THE INFLUENCE OF INFLAMMATION IN POSTERIOR CAPSULE OPACIFICATION DEVELOPMENT

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UTICAJ INFLAMACIJE U RAZVOJU OPACIFIKACIJE ZADNJE CAPSULE

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ABSTRACT

Cataract represents the reduction of the transparency of the crystalline lens. Cataract surgery is the most commonly performed surgical procedure worldwide. One of the most common postoperative complication of successfully performed cataract surgery is a development of posterior capsule opacification (PCO). In the postoperative period, lens epithelial cells (LECs) undergo proliferation, migration and differentiation, which is clinically manifested by the development of PCO. Inflammation has a central role in these processes. Cytokines, such as transforming growth factor β , fibroblast growth factor, interleukin 1, interleukin 6, matrix metalloproteinases have a huge effect on the activity of LECs. Understanding these processes can find a great usage in clinical practice. By prescribing anti-inflammatory therapy in the early postoperative period, the incidence of PCO can be significantly reduced.

Keywords: Posterior capsule opacification, inflammation, anti-inflammatory therapy.

SAŽETAK

Katarakta predstavlja smanjenje providnosti kristalnog sočiva. Operacija katarakte je najčešće izvođena hirurška procedura širom sveta. Jedna od najčešćih postoperativnih komplikacija uspešno izvedenih operacija katarakte je razvoj opacifikacije zadnje capsule sočiva. U postoperativnom periodu epitelne ćelije sočiva podležu proliferaciji, migraciji i diferencijaciji, što se klinički manifestuje razvojem opacifikacije zadnje capsule sočiva. Inflamacija ima centralnu ulogu u ovim procesima. Citokini, kao što su transformišući faktor rasta β , fibroblastni faktor rasta, interleukin 1, interleukin 6, matriks metalo-proteinaze imaju ogroman uticaj na aktivnost LEC. Razumevanje ovih procesa može naći veliku primenu u kliničkoj praksi. Propisivanjem antiinflamatorne terapije u ranom postoperativnom periodu, incidencija PCO se može značajno smanjiti.

Ključne reči: Opacifikacija zadnje capsule, inflamacija, anti-inflamatorna terapija.

ABBREVIATIONS

CAM - cell adhesion molecules
EGF - epidermal growth factor
FGF - fibroblast growth factor
HGF - hepatocyte growth factor
IOL - intraocular lens
IL 1 - interleukin 1
IL 6 - interleukin 6
LEC - lens epithelial cell

MMP - matrix metalloproteinase
PCO - posterior capsule opacification
PDGF - platelets derived growth factor
TGF β - transforming growth factor β
 α SMA - alpha-smooth muscle actin

INTRODUCTION

Cataract represents the reduction of the transparency of the crystalline lens (1). Today, cataract is considered to be the most common cause of blindness in the world (2). The most common cataract type is the senile cataract which begins to develop above 65 years old. The difference in metabolic processes determines whether senile cataracts will become clinical in each individual (3). Besides senile there are other forms of cataract: presenile, traumatic, iatrogenic, pathological, complicated. These forms of cataract occur due to the effect of various risk factors such as ophthalmic and systemic diseases, gene mutation, trauma, ultraviolet and beta irradiation, alcohol consumption, smoking, increased body mass index (4-6). Depending on the pathogenetic mechanism the most common clinical types of cataract are nuclear, cortical and subcapsular (5).

The most pronounced symptom of cataract is a decrease of visual acuity (7). Patients describe it as a gradual weakening of vision, more pronounced in intense light due to pupil constriction. Cataracts increase the refractive index of the lens, causing lenticular myopia. Intense blurring of the lens nucleus with a transparent peripheral cortex sometimes causes the appearance of monocular diplopia (Figure 1) (8). Decreased contrast sensitivity and glare are also symptoms which are associated with the cataract development (9).

