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Shared Triggering Mechanisms of Retinal Regeneration in Lower Vertebrates and Retinal Rescue in Higher Ones

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1. Introduction

Neural retina (NR) of the eye of vertebrates is underlined by retinal pigmented epithelium (RPE). NR↔RPE interconnection is critical for development, regeneration and function of both compartments of the retina. A disturbance of the normal quantitative correlation of RPE cells and photoreceptors, their structural and functional integrity unavoidably breaks visual cycle and induces retinal pathology. The majority of retinal diseases - inherent, age-related or systemic, links with a disturbance of NR↔RPE relationship.

In the lab NR↔RPE disintegration can be achieved under some experimental conditions, such as NR separation and explantation, elimination of photoreceptors by bright light, chemical or mechanical damage of RPE and photoreceptors, and etc. A usage of experimental models in studies on the retina of lower and higher vertebrates endows a lot for understanding of cellular and molecular mechanisms of retinal pathology, on one part, and natural mechanisms of its rescue, on the other.

In tailed amphibian (Urodela) complete removal of NR or NR artificial detachment leads to RPE cell transdifferentiation that two months later results in regeneration of functioning retina (Chiba & Mitashov, 2007; Grigoryan & Mitashov, 1979; Hasegawa, 1958; Mitashov, 1997; Stroeva & Mitashov, 1983). In mammals RPE-based NR regeneration has not been reported. It is well known that NR detachment causes serious complications and blinding diseases despite of switching on some protective mechanisms for NR rescue (Fisher et al., 2005; Fisher & Lewis, 2010a, b; Pasto, 1998). This review represents an attempt to study early cellular and molecular mechanisms triggering NR regeneration in amphibians and NR rescue/pathology in mammals.

RPE of all vertebrates being localized between choroidal coat and NR has a big range of very important functions. RPE protects NR photoreceptors against overabundant light, participate in visual cycle, releases growth factors, regulates ion balance, transports nutrients, etc. (Strauss, 2005). In development RPE and NR have a common origin and both derived from the neuroepithelium of the optic cup. The latter delaminates into two layers, NR and RPE. Differentiation of these two tissues is a result of the expression of complex molecular network that is recently named the "*oculome*" (Lachke & Maas, 2010). In the

development as well as in the adult state both retinal tissues are in precise, well coordinated interconnection. On the outer side of the eye RPE is separated from vascular (choroid) and scleral coat by Bruch "membrane" that is formed by basal membranes of RPE and choroidal endothelium (fig.1).

