; c*]. Moreover, the drainage function of an eye is simultaneously real-

ized by prostaglandins in the aqueous humour.

According to C.B. Toris and associates, numerous prostaglandin-dependent effects in post-barrier membranes of an eye are realized according to the receptor mechanism associated at the level of mRNAs [*Toris C.B. et al., 2008*]. Similar receptors were revealed in the trabecular meshwork, celiar muscle, and sclera.

Prostaglandin-dependent receptors in post-barrier eye membranes were revealed not only in humans, but also in rats, mice, rabbits, pigs and monkeys. Considering the vasoactive properties of prostaglandins, as well as their role in sustaining the drainage function of an eye, the sysnthetic analogs of prostaglandins are widely applied in ophthalmological practice for treatment of glaucoma [*Bucci F.A., Waterbury L.D., 2008; Toris C.B. et al., 2008*].

Therefore, it is no excluded that E_2 prostaglandins might participate in maintenance of the drainage function and, appropriately, the intraocular pressure as well; similar mechanisms of prostaglandins functioning in post-barrier membranes of the eye are realized exceptionally according to the receptor mechanism.

Taking into account the above mentioned, an assumption might be proposed according to which *in situ* produced E_2 prostaglandins are engaged into the pathological process observed at the area of post-barrier membranes of an eye at primary open-angle glaucoma.

2.2 The role of fibronectin in pathogenesis of primary open-angle glaucoma

Fibronectins are a group of cold-insoluble glycoproteids with the molecular mass 400.000–450.000 D localized both on the surface of connective tissue cells and in the extracellular matrix. The following functionally active domains were revealed in fibronectin structure: NH2 terminal domain includes sites of fibrin binding; then collagen and heparin binding domains and domain ensuring cells adhesion are localized; at COOOH-cone there is one more heparin binding domain [*Kuznik B. et al., 1989*]. Fibronectins have an important part in cells proliferation and differentiation, morphogenesis and embryogenesis of tissues. In particular, tissue fibronectin of fibroblastic genesis actively participates in collagen formation both at norm (at the stage-by-stage process of the connective tissue maturation), and in pathology state (different distrophic and inflammatory processes occurring at the site of the connective tissue. Thus, in particular, an important role is assigned to fibronectin in reparative processes, influence on cells migration, growth and proliferation. Fibronectin produced by cells of the connective tissue (fibroblasts, endotheliocytes, smooth-muscle cells of arterioles, etc.) in its turn actively participates in formation of the extra-cellular matrix, especially at early stages of the connective tissue formation. The following cells of different genesis serve as the main source of fibronectin synthesis: endothelium, hepatocytes, fibroblasts, smooth myocytes, Schwann's cells, alveolar and peritoneal macrophages, epitheliocytes, and thrombocytes [*Kuznik B. et al., 1989*].

Currently the sources of fibronectin synthesis in the post-barrier membranes of an eye are disputable as well. According to H.B. Hindman et al. (2010). corneal keratocytes might be considered as probable sources of fibronectin synthesis. This fact was revealed under cultivation of keratocytes localized in the anterior and posterior parts of cornea. Furthermore. in the process of cultivating corneal cells of fibroblastic line the authors established $TGF_{\beta\text{-}1}$-dependent activation of keratocytes. in which a marked activation of fibronectin synthesis occurred. Simultaneously. Thy-1 secretion increases in the same keratocytes. According to D. Karamichos et al. (2010). *in situ* (in post-barrier membranes of an eye) produced $TGF_{\beta\text{-}2}$. under conditions of pathology might serve as a provoking factor binging forth fibrosis of the cornea. Therefore. we cannot exclude that realization of this $TGF_{\beta\text{-}2}$ related effect is mediated due to the activation of fibronectin in the same keratocytes.

C. Stefan et al. (2008) use the immune enzyme assay to determine $TGF_{\beta\text{-}2}$ and fibronectin concentration in aqueous humour of patients with anterior open-angle glaucoma. The authors revealed a significant increase of $TGF_{\beta\text{-}2}$ concentration in this cohort of patients and draw a conclusion that $TGF_{\beta\text{-}2}$ produced in post-barrier membranes of the eye should be considered as a "special" cytokine that increases fibronectin concentration in the trabecular meshwork; moreover. it might be considered as a local pro-fibrotic factor.

Sporadic, though rather informative, evidences are available according to which the trabecular

meshwork localized in the angle of an anterior chamber of the eye serves as the possible source of fibronectin synthesis. In particular. R.J. Wordinger et al. (2007) studied the probable mechanisms of synthesis of the biologically active substances by trabecular meshwork cells. As known, the cells of trabecular meshwork synthesize and excrete "bone morphogenic protein" – BMP-4. The authors, under conditions of trabecular cells cultivation studied the synthetic potencies thereof at addition of BMP-4 and $TGF_{\beta-2}$ to the culture media. The study results demonstrated that $TGF_{\beta-2}$ treated cells of the trabecular meshwork launched an intense synthesisn of fibronectin, while BMP-4, if additionally introduced to $TGF_{\beta-2}$ containing media, blocked this induction of fibronectin.

Mentioned authors studied the expression of BMP-4 family gens in normal and glaucomatous cells of the trabecular meshwork. Under the influence of these receptors the levels of $TGF_{\beta-2}$ and BMP anatagonist, protein gremlin, significantly increased. The authors succeeded to establish that gremlin blocked the negative impact of BMP-4 towards $TGF_{\beta-2}$ induction of fibronectin.

Another result obtained by the same authors is of no less importance: gremlin introduced in the medium *ex vivo*, caused the prototype of increased intraocular pressure glaucoma. Research findings of these authors reflect the main statements of the hypothesis according to which in case of the anterior open-angle glaucoma the enhanced expression of gremlin by trabecular meshwork cells inhibits BMP-4 antagonism to $TGF_{\beta-2}$, eventually, might bring forth the increase in deposition of the extracellular matrix and intraocular pressure.

The analysis of rather informative data obtained by mentioned authors allows to draw a conclusion, according to which the trabecular meshwork of an angle of anterior chamber of the eyes should not considered as an object that passively ensures the drainage function thus sustaining optimally stable levels of the intraocular pressure.

To our mind, the drainage function of trabecular meshwork is an active process and the leading role here belongs to "secretory" cells of the meshwork predominantly functioning according to the autocrine mechanism. At dysfunctions of trabecular meshwork cells, especially in case of open-angle glaucoma, the synchronous activity of these cells is infringed; this latter might enhance their specific mediatory function – in view of the increased synthesis of fibronectin. Precisely, fibronectin depositions and the subsequent intensification of fibroblastic processes *in situ* might bring to disorders in drainage function of the trabecular meshwork of the angle of anterior chamber of the eye and, finally to the stable increase of intraocular pressure.

