Chapter 22

Regional Immune, Hormonal and Mediatory Mechanisms Responsible for Function of "Immune Privilege of an Eye" at Senile and Complicated Cataracts

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1. Introduction

Nowadays, in current biology and medicine the subject of wide discussion present paracrine and autocrine immune, endocrine and mediatory mechanisms functioning of which in all the integrative systems of the organism are realized due to principles of interregulation and interdependence. It is not excluded that similar mechanisms are also engaged in eye tunics, moreover that the hematoophthalmic barrier is characterized by a more stable selective permeability (as compared to other histohematic barriers) towards a wide range of endogenous active biological compounds of immune, hormonal and mediatory origin.

In this concern, to our mind, studies aimed at elucidation of autonomous mechanisms engaged in sustaining the immune and endocrine homeostasis in the eye tunics are rather promising.

Hence, during the last 40 years the subject of special investigation became scientific research works relevant to the aspects of pathogenesis "active immunological tolerance" originating in eye tunics as a response to baring of antigenic determinants in eye tunics and tissues at a wide range of ophthalmological diseases. The entire symptom complex of *in situ* occurring immunological reactions is defined in modern ophthalmology as "anterior chamber associated immune deviation" (ACAID).

At the same time, regional mechanisms responsible for ACAID function are studied rather insufficiently.

In the mentioned aspect, cells identified in certain eye tunics should become the subject of specific discussion; besides their "main functions' these cells are provided with the immune,

hormonal and mediatory activity as well. The matter is *in situ* synthesis of transforming growth factor-$_{\beta\text{-}2}$, cortisol, fibronectin, availability of receptors to prolactin and prostaglandins E_2.

This chapter will bring to the attention of readers the analysis of scientific evidence and our own research findings obtained during the last 10 years in respect of possible regional immune, hormonal and mediatory mechanisms engaged in formation and abolition of ACAID function.

To avoid artificially expanded volume of this chapter, we considered to be expedient to supplement the narrative description of own research results with Tables and Schemes, excluding all the methodic approaches to selection of patient cohorts, methods of investigation, which were comprehensively presented within our previous studies (Zilfyan A., 2009; 2012; 2013).

We should only mention those groups of patients under study in the aqueous humor of which we determined the spectrum of the above-mentioned endogenously active substances of the immune, hormonal and mediatory nature.

The first (control) group included patients with senile non-complicated cataract, the second group involved patients with cataracts occurring on the background of primary open-angle glaucoma and the third group embraced patients with cataracts on the background of glaucoma and pseudoexfoliative syndrome, the fourth group made patients with cataracts on the background of "arterial hypertension", the fifth group – cataracts on the background of diabetes mellitus and the sixth group was composed of patients with cataract on the background of previous eye injury.

To our mind, it was rather reasonable that we did not include in the current chapter issues dealing with the role of intracorporeal resident gram-negative and gram-positive microorganisms, as well as viruses, *Chlamidiae*, *Toxoplasmas*, etc. Despite the bulk of evidence-frequently of contradictory character – mechanisms of "bacterial translocation" of the above-mentioned microorganisms in the aspect of their passage through the hematoophthalmic barrier and/or penetration of their secretion and decomposition products into the eye tunics are almost none-investigated.

Similar approach was used by us regarding the role of pro-and anti-inflammatory immunocytokines, because of a known controversy of available scientific data on their role in mechanisms responsible for formation of reactions responsible for ACAID function. The controversial character of scientific publications to a known extent is connected with dose-dependent and pleiotropic potencies of immunocytokines even towards the same "immunocompetent" cells localized in the eye tunics.

2. Immune shifts in mechanisms of formation and abolition of the active immunological tolerance responsible for ACAID function

The term "immune privilege of an eye" implies the entire complex of regional immune cell-mediated and humoral reactions aimed at prevention of inflammatory and dystrophic

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processes development in tunics and fluid sections (slices) of an eye under conditions of a wide range of ophthalmologic maladies.

At the same time, this term first of all reflects the state of "local immune homeostasis" under conditions of normal functioning of an eye. The complete cascade of local protective/adaptive mechanisms is aimed to form immunological processes, which in total are defined as anterior chamber associated immune deviation (ACAID). To our mind based on available scientific publications, the general scheme of immunopathological process can be presented as the following chronologically occurring stages:

1. As a result of interaction of different pathogenetic factors there occurs "baring" (uncovering) of antigenic determinants (Orge Y., Gungor S., 1984; D'Orazio T., Niederkorn J., 1998; Sonoda A. et al., 2000; Camelo S. et al., 2005).

2. As a response to acquiring of antigenic properties by tissues of an eye in the region of damage (injury) there occurs no activation of the antibody formation process, as reactions of active immunological tolerance there prevail to dominate (Murray P. et al., 1990; Lightman S., Towler H., 1992; Fu T. et al., 2004; Kitaichi N. et al., 2005).

3. No formation of immune complexes occurs as under conditions of pathology there is engaged the regional mechanism preventing activation of the compliment (Streilein J., Stein-Streilein J., 2000).

4. Mechanisms of immune suppression (inhibition of antibody formation) are conditioned by targeted (directed) activation of T-suppressory and killer (killing) subpopulation (Wilbanks C., Streilein J., 1990; Muhaya M. et al., 1999).

5. Directed activation of T-killer lymphocytes occurs due to production of TGF_{β} (Streilein J. et al., 1992; Abrahamian A. et al., 1995; Fleenor D. et al., 2006).

6. The high level of CD_8 is mainly conditioned by the fact that in the region of eye tissues damage there occurs activation of the main histocompatibility class I complex, which functions as the initial factor ensuring triggering of receptor mechanisms underlying activation and proliferation of T-killer lymphocyte populations (Nishi O. et al., 1982; Martin W. et al., 1995; Bakunowicz L. et al., 1997; Muhaya M. et al., 1999).

It should be emphasized that certain pathogenetic mechanisms/links underlying induction and course of ACAID in case of non-complicated and complicated cataracts are currently the subject of a wide discussion (Orge Y., Gungor S., 1984; Uenoyama K. et al., 1989; Streilein J. et al., 1992; Zhou Z. et al., 1996; Cinatl et al., 2000; Robinson M. et al., 2000; Kawakami M. et al., 2005).

As a rule, the main reason of ACAID induction is 1-or 2-stage surgical intervention, as a result of which there occurs "baring" (uncovering) of antigenic determinants of lens tissues. As a result, in the "immunocompetent" tunics of an eye there occurs the synthesis of specific autoantibodies targeted to tissues of lens; by this latter are caused local processes of autoimmune aggression are caused being conditioned by the damaging action of both autoantibodies and locally formed immune complexes.

The activation of reactions of local humoral immunity is accompanied by significant increase of IgG levels in aqueous humor (in anterior and posterior chambers of eyes), due to which the aqueous humor is a rather informative media for studies on mechanisms of both formation and abolition of ACAID. At the same time, all the above-mentioned links underlying abolition of ACAID in case of cataracts are studied rather insufficiently.

It should be emphasized that regional immune mechanisms responsible for *in situ* formation of the active immunological tolerance, which ensures the ACAID function, is most comprehensively studied at senile non-complicated cataracts. At the same time, only single, sometimes even contradictory evidence is available on the course of the regional immune reactions engaged at complicated cataracts.

In our previous investigation (Zilfyan A., 2009) we studied the shifts of CD_4, CD_8 and IgG in the aqueous humor of patients with complicated cataracts: at cataracts on the background of primary open-angle glaucoma, pseudoexpfoliative glaucoma, diabetes mellitus, arterial hypertension, prior eye trauma.

The results of enzyme immunoassays for CD_4 and CD_8 in aqueous humor of patients are presented as Table 1.

Study groups (n=40)	Indices studied					
	CD_4			CD_8		
	M	*m*	*p*	*M*	*m*	*p*
I	10.7	± 2.1		53.9	±5.3	
II	28.4	±3.6	<0.0005	22.05	±5.4	<0.0005
III	30.2	±2.9	<0.0005	18.15	±2.3	<0.0005
IV	14.2	±2.4	*<0.25*	48.8	±4.2	<0.25
V	11.0	±2.5	"/>0.4	50.21	±2.54	<0.4
VI	17.5	±2.0	<0.025	33.7	±4.99	<0.005

Notes: *M* – mean; *m* – standard error of mean; *p* – confidence interval (indices of complicated cataracts as related to senile cataracts).