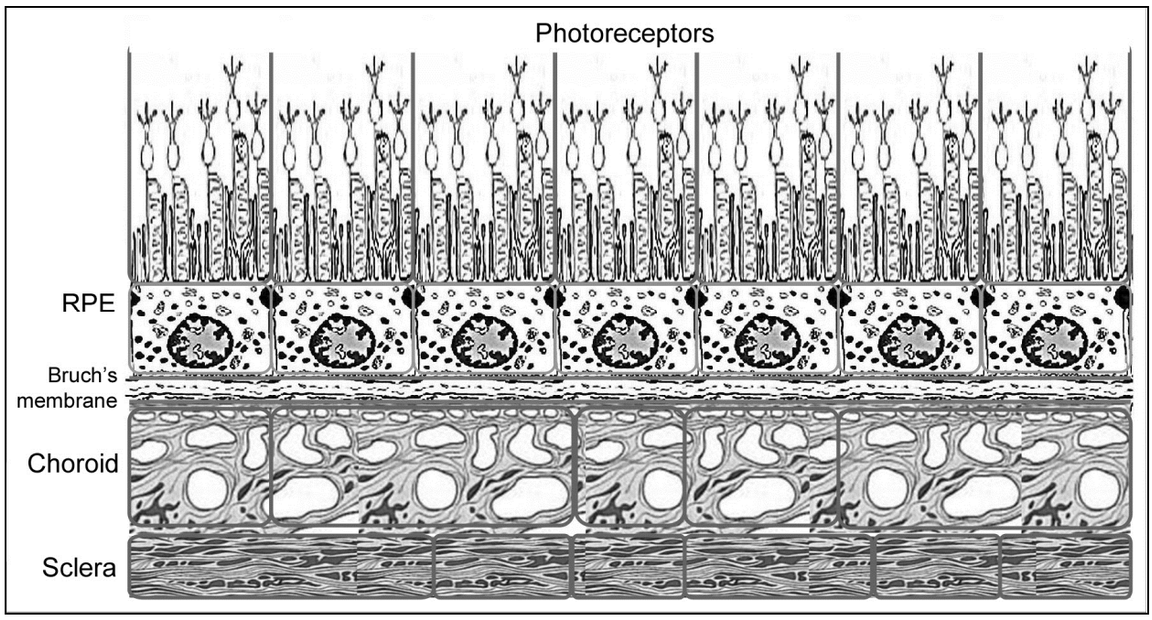

Fig. 1. Retinal pigmented epithelium interplay with other tissues of the eye back wall. Schematic representation, modified from: Strauss, 2005

In this review we concentrated on the early cellular and molecular events induced by disturbance of NR↔RPE interconnections. We should point out that even the very early changes induced by NR↔RPE separation are complex and effect not only on RPE and NR but also other tissues of the eye back wall. Inner part of NR: interneurons, Müller glial cells and ganglion cells, although somewhat later, undergo changes in their function and behavior as a response for alterations in the outer NR. In this review we do not consider these, secondary in time course, processes.

Initiation of retinal regeneration in Urodela and its rescue in mammals as well as progress of following events are represented by comprehensive processes, in which different molecular families and signaling pathways participate. These molecules introduced by NR as well as adjoining tissues, and, in particular by RPE, play important, controlling, and regulative roles. The study of the complexity of intercellular and intertissue communications requires approaches using animals whose RPE↔NR disintegration does not lead to retinal loss but, in contrast, induces epimorphic regeneration. These approaches allow us to understand what kind of molecular changes are introduced by RPE and NR and what subsequent cellular and molecular events they are able to induce. As we'll see the changes initiating retinal regeneration in lower vertebrates and retinal rescue in higher ones have a high degree of universality. This gives us a hope for an existing preservation of some regenerative responses in evolutionary row and not complete block of them on the top, in human.

2. Results and discussion

2.1 A disturbance of retinal cell contacts and behavior

One of the earliest events caused by NR↔RPE separation is the loss of the adhesion and communication between two tissues. Adhesion of NR to RPE is provided by interaction of the RPE apical processes with the outer segments of the photoreceptors. An adhesion force between NR and RPE is ensured by constant elimination of water from the subretinal space. The latter remains closely tight in the normal retina and is essential for retinal functions and visual processing (Ghazi & Green, 2003; Marmor, 1993). The interface between RPE and NR is the interphotoreceptor matrix (IPM) that serves for chemical cross-talk between two tissues for their coordinated function. IPM consists of ECM components but a disruption of them often causes NR detachment. For instance, when IPM chondroitin 6-sulfate proteoglycan is perturbed *in vivo* by intravitreal injections of xyloside (a sugar inhibited chondroitin sulfate proteoglycan synthesis), shallow NR detachment could be observed. This suggests that adhesion between NR and RPE is dependent on continuous presence and synthesis of IPM proteoglycans (Lazarus & Hageman, 1992). Moreover, there are evidences that IPM molecules responsible for adhesion have a neuroprotective effect as well. For instance in the rat galectin-3, participating in RPE↔NR adhesion, inhibits apoptosis through the bcl-2 or cysteine protease pathways and, in contrast, intravitreous injection of anti-galectin-3 antibody accelerates photoreceptor degeneration due to constant light (Uehara et al., 2001).

IPM disruption, subsequent weakening or even loss of RPE lateral contacts and attachment to NR and Bruch membrane, induces a change of RPE cell behavior. In parallel, after NR detachment when part of photoreceptors degenerate a large amount of their debris overwhelm the phagocytic ability of the RPE cells. As a response for altered conditions RPE manifests their multipotential capacity. After retinal removal in newts RPE cells stop to synthesize melanin and increase their proliferative activity (Grigoryan & Mitashov, 1979). In the same animals after NR detachment RPE also can display the unique capacity to transdifferentiate into retinal cells and to form new additional NR (Grigoryan & Mitashov, 1985) (fig. 2).