According to D. Fleenor et al. (2006), $TGF_{\beta-2}$ treatment of segments of trabecular meshwork cells of the angle of anterior chamber of the eye resulted in modulation of multiple gens regulating the structure of extracellular matrix. In the trabecular meshwork cells $TGF_{\beta-2}$ brings forth an increased secretion of fibronectin, $TGF_{\beta-2}$ action to cells of the trabecular meshwork was blocked by inhibitors of receptor type 1 TGF_{β}. In perfusion anterior segments of human eyes $TGF_{\beta-2}$ treatment increased the intraocular pressure and elution of fibronectin. In our opinion the authors come to the rather reasonable conclusion: $TGF_{\beta-2}$ influence on intraocular pressure might be "leveled" by $TGF_{\beta-2}$ -mediated receptors type 1 through prevention of $TGF_{\beta-2}$ stimulating effect to cells of the extracellular matrix.

According to mentioned authors, understanding these inter-mediatory and receptor interactions, which occur at the site of trabecular meshwork of an angle of anterior chamber of the eye, would then allow to develop new efficient approaches for treatment of glaucoma.

There is an opinion [*Gonzales J.M. et al., 1998*], according to which it is merely domain of heparin II (Hep II) in the structure of fibronectin that regulates the ability outflow (excretory system) in cultured anterior segments through the effects produced to the cytoskeleton in transformed cells of the trabecular meshwork of the angle of the anterior chamber of an eye. The mentioned authors cultivated cells of the trabecular meshwork under conditions of Hep II domain and revealed an active site of this domain that regulates the ability of aqueous humor efflux. According to researchers, precisely this site of a domain is responsible in case of disorders in actinic cytoskeleton of the trabecular meshwork at glaucomas.

Fibronectin concentration in aqueous (intraocular) humour of patients with cataracts and glaucomas, according to K.S. Kim et al. (1992),

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widely varies from 5 *ng/ml* to 100 *ng/ml* (data of immune enzyme assay – ELISA). Authors separated the aqueous humor by aspiration from the eyes of patients with cataract and glaucoma using a special puncture needle introduced through the limbal zone before the limbal incision in the anterior chamber of the eye, that is before the surgical intervention. Due to the performed immune enzyme assay the researchers managed to establish that at glaucomas the level of fibronectin significantly increases compared to its level in aqueous humour of patients with cataracts. At the same time, fibronectin levels in aqueous humor patients with cataract and glaucoma had no dependence on either age or gender of patients under preoperative study.

The aspects related to fibronectin sources in post-barrier membranes of the eye are also discussed. An assumption was made that at primary glaucomas relatively high concentrations of fibronectin accumulate in the anterior chamber of an eye, as it cannot escape the drainage pathways. There are quite opposite data, according to which in patients with the open-angle glaucoma fibrinogen concentration in the aqueous humor significantly did not differ from that of aqueous humor of patients with cataracts [*Vesaluoma M. et al., 1998*]. At the same time, upon comparison of obtained results of immune enzyme analysis for fibrinogen content on the one hand, in aqueous humor of patients with cataracts and primary glaucomas, and, on the other hand, in patients with exfoliative glaucoma, the level of fibronectin in aqueous humor significantly increased in the latter case. The authors consider that significantly higher concentration of fibronectin in patients with the pseudoexfoliative glaucoma might result from infringement of the hematoophthalmic barrier. There is evidence [*Tripathi B.J. et al., 2004*] that the growth factor ($TGF_{\beta\text{-}2}$) under conditions *in vivo* modulates fibronectin and stromelysin-1 (MMP-3) in trabecular cells of the anterior chamber of an eye. Mentioned authors studied expression of RNA and fibronectin protein at presence of growth factors in primary and secondary humour of the anterior chamber (taken in pre- and post-operative period, appropriately). In particular, under conditions of incubation of trabecular cells of the anterior chamber of the eye, growth factor containing aqueous humors taken from patients with glaucoma prior to and post the surgery were added to the culture medium. Compare to control, fibronectin mRNA expression by trabecular cells increased by 50 and 100% after incubation in primary samples of aqueous humor during 48 hours or 7 days, as well as by 50 and 160% after incubation in secondary samples of the aqueous humor, MMP-1 mRNA expression decreased by 25 and 50% after incubation in samples of primary aqueous humor during 48 hours or 7 days, as well as by 80 and 85% after incubation during 48 hours or 7 days in secondary samples of aqueous humor. The level of fibronectin increased 3.5 times and 6-fold after incubation during 48 hours with primary and secondary samples of aqueous humor.

Study results obtained by the above mentioned authors allow to draw a conclusion that induction of MMP-3 in the trabecular meshwork of glaucomatous eyes might decrease fibronectin formation in aqueous humor excretion pathways, thus decreasing the resistance of liquid outflow into the anterior chamber of an eye.

The analysis of publications relevant to the role of *in situ* produced fibronectin in post-barrier membrane of an eye allows to come the following conclusions.

Firstly, the role of *in situ* produced fibronectin in mechanisms on sustaining the local homeostasis remains debatable.

Secondly, the available scientific literature indicates to the fact that under conditions of norm fibronectin produced by cells of the trabecular meshwork performs the drainage function in outflow of the aqueous humor.

Thirdly, at some eye diseases and especially at primary open-angle glaucoma and pseudoexfoliative syndrome, the excessive synthesis of fibronectin by cells of the trabecular meshwork might bring forth a disorder of the drainage function that eventually in its turn is fraught with the increase of intraocular pressure.

Fourthly, it is not excluded that in post-barrier membranes of the eye there are engaged fibronectin-dependent mechanisms, which function according to both principles of inter-cellular interactions and the autocrine mechanism.

2.3. The role of cortisol in pathogenesis of anterior open-angle glaucoma

At present. aspects related to studies on "endocrine homeostasis" in post-barrier membrane of an eye at both norm and pathology are the subject of a wide discussion in ophthalmology. The available publications are not numerous; furthermore. they are of a rather statement-of-the-fact character [*Southren A. et al., 1976; Floman N., Zor U., 1977; Kasavina B. et al., 1977; Weinstein B. et al., 1983; Stone R., Wilson C., 1984; Stojek A. et al., 1991; Chiquet C., Denis P., 2004; Burch J. et al., 2005; Pleyer U. et al., 2005; Schwartz B. et al., 2005; Vessey K. et al., 2005*]. In particular. there are reports discussing the possibility of cortisol local synthesis in eye membranes.

The autopsy material (vitreous body and blood serum of healthy subjects with fatal injury) was subject to immune enzyme assay for determination of progesterone. estradiol. thyroxine. triiodothyronine. thyrotropic hormone, luteinizing hormone, follitropin. cortisol and prolactin [*Chong A., Aw S., 1986*]. The thyroid-stimulating hormone, luteinizing hormone, follitropin, cortisol and prolactin were revealed in the vitreous humour. As to other hormones, progesterone, estradiol, triiodothyronine and thyroxine, the results of immune enzyme assay were negative even despite their high solubility and relatively small size of their molecules. According to A. Steiger (2003), the role of somatotropin, somatostatin and adrenocorticotropic hormone (ACTH) in the genesis of a wide range of eye diseases with both inflammatory and degenerative genesis is also disputable.

The results obtained by mentioned authors testify in favour of the local synthesis of certain hormones in eye membranes and tissues.

It should be specially noted that regional neuroendocrine mechanisms underlying the induction of primary open-angle glaucoma have not been sufficiently studied yet. In this aspect the role of *in situ* produced cortisol in mechanisms of impaired ion exchange is exceptionally connected with disbalance of sodium ions transport between the cells and liquid media of an eye and the impaired catecholamines exchange.