Table 1. The content of CD_4 (*unit/ml*) and CD_8 (*unit/ml*) in aqueous humor of patients with senile and complicated cataracts.

As obvious from the Table, at complicated cataracts (study groups II and III) already in pre-surgery period in the aqueous humor there was a marked decrease of CD_8 on the background of CD_4 increase in the aqueous humor of the same cohort of patients.

It is rather remarkable that upon the 2-factor statistical analysis strong reverse correlation dependence was revealed between the studied indices (correlation index made-0.893 and-0.940, appropriately). Apparently, at complicated cataracts in study groups II and III the antigenic determinants in post-barrier eye tunics were bared already in pre-surgery period;

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relatively high levels of IgG revealed in the aqueous humor of the specified cohort of patients signified to this latter (Table 2).

Study groups (n=40)	IgG content		
	M	*m*	*p*
I	9.025	±0.73	
II	16.82	±2.20	<0.005
III	25.05	±2.25	<0.0005
IV	8.75	±1.71	"/>0.40
V	10.1	±0.74	<0.25
VI	14.57	±2.05	<0.025

Notes: *M* – mean; *m* – standard error of mean; *p* – confidence interval (indices of complicated cataracts as related to senile cataracts).

Table 2. IgG content (*IU/ml*) in the aqueous humor of patients with senile and complicated cataracts.

It appears, that in this precise case the intercellular mechanisms, which are conditioned by the cooperative activity of B-helper subpopulations and B-lymphocytic populations in the immune competent eye tunics and, first of all, of the ciliary body, are engaged in eye tunics; these latter eventually bring to the synthesis of anti-tissue autoantibodies. The performed 2-factor correlation analysis also signifies in favour of this circumstance: strong direct correlation dependence was revealed between CD_4 and IgG high levels in the aqueous humor of patients of the II and III study groups (correlation index made-0.891 and-0.935, appropriately). It should be mentioned that similar picture of immunological shifts was also observed in study group VI, i.e. at cataracts occurring on the background of trauma. Therefore, it is not excluded that prior trauma can be considered as a provoking factor bringing forth impairment of the immune homeostasis. In the aqueous humor of patients from all other study groups of complicated cataracts (groups IV and V) we registered CD_8, CD_4 and IgG indices similar to those registered in the aqueous humor of patients with senile cataracts.

The results of performed immunological analysis for IgG determination in aqueous humor of patients with senile and complicated cataracts are conformed by available data of scientific publications. In particular, N. Stambuk et al. (1994) established that IgG level in aqueous humor of patients with complicated cataracts was significantly higher than in patients with senile cataracts.

Thus performed, the comparative analysis in all study groups, though with due circumspection, signifies that at senile cataracts and, in all probability, at cataracts occurring on the background of diabetes mellitus and arterial hypertension during the pre-surgery period the regional immune homeostasis is not disturbed, i.e. only those mechanisms are engaged, which ensure the function of ACAID at norm.

At the same time, based on the studies performed by the above-mentioned authors (Lightman S., Towler H., 1992; Sonoda A. et al., 2000; Fu T. et al., 2004; Camelo S. et al., 2005; Kitaichi N. et al., 2005) it is difficult to consider if there is adequacy of inflammatory process, which occurs in eye post-barrier tunics as a response to surgery-related trauma, to what extent the local protective mechanisms work characterizing the immune deviation as related to "bared" autoantigens of the specified tunics. To our mind, it is possible to judge about the character and intensity of the inflammatory process in eye post-barrier tissues only under conditions of the lens transplantation into heterogenous sites of the organism. This problem was successfully solved by Japanese researchers already in 1989 (Uenoyama K. et al., 1989). The authors performed experiments aimed to study tissue specific shifts upon lens transplantation into the eye and intraperitoneally. Due to the complex approach with the use of cytological, immune-histochemical and electron microscopy methods the authors revealed that the degree of inflammatory reaction, the intensity of lymphomacrophagial infiltration were considerably more expressed at the site of lens transplantation, i.e.-in the peritoneum.

At the same time, even in patient with senile non-complicated cataract the surgery-related trauma might provoke disturbance of ACAID function, because as a response to baring of eye tunics antigenic determinants there occurrs the regional autoimmune process. The post-surgery period in those patients and the performed corrective therapy in the prevailing majority of cases proceed without complications; this latter allows us considering that the traumatic injury occurring in the course of surgery intervention is fraught with development of *in situ* immunopathological disorders, which are of exceptionally temporary, transient character.

3. Cortisol-and prolactin-dependent mechanisms responsible for formation and abolition of the ACAID function

In current scientific publications there is only scarce evidence according to which in certain eye tunics the cells of epithelial genesis and fibroblastic line – apart from their main function – also possess the hormone-producing property to synthesize cortisol (Chong A., Aw S., 1986). Due to experimental studies (Southern A. et al., 1979), the presence of receptors to glucocorticoids in cells of ciliary body and the cornea was established, whereas translocation of glucocorticoids from the surface towards the cell nuclei occurred during a rather short period of time. It is reasonable to mention another circumstance of no less importance. The authors failed to reveal similar mechanism of reception and translocation, which is characteristic for glucocorticoids, as related to a wide range of hormones: testosterone, estradiol, progesterone, T_3 and T_4. It was established that biological effects of cortisol are realized within the sclera, cornea, ciliary body and, mostly important, in the lens capsule (Kasavina B. et al., 1977). According to S. Rauz and associates (2001; 2003), cortisol is secreted in the ciliary body of both actually healthy contingent and in patients with the primary open-angle glaucoma.

Currently, the opinion dominates that the fundamental function of cortisol in eye tunics is sustaining the optimal level of intraocular pressure. Furthermore, this function has a dual

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realization: through regulation of the regional immune homeostasis and potentiating the adrenergic effect towards the system of vascularization in specific eye tunics (Jacob E. et al., 1996; Rauz S. et al., 2001).

Nowadays, the role of prolactin appears more disputable. At cataracts and uveitides the presence of prolactin was revealed in the anterior chamber of the eye (Pleyer U. et al., 1991). Efforts were done to interpret biological effects of prolactin within the specific eye structures functioning. In particular, S. Duenas and co-workers (2004) allow for the possibility of intraocular synthesis of prolactin within the blood vessels of retina. At retinopathies, the mentioned authors revealed a high level of prolactin in the anterior chamber of the eye. It is important to emphasize that authors did not reveal any correlation dependence between prolactin levels in the anterior chamber of the eye and in blood serum. Despite the fact that of prolactin revealment in tunics and liquid media of the eye, the role of this hormone in the integrative activity of the eye remains unstudied.

To our mind, the role of in situ produced hormones, cortisol and prolactin, in eye tissues is more versatile and is far beyond the functions ensuring processes of ion exchange and intraocular pressure regulation.

We propose a hypothesis according to which cortisol and prolactin play an important role in establishment of ACAID function through modulation of immunological processes in the aspects of both activation and/or inhibition of specific T-and B-populations and also targeted synthesis of cytokines with adaptogenic spectrum of action.

The mentioned supposition is confirmed by literary data, according to which in the mammalian organism cortisol and prolactin possess immunomodulatory functions. In particular, it is established that prolactin and cortisol at physiological concentrations maintain the stability of the immune homeostasis. However, at high concentrations cortisol acts as a factor that selectively inhibits the activity of T-killer and T-helper cytotoxic lymphocytes (Pazirandeh A. et al., 2002; Lindeman D., Racke K., 2003; Visser J. et al., 2003), while prolactin activates a number of cytokines (IL-I, VI, TNF, as well as γ-IFN in central and periphery organs of immunogenesis (Matera L., 1986; Yarilin A., Belyakov I., 1996). Furthermore, prolactin – in a dose dependent mode – activates B-lympocytic population (Berczi I. et al., 1981; McMurrey R. et al., 1991; Lahat N. et al., 1993).