Another of known differentiation potencies of urodelean RPE is the transformation to mobile cells with many of the characteristics of macrophages. The observation was made long time ago in the course of NR regeneration after retinal removal or optic nerve cutting in the newt (Keefe 1973) and in the case of NR experimental detachment in mammals (Johnson & Faulds, 1977). In those early works it was shown that after NR removal in Urodela some RPE cells withdrawn from the layer, moved along vitreal direction and phagocytosed retinal cell remnants (figure 3a, b). Due to this ability they were named “melanophages” (Keefe, 1973). Something comparable was carrying out in the rodent models of NR detachment (figure 3 c, d). When NR was separated from RPE in the rat and rabbit, epithelium underwent a phenotypic change resulted in the formation of macrophages.

The morphology of RPE cell conversion to macrophages was well described by electron microscopy (Johnson & Faulds, 1977). Nowadays using organotypic 3D culturing of the posterior sector (RPE+choroids+sclera) of the rat eye we found that RPE also gave rise to macrophages: double nuclei cells, morphologically different from typical monocytes, and expressing macrophage-specific antigenes (Grigoryan et al., 2007; Novikova et al., 2010b). Alternatively or additionally, the RPE of mammals can proliferate and then participate in the formation of multilaminar layer of cells with characteristics of mesenchimal ones in

connective tissue. The process of RPE transition to myofibroblasts is an attribute of well known ocular fibrotic disease, proliferative vitreoretinopathy (Saika et al., 2008).

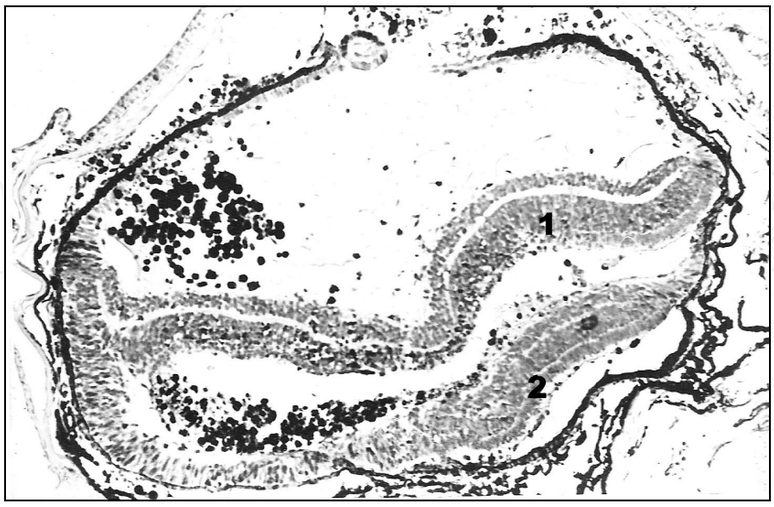

Fig. 2. Growth of additional neural retina (2) derived from RPE after detachment of the initial one (1) in the adult newt.

