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HYPOTHESES, THEORIES, CONCEPTS

HORMONAL-MEDIATORY MECHANISMS IN THE PROCESS OF ANTERIOR CHAMBER ASSOCIATED IMMUNE DEVIATION (ACAID)

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ABSTRACT

The given communication presents new data on the role of regional-mediatory mechanisms for formation and inhibition of immune reactions responsible for anterior chamber associated immune deviation (ACAID) making and course.

Until nowadays, the opinion dominates in modern ophthalmology that at induction of in situ immune reactions responsible for ACAID formation at a wide range of eye diseases the key role is attributed to transforming growth factor ($TGF_{\beta-2}$) produced in eye membranes: cornea, ciliary body and trabecular meshwork.

Furthermore, the entire cascade of in situ occurring immune reactions match the concept "active immunological tolerance" exceptionally connected with $TGF_{\beta-2}$-dependent activation of cytotoxic lymphocytes – in response to surgical trauma, as a result of which the antigenic determinants of damaged eye tissues are bared.

On the basis of not numerous, but rather informative scientific data referring to the probable synthesis of a number of biological active compounds, which apart from their main functions possess also the immunomodulatory specter of action (cortisol, prolactin, fibronectin and prostaglandins E_2) in eye membranes, as well as based on our own long-term research findings we propose the concept, according to which the $TGF_{\beta-2}$-dependent mechanism is not the only one in induction of active immunological tolerance. To our mind, in ACAID induction and abolition mechanisms earlier unknown hormonal-mediatory mechanisms are also engaged, functioning in eye membranes on the principles of paracrine-autocrine reciprocal regulation and conditionality.

KEYWORDS: *cataract, glaucoma, $TGF_{\beta-2}$, prolactin, cortisol, fibronectin, prostaglandins E_2, pathogenesis, eye immune privilege, lymphocytic indices.*

Unlike other histohematic barriers the hemato-ophthalmic barrier is practically impermeable for many biological active substances.

This circumstance for years made the scientists consider that in the post-barrier eye membranes of mammals evolutionary formed mechanisms are engaged to regulate regional immune homeostasis. At the same time, during the last fifty years new rather informative data were obtained regarding the immune processes occurring in eye membranes and thus ensuring the protective mechanisms towards the "hidden" antigenic determinants in post-barrier tissues of the eye [*Orge Y., Gungor S., 1984; D'Orazio T., Niederkorn J., 1998; Sonoda A. et al., 2000; Camelo S. et al., 2005*].

In the modern fundamental ophthalmology the entire cascade of *in situ* engaged immune reactions is defined as an "anterior chamber associated immune deviation (ACAID) syndrome".

Without reference to specific details, generally these reactions, *per se*, are of protective-adaptive character in response to surgical trauma, as a result of which the antigenic determinants of damaged eye tissues are "bared".

These reactions are considered from the stand-

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point of "active immunological tolerance" and underlying processes of selective stimulation of suppressor and killer sub-populations of lymphocytes [*Murray P. et al., 1990; Fu T. et al., 2004; Kitaichi N. et al., 2005*]. Due to *in situ* activation of cytotoxic lymphocytes, in immune competent cells localized in eye membranes the induction processes of specific autoantibodies against the antigenic determinants of damaged eye tissues are inhibited [*Wilbanks C., Streilein J., 1990; Muhaya M. et al., 1999*].

It should be emphasized that till nowadays, the opinion dominates in modern ophthalmology that transforming growth factor ($TGF_{\beta-2}$) acts as stimulator of cytotoxic lymphocytes in eye membranes [*Stefan C. et al., 2008; Dawes L. et al., 2009; Hindman H. et al., 2010; Pattabiraman P. et al., 2010*].

At the same time, recent studies revealed that in certain eye membranes – both at norm and at a wide range of eye diseases – there occurs synthesis of a number of biological active compounds, which apart from their main functions in the mammalian organism possess also the immunomodulatory specter of action

Cortisol, prolactin, fibronectin and prostaglandins E_2 make the matter of consideration. In particular, as a source for cortisol synthesis the cells of conjunctiva, cornea, ciliary body [*Jacob E. et al., 1996*] come, for prolactin – cells of retina and the anterior chamber of an eye [*Pleyer U. et al., 1991*], for fibronectin – cells of corneal membrane and the trabecular meshwork [*Wordinger R. et al., 2007; Hindman H. et al., 2010*].