As shown by the results of our earlier performed immune enzyme assays (Zilfyan A., 2009; 2012; 2013) (Table 3) in the aqueous humor of patients with complicated cataracts (cataract occurring on the background of primary open-angle and pseudoexfoliative glaucoma and cataract occurring on the background of preceding trauma) the level of cortisol significantly increased as compared to control.

The highest indices were recorded by us in aqueous humor of the III group patients: at cataracts occurring on the background of pseudoexfoliative glaucoma.

Until present it was considered to be established that the main function of cortisol in the eye tunics was to regulate the intraocular pressure (Jacob E. et al., 1996; Rauz S. et al., 2001). At the same time, due to results obtained, a supposition might be done: the revealed high concen-

Study groups (n=40)	Cortisol content					
	aqueous humor			blood serum		
	M	*m*	*p*	*M*	*m*	*p*
I	12.90	± 0.64		56.90	±4.15	
II	23.38	±1.46	<0.0005	64.84	±7.28	<0.25
III	30.4	±1.56	<0.0005	50.70	±6.91	<0.25
IV	14.10	±0.61	*<0.1*	115.60	±16.88	<0.005
V	9.70	±2.69	<0.25	70.50	±10.41	<0.25
VI	14.05	±0.69	<0.25	68.60	±8.13	<0.25

Notes: *M* – mean; *m* – standard error of mean; *p* – confidence interval (indices of complicated cataracts as related to senile cataracts).

Table 3. The content of cortisol (*pg/ml*) in blood serum and aqueous humor of patients with senile and *complicated cataracts.*

trations of cortisol in the aqueous humor of patients from study groups II, VI and, especially, from group III might produce alterative (damaging) action towards immunocompetent cells of the anterior chamber of the eye, because the cytotoxic effect of cortisol immunocompetent cells of organs of immunogenesis and blood is considered to be established long ago (Bell P., Munck A., 1973; Carr D., Blalock J. et al., 1989). Moreover, we considered it reasonable to the interpret data obtained on shifts of cortisol content in aqueous humor of patients with cataracts taking into account rather informative evidence on dose-dependent impact of cortisol towards the functional state of lymphocytic populations (Pazirandeh A. et al., 2002). The authors studied the direct hormonal influence of endogenous levels of glucocorticoids to thymocytes and peripheral T-lymphocytic subpopulations in transgenic mice with the altered sensitivity to glucocorticoids. According to mentioned researchers, 2-fold increase of sensitivity to glucocorticoids in the organism of transgenic mice was accompanied with the profound alterative changes in thymocytes followed by a marked increase in number of all T-lymphocytic subpopulations in the cortical layer of thymus.

To our mind, it is not ruled out that in mechanisms of ACAID formation and functioning precisely similar cortisol-dependent mechanism of reactions balanced functioning – simultaneously ensuring processes of proliferation and apoptosis of T-lymphocytic subpopulations in tunics and anterior chamber of an eye – is engaged.

At the same time, we cannot exclude that cortisol high concentrations recorded by us in the aqueous humor of patients from study groups II, III and VI might be the provoking factor in the aspect of an abrupt enhancement of apoptosis processes in the immunocompetent cells of eye tunics and the cells of inflammatory reaction in the anterior chamber of the eye.

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As seen in studies performed by our group a conclusion might be drawn that in organisms of mammals cortisol plays an important role in processes promoting ACAID functioning (Zilfyan A., 2009; Zilfyan A.A., Zilfyan A.V., 2013).

Moreover, at complicated cataracts (groups II, III and IV), especially at cataracts occurring on the background of the open-angle and pseudoexfoliative glaucoma, we should assign to cortisol an important role in mechanisms infringing the normal course of immunological reactions in tunics and the anterior chamber of an eye ensuring ACAID – in the aspect of abolishing the processes promoting *in situ* active and immunological tolerance.

Significant shifts were also observed on the part of prolactin determined in the aqueous humor of patients with complicated cataracts. In particular, in the aqueous humor of patients with complicated cataracts (study groups II, III and VI) relatively high level of prolactin was recorded. In the remaining patients with complicated cataracts (study groups IV, V) indices of prolactin were similar to those determined in aqueous humor of patients with senile cataracts (Table 4).

Study groups (n=40)	Prolactin content					
	aqueous humor			blood serum		
	M	*m*	*p*	*M*	*m*	*p*
I	0.34	±0.045		7.0	±3.6	
II	1.10	±0.08	<0.0005	9.5	±1.6	<0.10
III	2.23	±0.22	<0.0005	9.1	±2.2	<0.25
IV	0.300	±0.046	*<0.40*	7.50	±0.57	<0.25
V	0.49	±0.09	<0.10	6.40	±1.45	<0.40
VI	14.05	±0.07	*p*<0.0005	10.90	±3.66	<0.25

Notes: *M* – mean; *m* – standard error of mean; *p* – confidence interval (indices of complicated cataracts as related to senile cataracts).

Table 4. The content of prolactin (*ng/ml*) in aqueous humor and blood serum of patients with senile and complicated cataracts.

In the available literature the evidence on the role of prolactin in mechanisms of ACAID formation is lacking.

At the same time it is known that the organism of mammals prolactin possesses a profound stimulant action towards the specific subpopulations of lymphocytes and the cells of monocyte and lymphocyte line – in the aspect of synthesizing a number of immunocytokines: tumor necrosis factor alpha,-beta ($TNF_{\alpha,\beta}$), interleukins-IL-I, IL-II, IL-VI and γ-interferon. It is known that at senile and complicated cataracts relatively high levels of some pro-and anti-inflammatory cytokines (TNF, IL-I, IL-II, IL-IV, IL-VI, IL-X) are determined in the aqueous humor (Stambuk N. et al., 1994; Slepova O.S. et al., 1998; Patel J. et al., 2006; Sawada H., et al., 2010).

In consideration of the existing immune endocrine interrelations of prolactin and proinflammatory cytokines we can suppose that relatively high prolactin concentrations revealed by us in the aqueous humor of study groups II and III patients might be the cause of the enhanced synthesis of proinflammatory cytokines by immonocompetent cells of some eye tunics and cells of lymphocyte-monocyte line localized in the aqueous humor. This is one of the probable prolactin-dependent mechanisms underlying infringement of ACAID function at complicated cataracts.

Under conditions of pathology, i.e. at complicated cataracts, in the anterior chamber of the eye there might be also engaged another prolactin-dependent mechanism bringing to ACAID abolition. It is not excluded that prolactin acts as a co-factor participating in activation of *in situ* reaction of humoral immunity through the selective effect to B-cellular populations of eye tunics and the inflammatory exudates of the anterior chamber of the eye. Apparently, under conditions of increased prolactin content in the aqueous humor with precedent baring of antigenic determinants of eye tunics, prolactin in its turn stimulates the antigen-dependent function of B-lymphocyte populations. In favour of the proposed supposition also signify rather informative literary data depicting a direct dose-dependent stimulant effect of prolactin to the B-lymphocyte populations (Berczi I. et al., 1981; McMurray R. et al., 1991; Lahat N. et al., 1993).

On the base of our own findings and comparing them with the available scientific data on the role of prolactin in the immunological processes and its revealment in the anterior chamber of the eyes the following conclusion might be drawn. Prolactin-dependent mechanisms, which, on the one hand, stimulate the local synthesis of proinflammatory cytokines and, on the other hand, activate processes of *in situ* B-lymphocyte populations proliferation and thus worsen the course of an earlier developed autoimmune process in post-barrier tunics and the anterior chamber of the eye, are also engaged in mechanisms of ACAID abolition at complicated cataracts.

4. Fibronectin and prostaglandins E_2-dependent mechanisms responsible for abolition of reactions promoting the ACAID function

In our previous studies (Zilfyan A., 2009; 2012) data were presented on the important role of fibronectin and PgE_2 produced in the eye tunics regarding the mechanisms of disorders in the drainage function of the trabecular meshwork and the increase of intraocular pressure at complicated cataracts: cataracts occurring on the background of primary open-angle and pseudoexfoliative glaucoma.