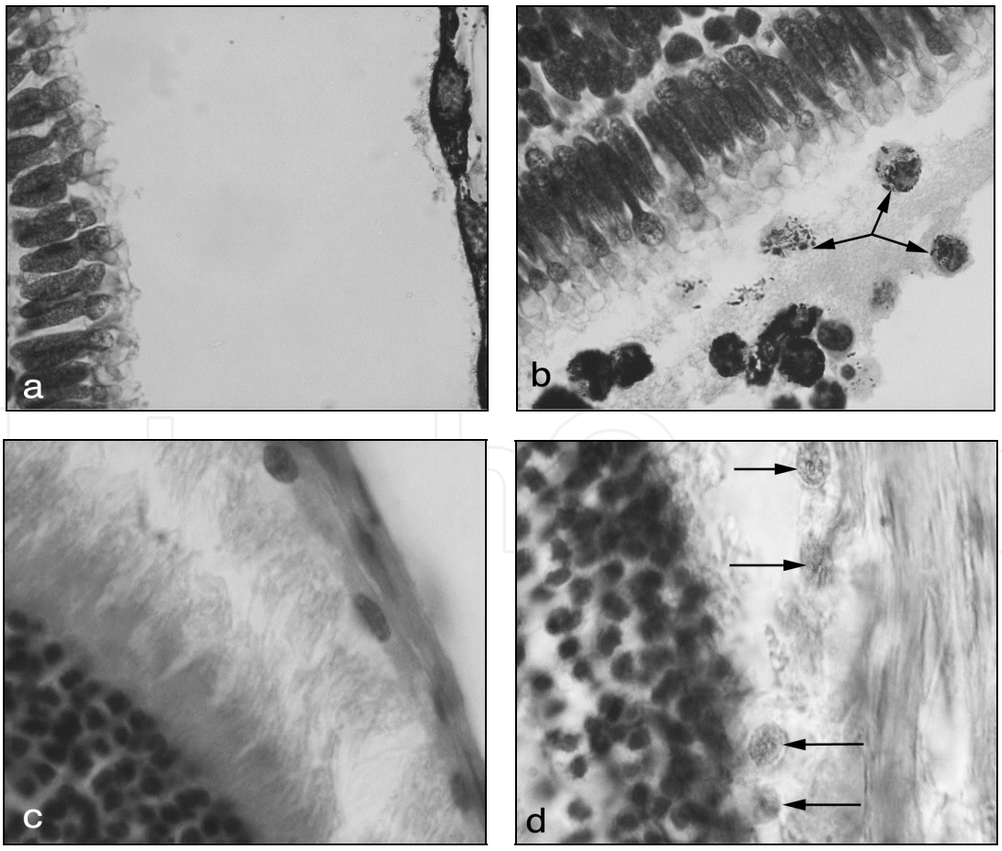

Fig. 3. Detachment of the neural retina in the newt (a,b) and albino rat (c,d) eye. In both cases RPE cells (arrows) withdraw from the layer and migrate in the vitreous direction.

Pigmented macrophage-like cells of RPE origin may be seen in a wide variety of pathological processes affecting the interface between NR and RPE. As we mentioned above a stimulus to cellular activity in the RPE is a loss of the milieu stabilizing RPE differentiation. Such an influence produced by adjacent tissues now finds explanations in terms of molecular biology. Various molecules, as like as: Na-K-ATPase, soluble component of the IPM interphotoreceptor retinoid binding protein (IRBP) (Duffy et al., 1993; Gonzalez-Fernandez, 2003), mucin-type components of IPM for the retinal adhesion, and the serum-type ones for the transport of metabolites (Uehara et al., 1991), are suggested to play a role in the maintenance of intact photoreceptor-RPE complex. In other words, in outer retina cell-to-cell and tissue-to-tissue contacts are participants of the maintenance of retinal integrity and destruction of which leads to NR cell death and RPE cell type transformation both in lower and higher vertebrates.

2.2 Visual cycle disturbance and apoptosis

Another event taking place soon after RPE↔NR separation is a disturbance of visual cycle. In the norm the latter represents a complex of biochemical reactions for regeneration of visual chromophore 11-*cis*-retinal from all-*trans*-retinol. It is well known that visual cycle is based on the renewal of photoreceptor outer segment disks. In this process disks are newly built from the base of the segments, at the connecting cilium and then, at the tips of the outer segments they are shed from the photoreceptors. Shed disks are phagocytosed by the RPE cells where they are digested. *Retinal* undergoes the RPE-specific part of visual cycle and then is redelivered as *11-cis-retinal* to photoreceptors (Bok, 1993). This interaction is essential for maintaining not only the visual function, but also structural integrity of photoreceptors. The processes of disk shedding, phagocytosis, and chromophore renewal must be tightly coordinated between RPE and NR photoreceptors. After disturbance of RPE↔NR interconnection caused by different reasons - from inherent to acquired pathology - the visual cycle gets unavoidably disturbed and brings a part into initiation and following progress of eye diseases.

Recent molecular biology studies of NR detachment suggest an essential inhibition of genes coding visual cycle proteins. “Genomic response” (Rattner et al., 2008) after NR detachment was studied in comprehensive analysis of changes in transcript abundance in the murine RPE. In that work all RPE transcripts coding visual cycle components (Rpe65, Lrat, Cralbp, Rdh5, Rdh10, and Rbp1) showed down-regulation. In parallel, an increase of a small set of transcripts for secreted proteins and cell surface receptors were registered. In accordance with Rattner and co-workers (2008) the decrease in RPE transcripts coding for the visual cycle proteins could be a protective strategy of retinal cells in conditions of detachment when slowing the light-dependent cycling of retinoids takes place. In this case the damage response of the RPE showed similarity to that described for the NR. In particular, a fraction of certain transcripts (e.g., *Cebpd*, *Osmr*, *Serpin a3n*) is induced in both tissues (Rattner & Nathans, 2005).