As known, in peripheral "epithelial" tissues sodium and water transport are regulated by corticosteroids, 11-β-hydroxysteroid-dehydrogenase (11-β-HSD), its isoform (11-β-HSD1), due to which there occurs formation of cortisol molecule from cortisone. Considering this latter, some researchers [*Rauz S. et al., 2003*] determined levels of cortisol, cortisone, 11-β-HSD and 11-β-HSD1 in ciliary body of actually healthy volunteers. The study was aimed to reveal the role of cortisol and 11-β-HSD in regulation of intraocular pressure that is sustained due to balance of aqueous humour (intraocular liquid) depending on the sodium transport through the ciliated epithelium and drainage via the trabecular meshwork. In both study groups cortisol concentrations were higher than cortisone levels. In both groups oral application of carbenoxolone, 11-β-HSD inhibitor, was accompanied by a marked decrease of intraocular pressure. To our mind, data obtained by mentioned authors, on the one hand, signify in favour of the above-mentioned cascade of reactions for maintenance of intraocular pressure, on the other hand, in favour of cortisol local synthesis in post-barrier membranes of the eye.

There is an opinion, according to which merely 11-β-HSD1 ensures receptor Nf-dependent mechanisms through the ciliated epithelium, thus regulating the level of intraocular pressure [*Rauz S. et al., 2001*]. Mentioned authors revealed the fine mechanisms, which provide the level of glucocorticoids mediated intraocular pressure. However, the potentiating role of corticosteroids in regulation of intraocular pressure was revealed much earlier [*Jacob E. et al., 1996*]. As known, the rate of aqueous humour production is stimulated by adrenalin. The authors studied the joint and isolated effects of adrenalin and hydrocortisone to the rate of aqueous humor production in 20 volunteers. As demonstrated by study results, joint oral application of adrenaline and hydrocortisone significantly (by 42%) enhanced production of aqueous humour compared to placebo. The authors consider that both factors simultaneously function within the post-barrier membranes of the eye (ciliary body), thus ensuring the rate of aqueous humour production.

Molecular mechanisms underlying the biological action of glucocorticosteroids in eye membranes were also studied. Specifically, in the experiment, under conditions of cornea transplantation the influence of glucocorticosteroids (SEGRA) was studied to the labeled synthesis of anti- and pro-inflammatory cytokines. The application of glucocorticosteroids brought forth more efficient engraftment. Moreover, the terms of engraftment

correlated with the low expression of cytokines, especially IL-I [*Pleyer U. et al., 2005*].

Southren et al. (1979) performed experiments in rabbits and revealed endoplasmatic reception of glucocorticoids in corneal cells and the ciliary body. Translocation of cortisol from the surface of the cell nucleus occurred within 30 minutes after injection. As to authors, this mechanism is a stereotype for glucocorticoids towards other sensitive tissues.

It is important to note the following phenomenon as well. Similar translocation was not observed when experimental animals were administered testosterone, estradiol and progesterone. At the same time, different membranes and liquid media of the eye possess different ability of affinity to glucocorticoids and their realization (accumulation and excretion).

In 1977, B. Kasavina et al. (1977) studied cortisol distribution in sclera, ciliary body, cornea, iris, lens capsule, vitreous body and the aqueous humour. Radionuclide methods of investigation allowed to reveal that tissues and media of the eye have different intensity of cortisol absorption and excretion. According to authors, the sclera, ciliary body, and lens capsule served as target tissues for cortisol.

3. REGIONAL MEDIATORY HORMONAL MECHANISMS OF IMPAIRED EYE DRAINAGE FUNCTION AT PRIMARY OPEN-ANGLE AND PSEUDOEXFOLIATIVE GLAUCOMAS (RESULTS OF OWN RESEARCH INVESTIGATION)

It is rather difficult to interpret issues relevant to pathogenesis of primary open-angle glaucoma, as this type malady is frequently associated with cataract and pseudoexfoliative syndrome.

In particular, according to D.S. Krol (1968; 1970), among the randomly selected contingent the pseudoexfoliative syndrome was observed in 6.2% subjects above 50. in 24% patients with senile cataract and in 47% patients with open-angle glaucoma, P.P. Frolova and G.Kh. Khamitova (1984) provided similar data, according to which pseudoexfoliative syndrome was diagnosed in 5.8% examined persons above 40. Furthermore, the higher the age, the more frequent was pseudoexfoliative syndrome encountered: at the age of 40-48 years old in 1% patients, at 50-59 – in 6.4%. at 60-69 – in 12.5%. above 70 – in 36.8%. It is especially important that among persons with pseudoexfoliative syndrome glaucoma was diagnosed in 35% cases, while cataracts made 69%.

According to clinical observations of A.P. Nesterov (2008) in persons with the pseudoexfoliative syndrome glaucoma originates 20 time more often than in the general population of the same age group. According to the author, approximately in 50% patients with open-angle glaucoma symptoms of pseudoexfoliative syndrome are revealed. The type of glaucoma associated with the pseudoexfoliative syndrome is called “pseudoexfoliative glaucoma”.

Nowadays, amongst the mechanisms of cataract induction and course, an importance is attributed to local immunepathological disorders, which all in all are defined as “anterior chamber associated immune deviation (ACAID) [*Wilbanks G., Streilein J., 1990; Streilein J. et al., 1992; Abrahamian A. et al., 1995; Muhaya M. et al., 1999; Fleenor D. et al., 2006*].

In pathogenesis of the primary open-angle glaucoma the specific gravity of regional immunepathological disorders, which are pathognomonic for cataracts, are open for a special discussion, because data of available scientific publications are scarce, fragmentary, sometimes contradictory and inconsistent.

At the same time, to our mind, it is rather expedient to perform studies at which in case of complicated cataracts associated with glaucoma and pseudoexfoliative syndrome the subject matter would be the entire specter of biologically active substances produced in eye membranes, which were earlier considered by us as pathogenetic factors of open-angle glaucoma. Such scientific and methodical approach is rather substantiated, as it will allow to answer the question: to what extent the processes of impaired synthesis of fibronectin, IGF-1, PgE_2 and cortisol in eye membranes are engaged in mechanisms of primary open-angle glaucoma, namely: in pathogenesis of impaired drainage function and increase of intraocular pressure.

Under our observation there were 960 patients with the senile and complicated cataracts operated at “Shengavit” Medical Center within a period of 2008-2012. The degree of lens opacity was assessed according to Emery colorimetric classification and generally accepted classification of cataracts proposed by Buratto. Undoubtedly, the state of lens capsule, folding, presence of elements of fibrous filaments, pseudoexfoliative deposits on the anterior surface of the capsule, lens subluxation to some

degree, were taken into consideration together with classification of phakodonesis suggested by Pashtaev. Actual expressiveness of the pseudoexfoliative syndrome was considered based on the classification proposed by Yeroshevskaya.

All operated patents were divided into three groups.

The studied groups of patients involved civil contingent: residents of Yerevan and different provinces (marzes) of Armenia; age range was from 40 to 82 years.

The first group included patients with senile cataract. The second group was made up of patients with the complicated cataract on the background of existing anterior open-angle glaucoma, with initial and developed stages of the glaucomatous process. The third group involved patients with complicated cataract on the background of existing pseudoexfoliative glaucoma and pseudoexfoliative syndrome.