At the same time, till present, the role of fibronectin and prostaglandins E_2 (PgE_2) at senile non-complicated cataract and complicated cataracts never became the subject of a special investigation.

Only scarce evidence is available that fibronectin is produced by keratocytes of the cornea, ciliary body and cells of the trabecular meshwork of the eye (Tripathi B., et al., 2004; Hindman

H. et al., 2010; Wordinger R.J. et al., 2007). The enhanced synthesis of fibronectin in the mentioned eye tunics might bring to activation of fibroplastic processes finally terminating in fibrosis of the eye tunics, including the lens. However, the role of fibronectin in processes of ACAID function formation and abolition is not studied. At the same time it is considered to be established that fibronectin might enhance phagocytosis; on the surface of macrophages there are receptors to fibronectin (Kuznik B. et al., 1989). Therefore, it is not excluded that fibronectin at a number of eye diseases might play a leading role in activation of macrophages of the eye tunics and the anterior chamber of the eye: both in the aspect of phagocytosis and synthesis of pro-inflammatory cytokines: interleukin-I (IL-I) and tumor necrosis factors alpha and beta (TNF-$_{\alpha,\beta}$) (Slepova O. et al., 1998; Sawada H. et al., 2010).

As demonstrated by our results of the performed immune enzyme assays, in patients of the study group II, i.e. at cataracts occurring on the background of primary open-angle and pseudoexfoliative glaucoma, relatively high indices of fibronectin were revealed in the aqueous humor (Table 5).

Study groups (n=40)	Fibronectin content		
	M	*m*	*p*
I	11.26	± 0.099	
II	20.71	±2.37	<0.005
III	33.83	±5.97	<0.005
IV	13.43	±2.57	*<0.25*
V	12.76	±1.14	*<0.25*
VI	12.04	±1.12	<0.40

Notes: *M* – mean; *m* – standard error of mean; *p* – confidence interval (indices of complicated cataracts as related to senile cataracts).

Table 5. The content of fibronectin (*ng/ml*) in the aqueous humor of patients with senile and complicated cataracts.

The highest indices of the cytokine were recorded by us in the aqueous humor of patients with cataract occurring on the background of pseudoexfoliative glaucoma (as compared to indices of the control group).

In all other study groups of patients with complicated cataracts low indices of fibronectin were determined in the aqueous humor; these indices were similar to those recorded in the aqueous humor of patients with senile cataracts.

Let us consider the role of fibronectin in processes of ACAID function formation and abolition. It is considered to be established that macrophages of eye tunics and aqueous humor play a role of in processes of pro-and anti-inflammatory cytokines synthesis; the balanced synthesis of mentioned cytokines ensures the normal course of reactions supporting ACAID.

Study groups (n=40)	Prostaglandins E_2 content		
	M	*m*	*p*
I	43.05	± 4.13	
II	66.11	±7.40	<0.01
III	76.64	±7.78	<0.005
IV	48.03	±3.02	*<0.25*
V	49.60	±6.37	*<0.25*
VI	58.96	±2.81	<0.25

Notes: *M* – mean; *m* – standard error of mean; *p* – confidence interval (indices of complicated cataracts as related to senile cataracts).

Table 6. Shifts in content of PgE_2 (*pg/ml*) in the aqueous humor of patients with senile and complicated cataracts.

As already mentioned by us earlier, at a number of diseases, including the complicated cataracts, this balance is broken and macrophages begin to produce immunocytokines – primarily of the proinflammatory – character: TNF_2 and IL I. Therefore, a role of no less importance should be assigned to macrophages in processes of abolishing reactions responsible for ACAID function.

At the same time, it is considered to be established that fibronectin has an ability to activate the cytokine function of macrophages. Hence, it is not excluded that at complicated cataracts fibronectin-dependent mechanisms are engaged in mechanisms of ACAID functions infringement; specified mechanisms are realized at the level of the regional monocyte-macrophageal system.

In our further research the shifts in PgE_2content in the aqueous humor of patients with senile and complicated cataracts were studied. There is only rather scarce literature on synthesis of prostaglandins in eye tunics. The local synthesis of prostaglandins was revealed only in epithelial cells of the lens capsule and was proved by experiments of O. Nishi and co-workers (1982), who performed model *in vitro* tests; in case of cataract surgery the isolated lens was placed in the incubation medium. Alongside with incubation time increase the content of prostaglandins in the incubation medium markedly increased. At the same time, in some eye tunics – the ciliary body, retina, sclera and trabecular meshwork of the anterior chamber angle receptors to PgE_2 were identified (Toris C. et al., 2008). The role of PgE_2 in maintaining the drainage function is widely discussed (Podos S. et al., 1972).

However, the role of PgE_2 in mechanisms of ACAID formation and infringement is almost not investigated. As shown by results of our own studies, the level of PgE_2 in aqueous humor of patients from study groups II, III and VI markedly increased as compared to the level of PgE_2 in the aqueous humor of the control group patients (Table 6).

The highest values were observed in aqueous humor of patients with cataract on the background of pseudoexfoliative glaucoma. In all other groups of complicated cataracts low indices

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were recorded in the aqueous humor; these indices were similar to those determined in aqueous humor of the control group patients. The high level of PgE_2 at complicated cataracts (study groups II, III, VI) might be considered as a factor bringing to disorder of the eye trabecular meshwork drainage function; moreover that on its cells receptors to PgE_2 were revealed. Despite the presence of receptors to PgE_2 in different eye tunics, epithelial cells of the lens capsule are the only possible source of PgE_2 local synthesis. Therefore, it is not ruled out that in complicated cataracts the lens cells are engaged in an enhanced synthesis of E_2 group prostaglandins, which might influence the course and duration of reactions promoting abolition of the ACAID function.

Our supposition is also grounded by data of scientific publications dealing with the functional activity of PgE_2 towards the numerous integrative systems of the organism, including the immune system. In particular, it is considered to be established long ago, that PgE_2 inhibit the synthesis of cytotoxic lymphocytes: T-suppressor and T-killer lymphocyte subpopulations. Hence, it is not excluded, that the high level of PgE_2 in the aqueous humor of patients with complicated cataracts (study groups II, III and VI) might be considered as a factor producing immunosuppressive action to cytotoxic lymphocytes localized in eye tunics and the aqueous humor; the latter is fraught with abolishing the reactions responsible for *in situ* abolition of ACAID function.

This is the precise reason for formation of "favourable" conditions for *in situ* intensification of autoimmune reactions in the post-surgery period under conditions of infringed integrity of the lens capsule and baring of its antigenic determinants; moreover, at complicated cataracts the immune stimulant mechanisms aimed at activation of T-cytotoxic lymphocytes is infringed already at the pre-surgery stage.

The investigation of E.L. Nelson (1976) also signified to the important role of prostaglandins in induction of local inflammatory processes. According to author, different traumatic injuries of the eye are followed with the enhanced synthesis of E_2 and $F_{2\alpha}$ in the iris and other eye tissues, as a result of which the content of mentioned prostaglandins in the aqueous humor is significantly increased. The enhancement of mentioned processes is accompanied with vasodilatation, increased permeability of micro-vessels, and increased protein content in the aqueous humor.

Apart from this, the mentioned author proposed a supposition, according to which at traumatic injuries of the eye leucocytes of inflammatory exudates in the aqueous humor might serve as a source of prostaglandins synthesis.

Furthermore, as considered by the authors, the cascade of molecular and cellular processes at induction of inflammatory process in eye tunics is eventually terminated by the reaction that, to a considerable degree, is conditioned by prostaglandins. On the other hand, the high level of PgE_2 in the aqueous humor, to a known extent, reflects *in situ* formation of protective-adaptive mechanisms – in the aspect of correlation of synthesis processes of specific pro-inflammatory cytokines produced in the post-barrier tunics of the eye as well.