As to prostaglandins E_2, their local synthesis in eye membranes was not finally revealed. However, in some eye tunics, in sclera and ciliary body, receptors to prostaglandins E_2 were found [*Toris C. et al., 2008*], thus allowing their involvement in sustaining the local hormonal-mediatory homeostasis.

Our previous studies revealed that at senile and complicated cataracts, already at the pre-surgery stage, the presence of cortisol, prolactin, fibronectin and prostaglandins E_2 in intraocular humor was confirmed [*Zilfyan A., 2009; 2012; 2013*].

We should emphasize that in case of the complicated cataracts the matter is cataract proceeding on the background of anterior open-angle glaucoma and pseudoexfoliative glaucoma, at which levels of the above-named biologically active compounds were much higher than those determined by us in intraocular fluid of patients with the senile uncomplicated cataract.

We propose a hypothesis, according to which regional hormonal-and-mediatory shifts at cataracts play an important role in mechanisms of abolishing the reactions responsible for formation of ACAID.

Cortisol and prolactin: Since at ACAID T-suppressor and T-killer subpopulations of lymphocytes act as the enabling link to control immunological resistance of post-barrier membranes of an eye, it is possible to make an assumption, according to which the balanced level of cortisol in the anterior chamber of an eye is one of the mechanisms providing a regional immune homeostasis. At the same time under conditions of pathology, in our precise case at the complicated cataracts proceeding against primary glaucoma and pseudoexfoliative glaucoma, the high level of cortisol found by us in intraocular fluid can act as a factor leveling the active immunological tolerance by direct alterational influence on T- and B-lymphocytic populations.

To our opinion, in abolishing the immunological reactions responsible for formation of ACAID a certain role has to be assigned to prolactin as well, because prolactin is known to activate processes of antibody generation in a dose-dependent way through the selective stimulation of T-helper subpopulations and B-lymphocytic populations [*McMurray R., et al., 1991*; *Lahat N. et al. 1993*].

Hence, in the mechanism of abolishing ACAID at cataracts, especially in case of complicated cataracts, the important part, in our opinion, has to be assigned to *in situ* produced cortisol and prolactin, which can act as the provoking factors engaged in induction of autoimmune processes even during the pre-surgical period, i.e. in conditions when the post-operational traumatic factor is not involved.

Fibronectin: It should be noted that the role of fibronectin in pathogenesis of ACAID was not considered at all. At the same time, it is known that in mammalian organism fibronectin, apart the modulatory influence on reparative-proliferative processes of connecting tissue, activates T-helper and B-lymphocytic populations thus leading to activation of humoral immunity reactions [*Kuznik V. et al., 1989*]. Considering that at ACAID abolishing the synthesis of antibodies is activated in eye membranes, it is not excluded that fibronectin, along with other locally

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developed biologically active substances, takes part in formation of humoral immunity reactions in post-barrier membranes of an eye.

Prostaglandins E_2: It is considered to be old-established that pleiotropic effects of prostaglandins E_2 extend to the immune system as well. In particular, prostaglandins E_2 in the organism of mammals render the expressed suppressive effect on cytotoxic lymphocytes [*Goodwin J., Ceuppens J., 1983*]. For this reason, it is not excluded that under conditions of eye pathology, and, first of all, complicated cataracts, in the general cascade of reactions testifying in favor of abolishing ACAID, prostaglandin-dependent mechanisms are also involved.

Thus, on the basis of own research it is possible to make an assumption, according to which in mechanisms of abolishing reactions responsible for ACAID formation, especially at complicated cataracts, the important role has to belong to *in situ* developed cortisol, prolactin, fibronectin and prostaglandins E_2. Apparently, $TGF_{\beta\text{-}2}$-dependent processes of ACAID induction and abolition should not be considered as the only mechanism. Hormonal-mediatory loops, the activity of which is realized according to the paracrine-autocrine mechanism, are also involved in these processes.

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