The analyses were performed using the main clinical laboratory methods accepted in ophthalmology.

Irrespective of the cataract degree and stage, all patients underwent microaxial Phacoemulsification – Microincision Cataract Surgery (MICS) through 2.2 *mm* incision with implantation of posterior chamber intraocular lens. Intra-chamber administration of antibiotics was not applied in these groups.

The methodical procedure of extracting aqueous humour was used intra-operatively under conditions of sterility. The corneocentis was done by insulin syringe through the limb; 0.1-0.2 *ml* aqueous humour was extracted. The fluid remained in a syringe until laboratory research was performed immediately after delivery of the material to the Scientific-Research Center of the Yerevan State Medical University after M. Heratsi.

All the operated patients were under intense observation and got the appropriate post-operative treatment and medical rehabilitation. We observed the patients in the early post-operative period.

Unfortunately, rather low amounts of isolated aqueous humour (0.1-0.2 *ml*) for immune enzyme assays and ion-selective analyses due to objective reasons, do not allow us simultaneously (in one and the same sample) determine two parameters of studied biological active compounds. Inclusion of a relatively high number of operated patients (by 320 persons) in each study group is connected with the mentioned circumstance. Thereby, in all the three study groups by 40 samples of aqueous humour and blood serum were allocated for each test.

The content of fibronectin, IGF-1, PgE_2 and cortisol in aqueous humour was determined with the use of appropriate kits (DRG-International Inc., USA). The immune enzyme assay was performed on the automatic spectrophotometer "Stat-Fax 3200" (USA) in the absorbance wavelength range 420-450 *nm*.

Determination of potassium, sodium and calcium ions was done according to ion-selective method of analysis with use of Kone-microlyte analyzer (Finland).

The obtained results were exposed to statistical analysis using Student's criteria and application of SPSS-13 programme (one Sample T-Test and Paired Sample T-Test).

The results of immune enzyme assay for fibronectin, IGF-1, and PgE_2 in aqueous humour of patients with the senile and complicated cataracts are presented in Table 1.

Table 1.

Fibronectin, IGF-1, and PgE_2 content in aqueous humour of patients with the senile and complicated cataracts.

Study groups of patients	Studied indices		
	Fibronectin (*ng/ml*)	IGF-1 (*ng/ml*)	PgE_2 (*pg/ml*)
I	11.26±0.99	1.10±0.18	43.05±4.13
II	20.71±2.37 $p_1<0.0005$	2.50±0.46 $0.0005<p_1<0.005$	66.11±7.40 $0.0005<p_1<0.005$
III	33.83±5.97 $p_1<0.0005$ $0.025<p_2<0.05$	2.60±0.39 $0.0005<p_1<0.005$ $p_2>0.4$	76.64±7.78 $p_1<0.0005$ $0.10<p_2<0.25$

Notes: *p_1 - indices of groups II and III compared to indices of the study group I; p_2 - indices of group II compared to indices of the study group III.*

As obvious from the Table, in patients with cataracts on the background of primary open-angle glaucoma (study group II) the level of fibronectin in aqueous humour 1.8 times exceeded analogous level in aqueous humour of patients with senile cataracts. In those cases when cataract was observed on the background of pseudoexfoliative glaucoma (study group III) the highest indices of fibronectin were determined in the aqueous humour; these indices were 3.0 and 1.6 times higher compared to those in patients of groups I and II, appropriately.

A similar regularity was traced upon revealing shifts in PgE_2 and IGF-1 content in aqueous humour of patients in study groups I and II. Thus, the level of PgE_2 in aqueous humour of the study group II patients 1.5 times exceeded PgE_2 level in aqueous humour of the study group I patients. In study group III PgE_2 high levels were also determined (compared to the study group I), being similar to those revealed in aqueous humour of the study group II patients. As obvious from the Table, in the aqueous humour of patients in study groups II and III we recorded approximately the same IGF-1 indices, which exceeded similar values in aqueous humour of study group I patients 2.27 and 2.36 times, correspondingly.

Table 2 presents the results of immune enzyme assay for determination of cortisol in the aqueous humour of patients with senile and complicated cataracts.

As obvious from Table 2, in patients of study group II the level of cortisol in aqueous humour markedly increased (as compared to hormone levels determined in aqueous humour of patients with the senile cataract – control group). Thus, the level of cortisol in aqueous humour of patients with cataract on the background of primary open-angle glaucoma was 1.8 times higher compared to norm. The highest indices of cortisol were observed in aqueous humour of patients of the study group III. In particular, cortisol levels in aqueous humour of patients with the senile cataract on the background of primary open-angle glaucoma and pseudoexfoliative glaucoma increased 2.3 times. The results of immune enzyme assays performed on aqueous humour were compared with cortisol levels in blood serum of the same cohort of patients. As demonstrated by the research findings, the level of cortisol in blood serum of patients of all the 3 study groups was almost similar and within the range of cortisol determined in actually healthy subjects. This latter, though indirectly, signifies in favour of the local synthesis of cortisol in the eye membranes, the cells of which apart from their main functions ensure processes of *in situ* cortisol secretion as well.

The next stage of our investigation involved biochemical analysis with the use of ion-selective method aimed to determine ions of sodium, potassium and calcium in the aqueous humour of patients with senile and complicated cataracts.

Table 3 presents results of analyses performed on the aqueous humour of patients with senile and complicated cataracts.

As obvious from Table 3, the levels of K^+. Na^+ and Ca^{++} in aqueous humour of patients with senile cataracts were similar to those in actually healthy cohort of subjects (we compared indices of ions in aqueous humour of patients with senile cataracts with the indices indicated in monograph of A. Pirie and R. van Heyningen (1968). In aqueous humour

TABLE 2.

Cortisol content in blood serum and aqueous humour of patients with the senile and complicated cataracts.

Study groups of patients	Studied indices	
	Aqueous humour	Blood serum
I	12.90 ± 0.64	56.90 ± 4.15
II	23.38 ± 1.46 p<0.0005	64.84 ± 7.28 0.1<p<0.25
III	30.4 ± 1.56 p<0.0005	50.70 ± 6.91 0.1<p<0.25

NOTE: *p - indices of complicated cataracts as related to indices of senile cataracts.*

TABLE 3.

K^+. Na^+ and Ca^{++} content in aqueous humour of patients with senile and complicated cataracts.

Study groups of patients	K^+	Na^+	Ca^{++}
I	5.00±0.21	133.3±14.4	0.99±0.06
II	2.30±0.26 p<0.0005	177.6±17.2 0.025<p<0.05	1.99±0.18 p<0.0005
III	1.92 ±0.28 p<0.0005	196.7±18.2 0.005<p<0.01	2.40±0.26 p<0.0005

NOTE: p – *indices of complicated cataracts as related to indices of senile cataracts*

of patients with cataract on the background of primary open-angle glaucoma low level of potassium ions was determined, it was 2.2 times lower than the level in aqueous humour of patients from the study group I. The lowest indices of potassium ions were recorded in the study group III, i.e., at cataracts on the background of pseudoexfoliative glaucoma. Thus, the level of potassium ions in aqueous humour of this study group decreased 2.15 times.