It is a common knowledge that prostaglandins of E and F group inhibit the synthesis of IL I in macrophages and leucocytes. Apparently, the similar mechanism is engaged in post-barrier

eye tunics both at norm and in case of some eye diseases. The following fact signifies in favour of the latter circumstance: at endotoxin-induced experimental uveitis in rabbit despite the expressed inflammatory reaction in post-barrier eye tunics the level of IL-I in the aqueous humor did not increase (Kulkarni P.S., 1991). It is not excluded that PgE_2 serve as a factor preventing the increase of IL-I and IL-II production in immunocompetent cells.

5. The role of transforming growth factor in pathogenesis of cataracts and glaucomas

Nowadays rather informative evidence is available on the role of $TGF_{\beta\text{-}2}$ in the mechanisms of immunological tolerance activation at senile and complicated cataracts. High regional immunological tolerance in eye tunics is ensured through the enhanced $TGF_{\beta\text{-}2}$ synthesis by the cells of eye tunics: ciliary body, cornea, and retina (Stefan C. et al., 2008; Dawes L. et al., 2009; Hindman H. et al., 2010; Pattabiraman P., Rao P., 2010).

It is established that the active immunological tolerance at senile non-complicated cataracts is targeted at activation of T-helper and T-suppressor subpopulations in immune competent cells of the eye; these latter play an important role in prevention of autoimmune reactions aimed to produce antibodies against the lens tissues (Streilein J. et al., 1992; Wilbanks G. et al., 1992).

In the most relief mode the entire cascade of immunological shifts is presented in the aqueous humor of patients with senile and complicated cataracts, as a result of which currently the aqueous humor is considered as a rather informative bio-object characterizing the course of immunological reactions responsible for anterior chamber associated immune deviation (ACAID) formation.

In the specified aspect there are rather informative scientific publications, according to which at senile non-complicated cataracts during the post-surgery period is engaged the similar $TGF_{\beta\text{-}2}$-dependent mechanism that underlies the suppresson of local humoral immunity reactions through *in situ* activation of cytotoxic lymphocytes (Fleenor D. et al., 2006; Streilein J. et al., 1992).

At the same time our own investigation (Zilfyan A., 2009) allowed establishing that unlike senile non-complicated cataracts occurring on the background of glaucoma and pseudoexfoliative syndrome already in the pre-surgery period in eye tunics there originated immunopathological disorders manifested as activation of reactions responsible for antibody formation (high level of CD_4 and IgG in the aqueous humor – on the background of a marked decrease in CD_8 level).

Data obtained signify in favour of the fact, according to which $TGF_{\beta\text{-}2}$-dependent mechanism engaged in ACAID formation is actually not the single one at complicated cataracts (Zilfyan A.A., Zilfyan A.V., 2013).

Thus, our studies revealed that at complicated cataracts in the aqueous humor there is a marked increase of cortisol, prolactin and PgE_2 (Zilfyan A., 2009; 2012). Moreover, high concentrations

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of mentioned hormones and PgE_2 are conditioned by their "non-arrival" from the periphery (as a result of increase in hematoophthalmic barrier permeability), or most likely, as a result of the enhanced synthesis in the eye tunics.

According to the proposed concept, relatively high concentrations of the above-mentioned biologically active compounds might act as endogenous factors activating *in situ* reactions of humoral immunity, because their selective influence towards the immune competent cells T-helpers and B-cellular populations is considered to be established (Goodwin J., Ceuppens J., 1983; McMurray R. et al., 1991; Lahat N. et al., 1993;).

Thus, in cases of complicated cataracts we revealed earlier unknown mediatory mechanisms engaged in launching the humoral immunity reactions, which apart the surgery-related trauma produce rather unfavourable impacts to the course of the regional pathological process.

In the light of data thus obtained, the role of $TGF_{\beta\text{-}2}$ in glaucomatous pathogenesis should be considered from the alternative standpoint. In particular, $TGF_{\beta\text{-}2}$ produced in the cornea and the ciliary body stimulates *in situ* synthesis of insulin-like growth factor-1 (IGF-1) and fibronectin, i.e. precisely those cytokines the excessive concentrations of which are considered as *provoking* factors hindering the normal outflow of the aqueous humor; this latter is fraught with the increase of aqueous humor in glaucoma.

Our previous studies also signify to the existence / presence of the similar $TGF_{\beta\text{-}2}$-dependent mechanism (Zilfyan A., 2013); it was demonstrated that at complicated cataracts on the background of glaucoma and pseudoexfoliative syndrome high concentrations of fibronectin and IGF-1 are determined in the aqueous humor (compared to those recorded in the aqueous humor of patients with senile non-complicated cataract).

Hence, the role of $TGF_{\beta\text{-}2}$ in pathogenesis of cataracts and glaucomas is far from being unambiguous. In particular, on the one hand, in senile non-complicated cataract $TGF_{\beta\text{-}2}$ modulates in the eye tunics processes of active immune tolerance aimed at prevention of autoimmune aggression against the antigenic determinants of the lens; on the other hand,-the same cytokine produced a rather unfavourable impact to the course and duration of glaucomas through its direct and/or indirect impact to the processes of fibronectin and IGF-1 enhanced synthesis in the trabecular meshwork of the eye. The excessive accumulation of both cytokines brings to impaired function of the eye anterior chamber trabecular meshwork, thus eventually accompanied by the increase of intraocular pressure.

On the basis of studies performed, within the entire context of available published data, from the qualitatively new positions we should consider the established, earlier unknown, $TGF_{\beta\text{-}2}$-independent hormonal mediatory mechanisms underlying the abolition of reactions responsible for ACAID formation and the increase of intraocular pressure at complicated cataracts.

6. Conclusion

Currently existing term "immune privilege of an eye" is mostly associated with evolutionary secured mechanisms, which ensure the regional immune homeostasis in eye tunics and in the

eye liquid media both at norm and pathology. In particular, at cataracts in some eye tunics there are engaged mechanisms promoting the "active immunological tolerance" that is selectively targeted against the "bared" (revealed) antigenic determinants of the lens tissues. In modern ophthalmology the symptom complex of immune reactions occurring in eye tunics is defined as "anterior chamber associated immune deviation – ACAID".

Hence, it is considered to be proved that at senile non-complicated cataracts in the post-surgery period there are *in situ* activated immune processes, which manifest as activation of cytotoxic lymphocytes (T-suppressors and T-killers) due to which the "active immunological tolerance" is formed averting the processes of autoimmune aggression against the bared antigenic tissues of the lens.

Based on the evidence of available modern literature and our own research findings new earlier unknown hormonal mediatory mechanisms appear to the proscenium of the stage; those mechanisms at complicated cataracts are responsible for abolition of reactions promoting the ACAID function.

Thereupon, from qualitatively new positions should be considered the role of cortisol, prolactin fibronectin, $TGF_{\beta\text{-}2}$ and PgE_2, which are produced in specific eye tunics, in mechanisms of *in situ* realization of the immune reactions responsible for ACAID formation and abolition. It should be emphasized that all the above-mentioned biologically active substances in case of complicated cataracts (cataracts on the background of anterior open-angle glaucoma and pseudoexfoliative glaucoma) act as "provoking" factors, which take an active part in both impairment of the eye trabecular meshwork drainage function and the increase of intraocular pressure.

At the same time, in complicated cataracts the specified factors might take an active part in abolishing the reactions providing the "active immunological tolerance" through *in situ* activity of cytotoxic lymphocytes and activation of autoimmune processes targeted against the antigenic determinants of the eye tissues and tunics.

Based on the analysis of the available literature and the presented own studies we consider it purposeful to present to the attention of the readers the main regional immune and hormonal-mediatory mechanisms responsible for ACAID formation and abolition in senile and complicated cataracts also depicting them in detail as summary Schemes 1 and 2.

Immune and hormonal-mediatory factors engaged in ACAID formation at non-complicated cataracts are presented as Scheme 1.

During the surgery intervention for phacoemulsification of cataract (PhEC) there occurs baring of antigenic determinants of the lens tissues (BADLT). According to available evidence of scientific publications, 3 mechanisms are engaged in ACAID formation.

The first mechanism is associated with the activation of $TGF_{\beta\text{-}2}$ synthesis in the eye cornea, ciliary body and retina as a result of which there occurs stimulation of cytotoxic lymphocytes (T-ct).