Figure 1. Senile nuclear cataract

The only efficient way of cataract treatment is the surgical way. Cataract surgery is the most commonly performed surgical procedure worldwide (10). Last few decades a surgical technique for crystalline lens aspiration is based on the use of a probe with ultrasonic energy. This technique is called phacoemulsification (11). In this way, extraction of the blurred crystalline lens and implantation of an artificial intraocular lens (IOL) is performed quickly, easily, under topical anaesthesia, without haemorrhage and suturing. Phacoemulsification significantly improved postoperative recovery of the visual function, as well as reduced the incidence of complications of cataract surgery (12). However, even this

method is not completely risk-free and can be accompanied by numerous intraoperative and postoperative complications (13). One of the most common postoperative complication of successfully performed cataract surgery is a development of posterior capsule opacification (PCO) (14).

POSTERIOR CAPSULE OPACIFICATION

The incidence of PCO depends of surgical technique, material and design of IOL, patient's age, presence of ocular and systemic comorbidities (15). In different studies the incidence of PCO development varies from 7 up to 50 % (16).

Even using phacoemulsification, as the most superior cataract surgery technique, it is impossible to remove all the lens epithelial cells (LECs). In the postoperative period, these cells undergo proliferation, migration and differentiation, which is clinically manifested by the development of PCO (17). Due to the decrease in visual acuity, PCO is also called secondary cataract (18). Inflammation has a central role in these processes.

In the postoperative period, residual LECs proliferate, migrate and differentiate to form clusters of oval, balloon cells, called Wedl cells (19). Their diameter is usually 0.5–1.0 mm. Clinically, this form of posterior capsule opacification is called Elshing pearls (Figure 2) (20). Each pearl is considered to be a failed attempt to synthesize a lens fiber.

Figure 2. Posterior capsule opacification

In the formation of PCO the three most important processes are proliferation, migration and differentiation of LECs (17). Proliferation is most pronounced in the first weeks after cataract surgery. Factors that potentiate the inflammatory reaction are the residual lens cortex, the dispersion of the iris pigment, as well as numerous pro-inflammatory cytokines released by the breakdown of the blood-ocular barrier during the cataract surgery (14). An additional

inflammatory stimulus, in the form of the body's response to a foreign body, is an intraocular lens implanted in the capsular bag (21).

Cytokines, such as transforming growth factor β (TGF β), fibroblast growth factor (FGF), epidermal growth factor (EGF), platelets derived growth factor (PDGF), hepatocyte growth factor (HGF), interleukin 1 (IL 1), interleukin 6 (IL 6), matrix metalloproteinases (MMPs), have a huge effect on the activity of LECs (18). However, a numerous number of studies suggest that TGF β and FGF play a central role in PCO formation (16,17, 22).

The concentration of TGF β in the aqueous humour decreases during the first two postoperative weeks, after which it returns to preoperative values and is maintained until the end of the first month (23). A possible cause of this is the breakdown of the blood-ocular barrier and the extravasation of $\alpha 2$ macroglobulin (19). The concentration of this macroglobulin is increased in the first days after cataract surgery and it is believed that it neutralizes the effect of TGF β . During those two weeks, the concentrations of FGF and other growth factors are increased. Decreased TGF β concentration is believed to potentiate inflammation and proliferation, due to the inhibitory effect that TGF β has on the proliferation of LECs (23, 24). TGF β acts on LECs by inducing their epithelial mesenchymal transition, leading to the formation of an extracellular matrix.

TGF β is a serine-threonine kinase, a member of the growth factor family, which affects the proliferation and differentiation of different cell types in the body. This enzyme is synthesized in activated macrophages, fibroblasts and keratinocytes (25). The active form of TGF β is a 24 kDa dimer. The dimer consists of two linked disulfide polypeptide chains each of 390 and 412 amino acids. TGF β isoforms are TGF $\beta 1$, TGF $\beta 2$, TGF $\beta 3$ (26). The enzyme TGF β inhibits the growth of epithelial cells in the body, but on the other hand potentiates the division of mesenchymal cells. It is also an important factor in the synthesis and remodeling of the extracellular matrix, so TGF β is considered to play a key role in the wound healing process. The TGF $\beta 2$ isoform is most abundant in the anterior segment of the eye. Lens epithelial cells have the ability to synthesize TGF β . These cells also possess receptors for TGF β indicating the autocrine effect of TGF β on LECs (27). The researcher, *Zhu* measured the concentration of TGF β in aqueous humor in humans. He found that it was 1598.89 ± 583.75 pg / mL (28).