Unlike the shifts in potassium content in the aqueous humour of patients from study groups II and III, regarding the increase of sodium and calcium ions content a diametrically opposite picture was observed in the same groups. The content of sodium ions in the study group II increased 1.3 times, in the study group III – 1.5 times, compared to corresponding indices in aqueous humour of patients with senile cataracts.

Similar tendency was also observed on calcium ions content in aqueous humour of patients from study groups II and III. Thus, the level of calcium ions in aqueous humour of patients with cataracts on the background of primary open-angle glaucoma was 2.0 times above the control (group I), while in patients with cataracts on the background of pseudoexfoliative glaucoma it was 2.4 times higher.

We considered purposeful to present interpretation of our research findings of immune enzyme assay for determination of fibronectin, IGF-1, PgE_2, and cortisol in the aqueous humour of patients with cataracts associated with primary open-angle glaucoma and pseudoexfoliative glaucoma taking into account data of scientific publications relevant to sources for the synthesis of mentioned substances in specific eye membranes and their possible biological effects realized at the level of inter-cellular relations in different cell populations of the eye.

In line with this, first of all, we considered the essential role that is related to the biological activity of TGF_2 produced in cornea and trabecular meshwork of an eye in mechanisms of inter-cellular relations *in situ* ensuring the drainage function of the eye.

It is considered to be generally accepted that in case of senile and complicated cataracts processes of $TGF_{\beta\text{-}2}$ synthesis are markedly intensified in the cornea and trabecular meshwork [*de Iongh R.U. et al., 2005; Stefan C. et al., 2008; Dawes L.J. et al., 2009; Pattabiraman P.P., Rao P.V., 2010*]. Therefore, we cannot exclude that relatively high levels of fibronectin and IGF-1 in the aqueous humour of patients with complicated cataracts are resulting from a direct stimulating influence of $TGF_{\beta\text{-}2}$ to cell populations localized in the cornea and trabecular meshwork of the eye selectively synthesizing fibronectin and IGF-1.

The proposed statement, to a known extent, is also confirmed by the available literature data relevant to the biological activity of $TGF_{\beta\text{-}2}$ – in the aspect of its selective modulatory impact to the processes of fibronectin and PgE_2 synthesis and secretion in the eye membranes.

As known, keratocytes of the cornea and trabecular meshwork cells of the eye serve as the main sources of fibronectin synthesis *in situ*, i.e. in the eye tissues. Dose-dependent stimulant effect of $TGF_{\beta\text{-}2}$ to processes of fibronectin synthesis was established [*Wordinger R. et al., 2007; Hindman H. et al., 2010; Karamichos D. et al., 2010*] under the conditions of mentioned cells cultivation. Moreover, according to [*Stefan C. et al., 2008*]. $TGF_{\beta\text{-}2}$ produced in eye membranes should be considered as a "special" cytokine that under conditions of the eye barrier functions disturbance might increase fibronectin concentration in cells of trabecular meshwork of the eye anterior chamber's angle.

The IGF-1 elevated level revealed in aqueous humour of patients with the complicated cataracts should be considered as a factor hindering drainage function of trabecular meshwork and thus facilitating the increase of intraocular pressure. It is not excluded that similar mechanism functions in association with fibronectin-dependent mechanisms underlying the disturbed drainage function of the trabecular meshwork in the senile and, moreover, in the complicated cataracts.

Literature data [*Izumi K. et al., 2006; Yanai R. et al., 2006; Ko J. et al., 2009*] signify in favour to the proposed assumption: IGF-1 produced in corneal epitheliocytes and cells of the trabecular meshwork significantly activates fibroplastic processes *in situ*. To our mind, in processes of IGF-1 enhanced synthesis in the above mentioned structures of an eye the role should be assigned to $TGF_{\beta\text{-}2}$ produced in the same eye membranes, because the latter is known to markedly activate synthesis of IGF-1 and mediators, which take an active part in stimulation of fibroplastic processes [*Yamada N. et al., 2005; Izumi K. et al., 2006; Ko*

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J. et al., 2009], in corneal epitheliocytes and cells of trabecular meshwork.

In the light of our own and literature data, the role of $TGF_{\beta-2}$ in mechanisms of ACAID induction and withdrawal should be considered from qualitatively new positions. No doubt, the immunomodulatory effect of $TGF_{\beta-2}$ *in situ* that is conditioned by the targeted activation of the cytotoxic lymphocytes subpopulations (T-suppressors and T-killers) is determinant in processes of forming intercellular correlation among different lymphocytic subpopulations localized in eye membranes. hence ensuring reactions underlying ACAID. However, it is not excluded that the sphere of $TGF_{\beta-2}$ activity under conditions of norm is more versatile, as *in situ* produced mentioned cytokine directly and/or indirectly (activating the synthesis of fibronectin and IGF-1 in a mediated manner) participates in processes of maintaining the drainage function of trabecular meshwork, thus ensuring the constant level of intraocular pressure. Apparently, the above-mentioned mediatory effects of $TGF_{\beta-2}$ are strictly dose-dependent, as under conditions of pathology (in the given case: at senile and, especially, at the complicated cataracts) a significant elevation of $TGF_{\beta-2}$ in eye membranes brings to trabecular meshwork dysfunction; the latter is fraught with the increase of intraocular pressure.

The analysis of our own research results in the context of available publications allows to consider the important role of $TGF_{\beta-2}$ and IGF-1, which are produced in cornea and trabecular meshwork, in mechanisms ensuring the drainage function of an eye.

The facts of detection of receptors to PgE_2in cells of trabecular meshwork and sclera allow possibility of PgE_2 participation in processes of intraocular pressure regulation.

The high level of PgE_2 found by us in aqueous humour allows possibility of its participation in processes of the impaired drainage function and increase of intraocular pressure at cataracts proceeding on the background of primary open-angle glaucoma pseudoexfoliative glaucoma.

The following phenomenon of no less importance should specially mentioned: high levels of fibronectin IGF-1 and PgE_2 in the aqueous humour of patients under study were pathognomonic for the course of the primary open-angle glaucoma and not for cataracts, as in this latter case all the indices studied in aqueous humour were much lower than analogous indices at senile non-complicated cataract.

Our research revealed a direct correlation dependence between the high level of cortisol, on the one hand, and the content of sodium and calcium ions, on the other hand. Based on the results obtained a conclusion might be drawn that the increase of intraocular pressure in persons with complicated cataracts on the background of glaucoma is mostly conditioned by impairment of ion transfusion between the ciliary body and aqueous humour and the processes of cortisol "hyperproduction" by hormone-producing cells in post-barrier membranes of the eye.

Conclusion

This chapter deals with one of the urgent problems of modern ophthalmology: revealing the mechanisms underlying induction of primary open-angle and pseudoexfoliative glaucoma. Till nowadays the problem remains rather actual, as the issue is open to discussion: what are the regional mechanisms underlying the disorders in functions of the trabecular apparatus of the angle of anterior chamber of an eye and in the increase of intraocular pressure at the mentioned disease case.