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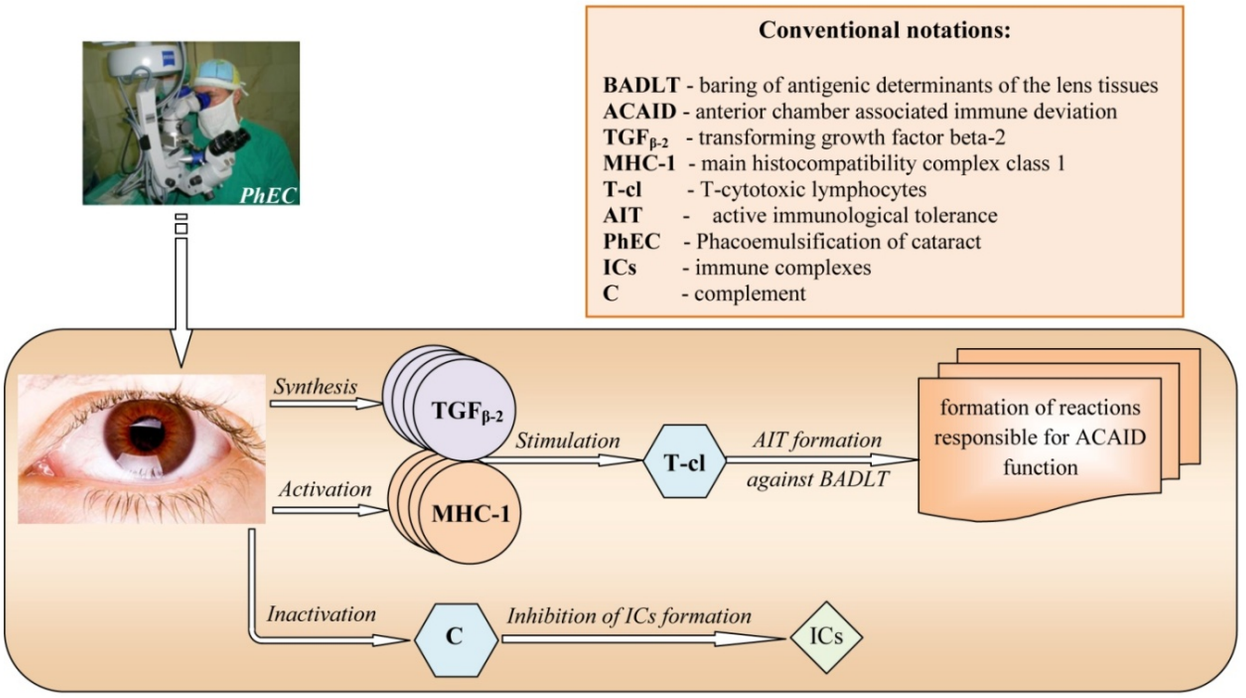


Scheme 1. Regional immune andmediatory mechanisms responsible for ACAID function.

As a result of the targeted stimulation of T-suppressor and T-killer subpopulations there occurs an active immunological tolerance (AIT) against the bared antigenic determinants of lens tissues, in particular through inhibition of activity in T-helper subpopulation of lymphocytes.

The second mechanism is associated with *in situ* activation of the main histocompatibility complex class 1 (MHC-1) with the subsequent activation of T-killer subpopulations.

The third mechanism is associated with *in situ* inactivation of the complement (C); therefore, the formation of immune complexes (IC) does not occur.

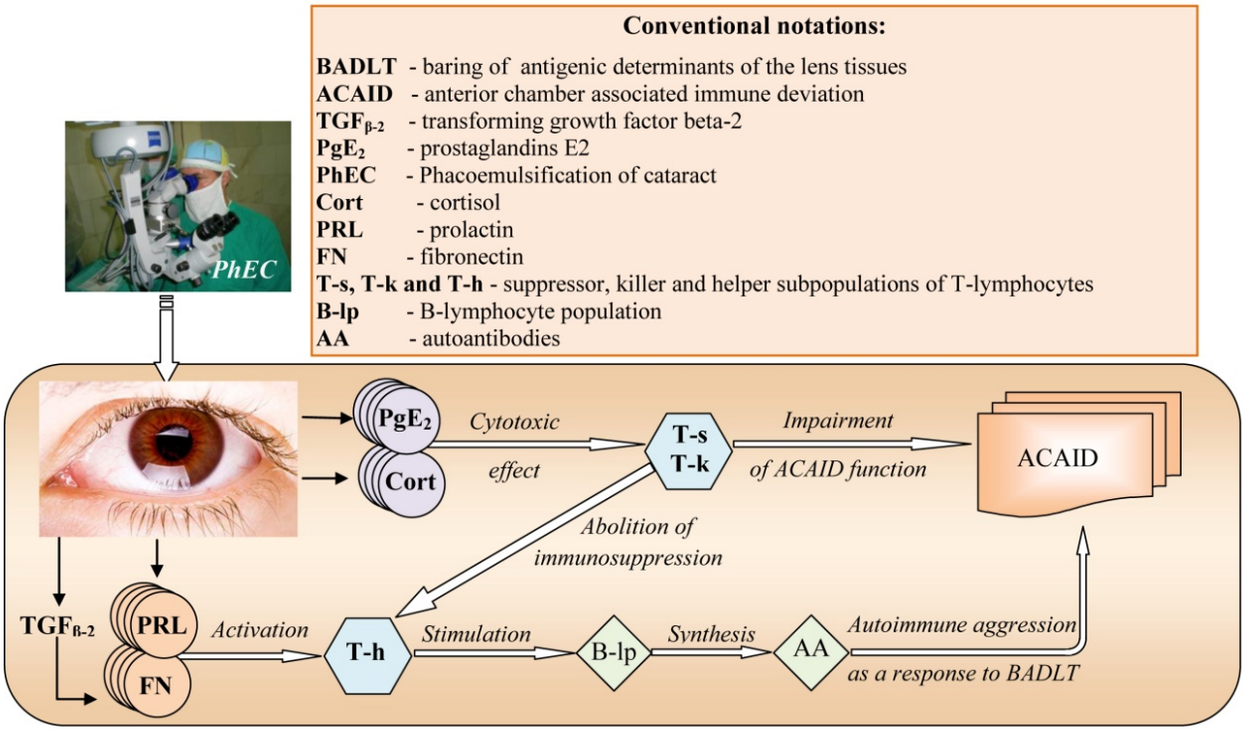
As a result, one of the possible mechanisms of autoaggression is excluded through deposition of the immune complexes on the lens tissues followed by their subsequent impairment.

According to the bulk of scientific data, similar mechanism is engaged in the post-surgery period at senile non-complicated cataracts.

From the result of our investigations we do not exclude that ACAID function is also engaged in cataracts occurring on the background of diabetes mellitus and arterial hypertension, because in both cases the recovery process was without complications, even without the aseptic autoimmune iridocyclitis.

Thus performed, our studies allowed establishing that at specific types of complicated cataracts (cataract on the background of primary open-angle and pseudoexfoliative glaucoma) regional immune mechanisms responsible for ACAID function were impaired (Scheme 2).

Thus, in both cases after the performed phacoemulsification of cataract (PhEC) and baring of antigenic determinants of the lens tissues (BADLT) the aqueous humor levels of cortisol (Cor)



Scheme 2. Regional immune and hormonal mediatory mechanisms responsible for abolishing the ACAID function at complicated cataracts.

and PgE_2 increased. Both factors had unidirectional cytotoxic action towards the specific lymphocytic subpopulations – T-suppressors and T-killers (T-s, T-k). Hence, there occurred the abolition of the immunosuppressive action of those latter to the T-helper subpopulation of lymphocytes (T-h). Against this background we recorded high concentrations of prolactin (PRL) and fibronectin (FN) in the aqueous humor. The FN high level was conditioned by the stimulant influence of transforming growth factor beta-2 ($TGF_{\beta\text{-}2}$) towards the eye cornea cells and the trabecular meshwork. Both factors, prolactin (PRL) and fibronectin (FN), activate T-helper subpopulation of lymphocytes (T-h). As a result of surgery-related impairment of the lens tissues on the background of cytotoxic lymphocytes-abolished suppression there occurs stimulation of T-helper subpopulation that is fraught with formation of autoantibodies (AA) against the impaired tissues of lens followed with their autoimmunoaggrression towards both impaired and "structurally" preserved tissues of lens.