Fibroblast growth factor, along with TGF β , is thought to be probably the most important factor in PCO formation (21). By composition, it is a polypeptide that affects the proliferation and differentiation of different cell types of origin from all three leaf germs (8). It is also present in the lens and participates in its development. The increased concentration of FGF in the first month after cataract surgery indicates its role in the formation of PCO (19). FGF directly stimulates the proliferation of LECs as well as collagen synthesis by these cells (20).

Interleukin 1 is a mediator of intercellular interaction within the immune system (14). It also acts as a signal mediator between the immune system and other organ systems. It is synthesized by activated monocytes, lymphocytes, macrophages, fibroblasts (15). Released, IL 1 triggers a whole range of inflammatory reactions and the synthesis of new mediators. IL 1 acts on LECs causing their proliferation and collagen synthesis (22). Under the action of interleukin 1, prostaglandin E2 is also synthesized, which additionally intensifies inflammation (29). This can be used in clinical practice to reduce the development of PCO by the use of cyclooxygenase blockers.

During the inflammatory phase of PCO development, the proliferation of LECs is controlled by stimulatory and inhibitory factors. TGF β inhibits the proliferation of LECs, while proinflammatory cytokines stimulate it (23). With the exception of TGF β which is decreased, the concentrations of all other growth factors are elevated during the first two postoperative weeks, so LECs are subject to proliferation (30). At the end of the second week, the concentration of TGF β reaches preoperative values, and the effect of other growth factors is suppressed.

The migration and then the adhesion of LECs to the posterior capsule of the lens is enabled due to the adhesive molecules located on the surface of the LECs. These molecules belong to the integrin family. The best known are cell adhesion molecules (CAM) and CD44 receptors (31). Fibronectin and collagen type IV are an integral part of the lens capsule. In vitro studies showed that the adhesion of LECs is inhibited on a medium containing type IV collagen and fibronectin by the addition of a monoclonal antibody to CAM (32). From this it can be concluded that, after cataract surgery, the adhesion of the LECs to the posterior lens capsule is performed exactly through the CAM. Also, the use of antibodies to CAM in clinical practice can have an inhibitory effect on the development of PCO (23). Metalloproteinase matrix also plays an important role in the migration of LECs. This family consists of just over 25 proteolytic enzymes that degrade the extracellular matrix (33). After cataract surgery, MMPs facilitate the migration of LECs by degrading the extracellular matrix. In this way, they emphasize the development of PCO (34). On the other hand, matrix metalloproteinase inhibitors are also present in the body. Their activation inhibits the migration of LECs, which makes it difficult to develop opacification of the posterior lens capsule. As with CAM antibodies, the use of MMP inhibitors can be used in prevention of PCO formation (35).

Lens epithelial cells have a dual ability to differentiate, normal and abnormal. By normal differentiation, oval, bubble cells are formed from them, building an Elshing's pearly structure. Abnormal differentiation of LECs leads to epithelial mesenchymal transition and myofibroblast formation. They are elongated, spindle-shaped, and contain the protein alpha-smooth muscle actin (α SMA), which is thought to give them contractile characteristics (36). Myofibroblasts deactivate synthesizing of collagen type IV and begin to produce

abnormal amounts of extracellular matrix proteins: collagen type I, collagen type III, fibronectin, chondroitin sulfate, keratan sulphate (37). As a result of this process, a fibrous plaque forms under the anterior lens capsule. Due to the presence of α SMA in myofibrils, fibrous plaque can cause the posterior lens capsule to wrinkle (38). FGF reduces α SMA expression, thereby antagonizing the effect of TGF β .

CONCLUSION

The treatment of the developed PCO includes the usage of YAG laser to create a perforations on the posterior lens capsule (39). This procedure, although routine, is not completely risk-free and can have numerous complications. Therefore, investigators agree that the best treatment of PCO is its prevention (28, 29).

In preventing posterior capsule opacification many methods and medications were used. A correction of preoperative risk factors, improvement of surgical techniques in order to remove as many lens epithelial cells as possible, implantation of IOLs designed to represent a barrier of LECs' migration (32) (33). However, thanks to a good knowledge of the PCO pathogenesis, the use of anti-inflammatory drugs in the early postoperative period can be considered the standard of modern cataract surgery.

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