One of severe complications of glaucoma is the steady persistent increase of intraocular pressure that is fraught with compression of the head of optic nerve that results in its partial or complete atrophy with the partial and/or complete sight loss. Currently, the majority of specialists engaged in clinical and experimental ophthalmology are inclined to the opinion that the increase of intraocular pressure is not the consequence of general hemodynamic disorders resulting from the permeability increase in hematoophthalmic barrier, but rather originates from pathological processes occurring in the membranes and chambers of an eye,

In line with the modern views, processes underlying the increased intraocular pressure originate in the eye structures as such: in connective-tissue, epithelial and endothelial cells of the ciliary body, cornea, retina, lens, trabecular apparatus of the angle of the anterior chamber of an eye. These cells possess selective secretory activity in the aspect of producing a number of biologically active substances exerting direct and/or indirect action to the processes regulating intraocular pressure.

Moreover, numerous pathological processes

proceeding in case of primary open-angle glaucoma at the site of eye membranes are fraught with the infringement of chamber humour osmolarity; furthermore, one of mechanisms increasing the volume of aqueous humour and not infrequently hindering its outflow is the impaired K^+/Na^+ balance in favour of the accumulation of this latter in the anterior chamber of an eye.

Available literary data of the last 30 years which discuss mediatory functions realized by cells of fibroblastic, epithelial and endothelial line in a ciliary body, cornea, retina, lens, a trabecular network formed a basis for carrying out the research directed at clarification of a role of *in situ* produced fibronectin, IgF-1 and a cortisol at primary open-angle glaucoma.

The drainage function of trabecular meshwork of an angle of the anterior chamber of an eye is an active process, in which the leading role belongs to secretory cells of this network. As it was specified above, secretory cells of the trabecular meshwork develop TGF_{β}-$_2$, fibronectin and an insulin-like growth factor -1, PgE_2. It is not excluded that the mentioned substances play an important role in ensuring drainage function of a trabecular meshwork, and thus, to a certain extent, in maintenance of an optimum level of the intraocular pressure.

For this reason, high indices of fibronectin and IGF-1 found in aqueous humour of patients with primary open-angle glaucoma testify in favor of hypersecretion of mentioned cytokines by cells of a trabecular meshwork, The presence of fibronectin and insulin-like growth factor-1 high concentrations at the primary open-angle glaucoma, and also at pseudoexfoliative glaucoma, testifies to violation of drainage function of a trabecular meshwork of an angle of the anterior chamber of an eye; this latter, to a certain extent, preconditions the high level of intraocular pressure. At the same time, the specific weight of fibronectin and insulin-like of growth factor -1 in hypertension formation in the aqueous humour is far from being equivalent, as on the one hand, fibronectin level in aqueous humour of patients from investigated groups II and III 10 times exceeds concentration of insulin-like growth factor-1 in the same liquid, on the other hand, as known, the weight of soluble fibronectin makes 440.000-150.000 D, while the mass of insulin-like growth factor-1 is 7.649 D [*Panteleev M. A. et al., 2011*].

Thus, on the basis of the analysis of literary data and carried-out own research it is possible to conclude that at glaucomas the infringement of drainage function and increase of intraocular pressure is in many respects caused by high concentration of fibronectin and, partially, insulin-like growth factor-1 in the intraocular liquid.

As it was noted above, the content of PgE_2 considerably increases in aqueous humour of patients with primary open-angle glaucomas and pseudoexfoliative glaucomas.

There is scanty literature about the synthesis of prostaglandins in eye membranes. Local synthesis of prostaglandins is found out only in cells of crystalline lens that was proved by research of O. Nishi et al. (1992) in model experiments *in vitro*: at cataract the extracted lens in the course of operation was located on incubation medium. With the increase of incubation terms the content of prostaglandins E_2 in the incubation environment considerably increased. At the same time, in a number of eye membranes, the ciliary body, sclera and the trabecular meshwork of an angle of the anterior chamber of an eye receptors to prostaglandins E_2 were found [*Toris C.B. et al., 2008*].

It is not excluded that the high content of PgE_2 in aqueous humour is fraught with an increase of intraocular pressure at glaucomatous patients, as according to [*Podos S.M. et al., 1972 a; b; Podos S.M., 1976 a; b; c*]. PgE_2 takes an active part in maintenance of drainage function of an eye.

It is known that ionic balance in liquid media of an organism (blood, spinal, gingival, synovial and intraocular liquids) is a necessary condition for maintenance of the osmotic pressure.

The anterior and posterior chambers of an eye are main depots; water makes about 93% and a very insignificant share make proteins. It is considered established that the delay of outflow of aqueous humour or its intensive more "production" promotes considerable elevation of pressure inside an eye.

Thus, one of the factors leading to increase of intraocular pressure at glaucomas is the increase of osmolarity of intraocular liquid.

It is considered to be established long ago that at anterior open-angle glaucoma in aqueous humour there are serious impairments in its ionic structure that was shown by disorders in functioning of sodium – potassium pomp, with the superfluous accumulation of sodium ions.

In our research as demonstrated by the results of ion-selective analysis, at primary open-angle

glaucomas and pseudoexfoliative glaucomas rather high indices of ions of sodium and calcium and low indices of potassium were determined in aqueous humour, as compared with the indices defined in aqueous humour of patients with senile not complicated cataracts.

The similar imbalance, being shown as superfluous accumulation of sodium and calcium in aqueous humour, complicates normal outflow of aqueous humour from the anterior chamber of an eye that, in its turn, is fraught with the increase of intraocular pressure.

Without considering the questions connected with mechanisms of shifts found by us regarding electrolytes content in aqueous humour (that was not an actual problem of the present research), nevertheless we consider expedient to discuss some aspects connected with the fact established by us on impaired ionic balance between eye membranes and the intraocular liquid.

Firstly, the increase of Na^+ and Ca^{++} levels observed by us in aqueous humour should be considered from positions of the broken ionic balance between specific membranes of an eye and intraocular liquid, and not as a result of the general disorder of electrolytes composition in blood of experimental animals, because the level of studied electrolytes in blood serum was within the limits of control values.

Secondly, the high level of a cortisol found by us in aqueous humour can serve one of possible causes of infringement of the ionic balance. This assumption appears very reasonable, as it is known that high concentrations of cortisol in separate membranes of an eye lead to ionic imbalance in connection with enhanced inflow of ions of sodium in aqueous humour that results in an increase of intraocular pressure.

Thirdly, it is not excluded that realization of hormonal and cytokine-dependent processes conditioned by regional shifts in the content of cortisol, prolactin, fibronectin, insulin-like growth factor-1 at cataracts proceeding on the background of primary open-angle glaucoma and pseudoexfoliative glaucoma, is caused by activation of calcium-dependent reactions in secretory cells of eye membranes.

It is considered established that the pseudoexfoliative syndrome represents itself as a provoking factor for development of the open-angle glaucoma, the course of which has a progressing character and is characterized by high resistance to carried-out medicamentous therapy and an unfavourable forecast [*Prince A.J. Ritch R., 1986; Streeten B.W. et al., 1990; Tarkkanen A. et al., 2002; Takhchidi K.P. et al., 2010*].

One of severe complications at development of a pseudoexfoliative syndrome is cataract as well [*Küchle M. et al., 1997; Puska P., Tarkkanen A., 2001*].