As a rule, such a complication as aseptic autoimmune iridocyclitis developed in the specified contingent of patients during the post-surgery period.

Undoubtedly, the presented Schemes 1 and 2 are not ultimate; moreover, they are not comprehensive. These Schemes should be supplemented (enriched) with new evidence on the role of earlier unknown biologically active substances of immune, hormonal, mediatory genesis, which are produced in eye tunics, in formation of in situ reactions responsible for formation and abolition of the ACAID function.

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References

[1] Abrahamian A., Xi M., Donnelly J., Rockey J. Effect of interferon-gamma on the expression of transforming growth factor-beta by human corneal fibroblasts: role in corneal immunoseclusion. J. Interferon Cytokine Res. 1995; 15(4): 323-330.

[2] Bakunowicz L., Lazarczyk A., Moniuszko T. et al. Levels of selected cytokines in aqueous humor of patients with cataract extraction. Klin. Oczna. 1997; 99(4): 235-237.

[3] Bell P., Munck A. Steroid-binding properties and stabilization of cytoplasmic glucocorticoid receptors from rat thymus cells. Biochem. J. 1973; 136(1): 97-107.

[4] Berczi I., Nagy E., Kovacs K., Horvath E. Regulation of humoral immunity in rats by pituitary hormones. Acta Endocrinol. Copenhagen. 1981: 98: 506-513.

[5] Camelo S., Kezic J., McMenamin P. Anterior chamber-associated immune deviation: a review of the anatomical evidence for the afferent arm of this unusual experimental model of ocular immune responses. Clin. Exper. Ophthalmol. 2005; 33(4): 426-432.

[6] Carr D., Blalock J. A molecular basis for intersystem communication between the immune and neuroendocrine systems. Int. Rev. Immunol. 1989; 4(3): 213-228.

[7] Chong A., Aw S. Postmortem endocrine levels in the vitreous humor. Ann. Acad. Med. Singapore. 1986; 15 (4): 606-609.

[8] Cinatl J., Blaheta R., Bittoova M., Scholz M., Margraf S., Vogel J., Cinatl J., Deorr H. Decreased neutrophil adhesion to human cytomegalovirus-infected retinal pigment epithelial cells is mediated by virus-induced up-regulation of Fas ligand independent of neutrophil apoptosis. J. Immunol. 2000; 165(8): 4405-4413.

[9] D'Orazio T., Niederkorn J. The nature of antigen in the eye has a profound effect on the cytoki milieu and resultant immune response. Eur. J. Immunnol. 1998; 28(5): 1544-1553.

[10] Dawes L.J., Sleeman M.A., Anderson I.K., Reddan J.R., Wormstone I.M. TGFbeta/Smad4-dependent and-independent regulation of human lens epithelial cells. Invest. Ophthalmol. Vis. Sci. 2009 Nov; 50(11): 5318-5327. Epub 2009 Jun 10.

[11] Duenas Z., Rivera J., Quiroz-Mercado H., Aranda J., Macotela Y., Montes de Oca P., Lopez-Barrera F., Nava G., Guerrero J., Suarez A., De Regil M., Martinez de la Escalera G., Clapp C. Prolactin in eyes of patients with retinopathy of prematurity: implications for vascular regression. Invest. Ophthalmol. Vis. Sci. 2004; 45(7): 2049-2055.

[12] Fleenor D., Shepard A., Hellberg P., Jacobson N., Pang I., Clark A. TGFbeta2-induced changes in human trabecular meshwork: implications for intraocular pressure. Invest. Ophthalmol. Vis. Sci. 2006: 47(1): 226-234.

[13] Fu T., Yang P., Huang X., Zhou H., Li F., Huang Q. Preventive effect of anterior chamber associated immune deviation on endotoxin-induced uveitis. Zhonghua Yi Xue Za Zhi. 2004; 84(18): 1562-1566.

[14] Goodwin J.S., Ceuppens J. Regulation of the immune response by prostaglandins. J. Clin. Immunol. 1983; 3(4): 295-315.

[15] Hindman H.B., Swanton J.N., Phipps R.P., Sime P.J., Huxlin K.R. Differences in the TGF-{beta}1-induced profibrotic response of anterior and posterior corneal keratocytes in vitro. Invest. Ophthalmol. Vis. Sci. 2010 Apr; 51(4): 1935-1942. Epub 2009 Nov 11.

[16] Jacob E., FitzSimon J., Brubaker R. Combined corticosteroid and catecholamine stimulation of aqueous humor flow. Ophthalmology. 1996; 103: 1303-1308.

[17] Kasavina B., Ukhina T., Churakova T. Distribution of labeled cortisol in the tissues and media of the eye. Bull. Exp. Biol. Med. 1977; 83: 401-402.

[18] Kawakami M., Nakata J., Ohguro N., Yoshihara S., Inoue T., Tatekawa T., Ikegame K., Oka Y., Kawase I., Ogawa H. A case of immune recovery vitritis induced by donor leukocyte infusion for the treatment of cytomegalovirus retinitis. Eur. J. Haematol. 2005; 75(4): 352-354.

[19] Kitaichi N., Namba K., Taylor A. Inducible immune regulation following autoimmune disease in the immune-privileged eye. J. Leukoc. Biol. 2005; 77(4): 496-502.

[20] Kulkarni P.S. The role of endogenous eicosanoids in rabbit-intraocular inflammation. J. Ocul. Pharmacol. 1991; 7(3): 227-241.

[21] Kuznik B., Vasiliev N., Zybikov N. [Immunogenesis, homeostasis and non-specific resistance of the organism][published in Russian]. Moscow. Medicina ("Medicine" Publishers). 1989. 320p.

[22] Lahat N., Shitler R., Zlotnik A.Y., Merin G. Early IL-2/sIL-2R surge following surgery leads to temporary immune refractoriness. Clinical and Experim. Immun. 1993 June; 92(3): 482-486.

[23] Lightman S., Towler H. Immunopathology and altered immunity in posterior uveitis in man: a review. Curr. Eye Res. 1992; 11(Suppl.): 11-15.

[24] Lindemann D., Racke K. Glucocorticoid inhibition of interleukin-4 (IL-4) and interleukin-13 (IL-13) induced up-regulation of arginase in rat airway fibroblasts. Naunyn Schmiedebergs Arch. Pharmacol. 2003; 368(6): 546-550.

[25] Martin W., Egan R., Stevens J., Woodward J.G. Lens-specific expression of a major histocompatibility complex class I molecule disrupts normal lens development and induces cataracts in transgenic mice. Invest. Ophthalmol. Vis. Sci. 1995; 36(6): 1144-1154.

[26] Matera L. Endocrine, paracrine and autocrine actions of prolactin on immune cells. Life Sci. 1986; 59(8): 593-614.

[27] McMurray R., Keisler D., Kanuckel K., Izui S., Walker S.E. Prolactin influences autoimmune disease activity in the female B/W mouse. J. Immunol. 1991; 147: 3780-3787.

[28] Muhaya M., Calder V., Towler H. et al. Characterization of phenotype and cytokine profiles of T-cell lines derived from vitreous humor in ocular inflammation in man. Clin. Exp. Immunol. 1999; 116(3): 410-414.

[29] Murray P., Hoekzema R., Luyendijk L., Konings S., Kijlstra A. Analysis of aqueous humor immunoglobulin G in uveitis by enzyme-linked immunosorbent assay, isoelectric focusing, and immunoblotting. Invest. Ophthalmol. Vis. Sci. 1990: 31(10): 2129-2135.

[30] Nelson E.L. Prostaglandins and inflammation in the eye. Review. Mod. Probl Ophthalmol. 1976; 16: 125-130.

[31] Nishi O., Nishi K., Imanishi M. Synthesis of interleukin-1 and prostaglandin E2 by lens epithelial cells of human cataracts. Br. J. Ophthalmol. 1982; 76: 338-341.

[32] Orge Y., Gungor S. Immunological etiopathogenesis of senile and complicated cataract. Microbiol Bul. 1984; 18(3): 145-153.

[33] Patel J.I., Hykin P.G., Cree I.A. Diabetic cataract removal: postoperative progression of maculopathy – growth factor and clinical analysis. Br. J. Ophthalmol. 2006; Jun; 90(6) 697-701. Epub 2006 Mar 15

[34] Pattabiraman P.P., Rao P.V. Mechanistic basis of Rho GTPase-induced extracellular matrix synthesis in trabecular meshwork cells. Am. J. Phys. Cell Phys. 2010 Mar; 298(3): 749-763. Epub 2009 Nov 25.

[35] Pazirandeh A., Xue Y., Prestegaard T., Jondal M., Okret S. Effects of altered glucocorticoid sensitivity in the T cell lineage on thymocyte and T cell homeostasis. FASEB J. 2002; 16(7): 727-729.

[36] Pleyer U., Gupta D., Weidle E., Lisch W., Zierhut M., Thiel H. Elevated prolactin levels in human aqueous humor of patients with anterior uveitis. Graefes. Arch. Clin. Exp. Ophthalmol. 1991; 229(5): 447-451.

[37] Pleyer U., Yang J., Knapp S., Schacke H., Schemes N., Orlic N., Otasevic L., De Ruijter M., Ritter T., Keipert S. Effects of a selective glucocorticoid receptor agonist on experimental keratoplasty. Graefes. Arch. Clin. Exp. Ophthalmol. 2005; 243(5): 450-455.

[38] Podos S.M., Jaffe B.M., Becker B. Prostaglandinsand glaucoma. Br. Med. J. 1972 Oct 28; 4(5834): 232.

[39] Rauz S., Cheung C., Wood P., Coca-Prados M., Walker E., Murray P., Stewart P. Inhibition of 11β-hydroxysteroid dehydrogenase type 1 lowers intraocular pressure in patients with ocular hypertension. QJM. 2003; 96(7): 481-490.

[40] Rauz S., Walker E., Shackleton C., Hewison M., Murray P., Stewart P. Expression and putative role of 11 beta-hydroxysteroid dehydrogenase isozymes within the human eye. Invest. Ophthalmol. Vis. Sci. 2001; 42(9): 2037-2042.

[41] Robinson M., Reed G., Csaky K., Polis M., Whitcup S. Immune-recovery uveitis in patients with cytomegalovirus retinitis taking highly active antiretroviral therapy. Am. J. Ophthalmol. 2000: 130(1): 103-106.

[42] Sawada H., Fukuchi T., Tanaka T. Abe H. Tumor necrosis factor-alpha concentrations in the aqueous humor of patients with glaucoma. Invest. Ophthalmol. Vis. Sci. 2010 Feb; 51(2): 903-906.

[43] Slepova O.S., Gerasimenko V.A. Makarov V.P., Kushnir V.N., Zakharov G.Iu., Bykovskaia G.N., Vartanian I.R., Sadrislamova L.F. [Comparative study of the role of cytokines in different forms of eye diseases. 1. Tumor necrosis factor-alpha][Article in Russian]. Vestn. Ophthalmol. 1998 May-Jun; 114(3): 28-32.

[44] Sonoda A., Sonoda Y., Muramatu R., Streilein J., Usui M. ACAID induced by allogeneic corneal tissue promotes subsequent survival of orthotopic corneal grafts. Invest. Ophthalmol. Vis. Sci. 2000; 41(3): 790-798.

[45] Southren A., Gordon G., Yeh H., Dunn M., Weinstein B. Nuclear translocation of the cytoplasmic glucocorticoid receptor in the iris-ciliary body of the rabbit. Invest. Ophthalmol. Vis. Sci. 1979; 18(5): 517-521.

[46] Stambuk N., Curkovic T., Trbojevic-Cepe M., Dujmov I. Interleukin-4, IgG and oligoclonal IgG in aqueous humor of cataract patients. Graefes Arch. Clin. Exp. Ophthalmol. 1994; 232(2): 103-106.

[47] Stefan C., Dragomir L., Dumitrică D.M., Ursaciuc C., Dobre M., Surcel M. [TGF-beta-2 involvements in open angle glaucoma][published in Romanian]. Oftalmologia. 2008; 52: 110-112.

[48] Streilein J., Stein-Streilein J. Does innate immune privilege exist? J. Leukoc. Biol. 2000; 67(4): 479-487.

[49] Streilein J., Wilbanks G., Taylor A., Cousins S. Eye-derived cytokines and the immunosuppressive intraocular microenvironment: a review. Curr. Eye Res. 1992: 11(Suppl.): 41-47.

[50] Toris C.B., Gabelt B.T., Kaufman P.L. Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction. Surv. Ophthalmol. 2008; 53: 107-120.

[51] Tripathi B.J., Tripathi R.C., Chen J., Gotsis S., Li J. Trabecular cell expression of fibronectin and MMP-3 is modulated by aqueous humor growth factors. Exp. Eye Res. 2004; 78: 653-660.

[52] Uenoyama K., Kanagawa R., Tamura M., Matoba M., Enomoto Y., Ohmi S. Experimental intraocular lens implantation in the rabbit eye and in the mouse peritoneal space. Part IV: Cell adhesion, fibroblast-like cell, and lymphocytic cluster observed on the implanted lens surface. J. Cataract. Refract. Surg. 1989; 15(5): 559-566.

[53] Visser J. Sparing interleukin-10 receptor expression by glucocorticoids is a prerequisite for the synergistic immunosuppressive effects of interleukin-10 and glucocorticoids. Transplantation 2003; 76(10): 1534-1535.

[54] Wilbanks G., Mammolenti M., Streilein J. Studies on the induction of anterior chamber-associated immune deviation (ACAID). III. Induction of ACAID depends upon intraocular transforming growth factor-beta. Eur. J. Immunol. 1992; 22(1): 165-173.

[55] Wilbanks G., Streilein J. Characterization of suppressor cells in anterior chamber-associated immune deviation (ACAID) induced by soluble antigen. Evidence of two functionally and phenotypically distinct T-suppressor cell populations. Immunol. 1990; 71(3): 383-389.

[56] Wordinger R.J., Fleenor D.L., Hellberg P.E., Pang I.H., Tovar T.O., Zode G.S., Fuller J.A., Clark A.F. Effects of TGF-beta2, BMP-4, and gremlin in the trabecular meshwork: implications for glaucoma. Invest. Ophthalmol. Vis. Sci. 2007 Mar; 48(3): 1191-1200.

[57] Yarilin A., Belyakov I. [Thymus as an organ of endocrine system][Article in Russian]. Immunologiya. 1996. P. 4-10.

[58] Zhou Z., He S., Liang Y. An experimental study of pathomorphology in the iris and ciliary body after intraocular lens implantation. Zhonghua Yan Ke Za Zhi. 1996; 32(6): 421-423.

[59] Zilfyan A.A. Modern Aspects of Glaucoma Pathogenesis Local Factors for Development of Primary Open-Angle Glaucoma Associated with Impairment of Secretory Functions of the Eye Membranes. Chapter 5 in: "Glaucoma – Basic and Clinical Aspects". Edited by Shimon Rumelt. INTECH. Croatia. 2013. P. 75-102.

[60] Zilfyan A.A. Shifts in content of fibronectin, insulin-like growth factor-1 and E_2 prostaglandins in aqueous humor in case of senile and complicated cataracts. The New Armenian Medical Journal. 2012; 6(3): 34-41.

[61] Zilfyan A.A. The role of cortisol, prolactin, CD_4 and CD_8 in induction of anterior chamber associated immune deviation (ACAID) in case of cataracts. The New Armenian Medical Journal. 2009; 3(1): 59-67.

[62] Zilfyan A.A., Zilfyan A.V. Hormonal-Mediatory Mechanisms in the Process of Anterior Chamber Associated Immune Deviation. The New Armenian Medical Journal. 2013; 7(3): 85-88.