The impairment of immunological tolerance (of immunological privileges of an eye – ACAID) acts as an initiating factor for development of pseudoexfoliative syndrome [*Takhchidi K.P. et. al., 2010*].

It is not excluded that in pathogenesis of pseudoexfoliative syndrome emergence are also involved the local hormonal-mediatory mechanisms connected not with the operational intervention, but rather with infringement of processes of synthesis and secretion of such cytokines as $TgF_{\beta\text{-}2}$, IGF-1 and, first of all, fibronectin in cornea, ciliary body and trabecular meshwork of synthesis.

At a pseudoexfoliative syndrome essential physical and chemical changes occur in aqueous humour: the concentration of proteins considerably raises, including fibronectin as well [*Takhchidi K.P. et al., 2010*]. At the same time, shifts found by us in aqueous humour of patients with cataract on the background of pseudoexfoliative glaucoma, in many respects depend on the character of disease course: not so much of cataract, as glaucoma and the pseudoexfoliative syndrome. It is not excluded that in this studied group the high level of fibronectin in aqueous humour in many respects depends on features of pseudoexfoliative syndrome development.

On the basis of the analysis of literary data, it is possible to come to conclusion, according to which $TGF_{\beta\text{-}2}$ developed in eye membranes plays far not the last role in pathogenesis of primary open-angle glaucoma, including pseudoexfoliative glaucoma as well. So, at glaucomas of $TGF_{\beta\text{-}2}$ stimulates synthesis of such cytokines as insulin-like growth factor-1 and fibronectin in cornea, ciliary body and a trabecular meshwork of an angle of the anterior chamber of an eye. Their high levels found by us in aqueous humour testify to possible violation of drainage function of the trabecular meshwork that is fraught with an increase of intraocular pressure.

In conclusion, in the form of generalized schemes 1 and 2 the possible pathogenetic links engaged in the induction and a course of primary open-angle glaucoma, including pseudoexfoliative glaucoma as

well, are presented to attention of ophthalmologists. The specific subject matter is regional disorder that is fraught with impairment of secretory activity of the polypotent cells localized in various eye membranes, which besides the main functions produce a number of biologically active substances of the cytokine, hormonal and mediatory nature.

At anterior open-angle glaucoma (see schemes 1 and 2) the synthesis of fibronectin in cells of the trabecular meshwork is considerably activated which is caused by the stimulating influence of fibroblasts transforming growth factor ($TGF_{\beta-2}$). Realization of this effect, to a certain extent, is caused by blocking of inhibitory effect of a bone morfogenic protein (BMP-4) towards the activity of $TGF_{\beta-2}$ due to which the stimulating effect of the latter on processes of fibronectin intra-cellular synthesis is realized. It is not excluded that at the same time there occurs blocking of inhibitory effect of $TGF_{\beta-1}$ on domain of heparin (Hep-2) responsible for synthesis of fibronectin in a cell.

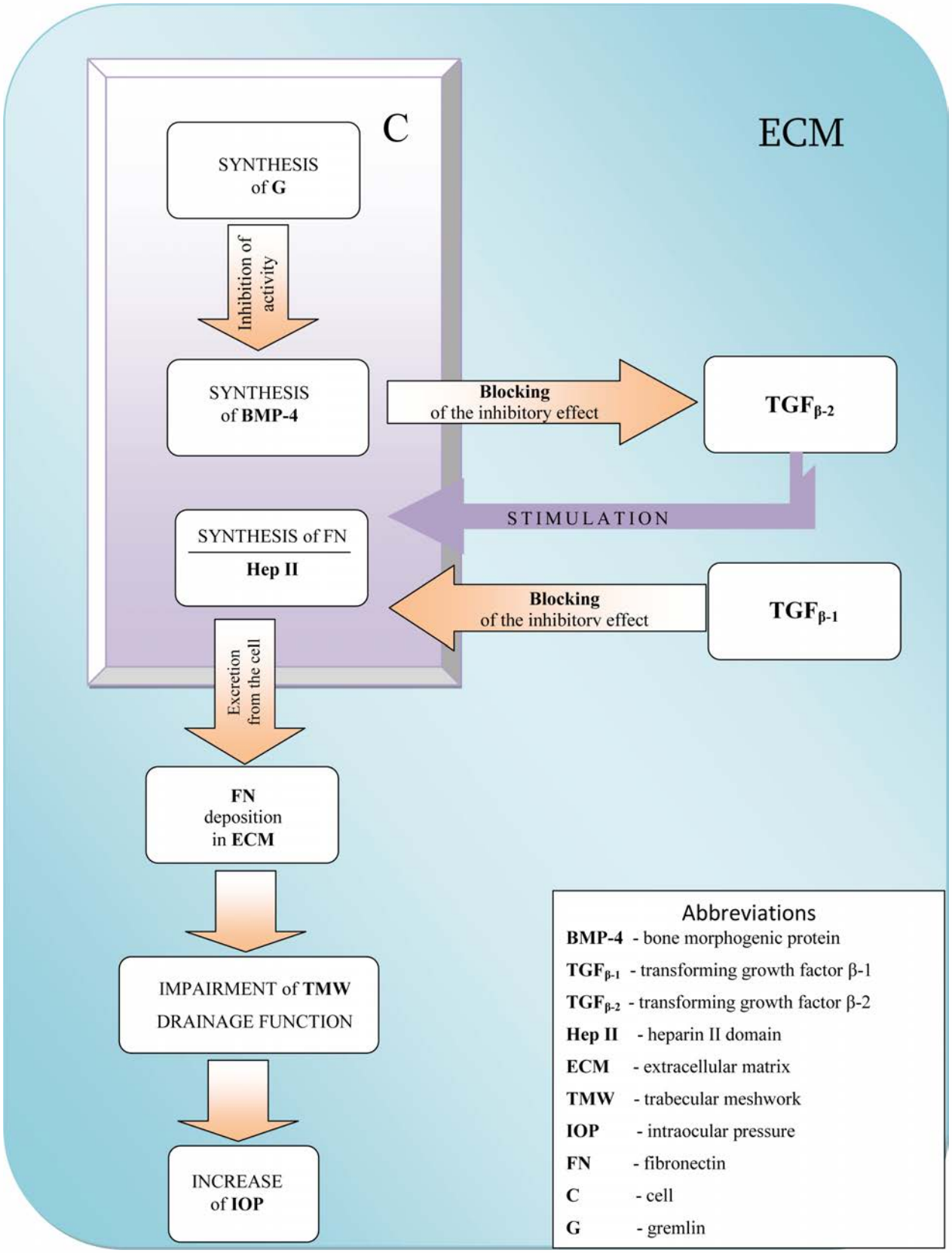
Further, as a result of fibronectin "hyper production", there is a deposition of fibronectin in extracellular matrix (EM) owing to which, as a result of drainage function impairment in trabecular meshwork, there proceeds an increase of intraocular pressure.

It is not excluded that in the conditions of physiological activity of trabecular meshwork cells the processes of intra-cellular synthesis of fibronectin are regulated according to cytokine mechanisms in realization of which, on the one hand, $TGF_{\beta-2}$ serves as a stimulating factor, on the other hand, this stimulating effect is adjusted due to gremin (G) and BMP-4 produced in trabecular meshwork cells. It is precisely the coordinated activity of aforementioned cytokines, $TGF_{\beta-2}$, G and BMP-4, that strictly supervises the balanced synthesis of fibronectin cells by trabecular network cells in the conditions of norm.

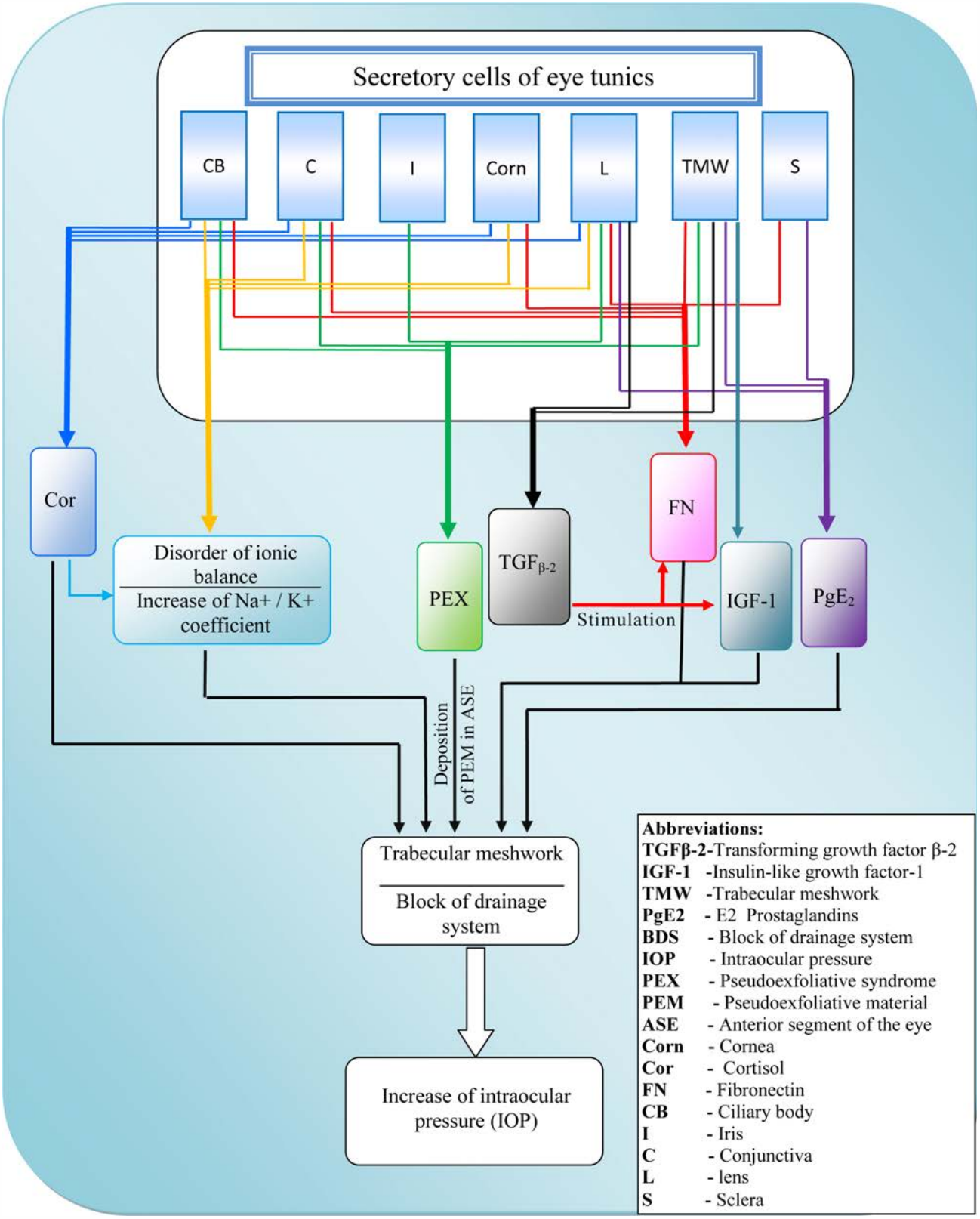
The specified Scheme 1 was constructed by us upon the analysis of the modern data concerning a role fibronectin, which is produced in keratocytes and cells of a trabecular meshwork, in violation of the drainage function of an eye at glaucomas and complicated cataracts [*Gonzales J.M. et al., 1998; Fleenor D. et al., 2006; Wordinger R.J. et al., 2007; Stefan C. et al., 2008; Zilfyan A., 2009; 2012; Hindman H.B. et al., 2010*].

In addition, due to analysis of the modern scientific data in the aspect of our own research findings we propose a summary scheme (Scheme 2) that presents the role of *in situ* produced biologically active compounds, which under conditions of disorders in synchronous activity of secretory cells localized in various membranes of the eye might bring to impairment of the drainage function and development of a symptom complex that is characteristic for primary open-angle and pseudoexfoliative glaucoma.

As obvious from Scheme 2, regional factors engaged in mechanisms of drainage function impairment and intraocular pressure increase might be conditionally divided into 2 categories. Secretory processes associated with dysfunction of cornea and trabecular meshwork cells (in the aspect of their targeted synthesis of $TGF_{\beta-2}$ should be related to category 1. Category 2 should embrace hormonal disorders, impairment of the regional ionic homeostasis and destructive processes, mechanisms of which are not sufficiently studied until present. In the given scheme we consider only 1 point of application that is affected by the influence of all the above mentioned factors: as a "target" here serves the trabecular meshwork of the anterior chamber of an eye with impaired drainage function that eventually rings to an increase of intraocular pressure. As evident from Scheme 2, in case of anterior open-angle glaucoma the regional $TGF_{\beta-2}$ dependent mechanisms are engaged, being conditioned by its stimulating influence to secretory cells of some eye membranes: in the aspect of their "excessive" synthesis of fibronectin and $IGF_{\beta-2}$, which cumulate both in stroma of the trabecular meshwork and in the aqueous humour finally resulting in block of drainage system and an increase of intraocular pressure. The hyperproduction of PgE_2 in secretory cells of trabecular meshwork, sclera and, probably, the lens, also brings forth impairment of the drainage function. In impairment of drainage network functions a definite role is also devoted to *in situ* produced cortisol and processes resulting in disorders of ionic balance between the membranes and liquid media of an eye (first of all: between the cells of the ciliary body, cornea, trabecular meshwork and the aqueous humour). In the mechanism of impaired ionic balance that at the primary open-angle glaucoma is characterized by excessive accumulation of sodium ions in aqueous humour a certain part belongs also to cortisol produced in eye membranes. In cases of pseudoexfoliative glaucoma deposition of pseudoexfoliative matter in the anterior segment of an eye might cause blocking of the drainage system.



Scheme 1. The role of trabecular meshwork cells of the anterior chamber angle of an eye in mechanisms of fibronectin-dependent drainage function impairment and the increase of intraocular pressure at anterior open-angle glaucoma.



Scheme 2. The role of mediators and hormones in mechanisms of intraocular pressure increase at complicated cataracts: cataracts on the background of primary open-angle glaucoma and pseudoexfoliative glaucoma.

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