Meanwhile, there are numerous data suggested a decrease of the expression of particular components of visual cycle. Thus, in human IRBP (interphotoreceptor retinoid- binding protein) principal for transport of visual cycle proteins is down-regulated after NR detachment associated with diabetes retinopathy (Garcia-Ramirez et al., 2009). When we compared RPE in the intact eye and RPE soon after NR removal in Urodela we found by

PCR a considerable decrease of RPE65 transcript abundance (Avdonin et al., 2008). Other results strongly suggest that RPE65 in the RPE-derived cells of early retinal regenerate in Urodela is the only reminder after protein degradation or discharge (Chiba et al., 2006).

When RPE and NR are disintegrated, there is not only a decrease of visual cycle protein synthesis but also protein translocation into the inner compartments of photoreceptors. We observed the phenomenon not at once in experiments on the model of NR detachment in the newt *in vivo* or in isolated NR under conditions *in vitro*. In those experiments we used recoverin (the protein involved in calcium-dependent regulation of rhodopsin phosphorylation) as a marker protein of photoreceptors (Grigoryan, 2007; Grigoryan et al., 2009; Krasnov et al., 2003; Novikova et al., 2010a). In both cases: *in vivo* after NR detachment and *in vitro* newt retina retained the ability to express recoverin but its immunoreactivity was displaced from the segments to perikarya and even axons of photoreceptors. As suggested by Liljekvist-Larsson et al. (2003) who observed the same phenomenon in cultured retina of newborn rats, the synthesis of recoverin in the cytoplasm of retinal cells continues, but the transport of its newly synthesized molecules within the cell is impaired. It seems in vertebrates a decrease of expression of visual protein genes and a change of synthesized protein location in RPE and photoreceptors is the characteristic closely related with RPE↔NR separation.

One more event in cohort of those induced by experimental NR separation is an activation of mitochondrial DNA synthesis in retinal photoreceptors. Recently we showed that in the rat NR isolated from RPE and cultivated "whole amount" in 3D conditions *in vitro* the intensive incorporation of DNA synthesis precursor (BrdU) is localized in photoreceptor inner segments - cell compartments extremely rich with mitochondria (Novikova et al., 2010b). We believe that increased synthetic activity of mitochondrial DNA in photoreceptors is an attempt of photoreceptor cells to rescue and avoid apoptosis. It should be also noted that there are some other mechanisms, for instance protein degradation, taking a part in the decrease of the expression or content of visual cycle proteins in RPE and NR after loss of these tissue integrity.

A suppression of biochemical machinery of visual cycle in RPE and NR undoubtedly affects their vitality and differentiation stability. Disturbance of visual cycle and/or other RPE↔NR co-reactions lead to photoreceptor cell apoptosis. This can be a result of accumulation of photochemically active molecules and ROS which in the absence of regular visual cycle trigger an apoptotic cascade. Apoptosis includes a formation of AP-1 complex (transcription factor) and up-regulation of genes coding apoptotic enzymes – caspases (Reme et al., 2003). An evaluation of the possible induction of RPE cell apoptosis by transforming growth factor-beta (TGF-beta) was undertaken by Esser and colleagues (1997). Proapoptotic effect of TGF-beta was well demonstrated in cultured human RPE cells by electron microscopy, in situ DNA end labeling, comet assay, and a photometric enzyme immunoassay for histone associated DNA fragments. In Urodela the occurrence of apoptosis following ablation of the retina was examined by an in situ technique for detecting DNA fragmentation. It was shown that apoptosis occurs not only just after retinal removal but at the initial phase of NR regeneration as well. Authors of the work (Kaneko et al., 1999) came to a conclusion that the apoptosis is closely related to the phenomena of retinal regeneration in Urodela. Therefore, at the early time subsequent to NR↔RPE separation, both in Urodela and in mammals, the programming cell death is one more of

cellular responses to destroyed RPE↔NR communication in the retina. However, it's necessary to note that NR detachment from the RPE does not lead to immediate death of the cells and retinal apoptosis is a secondary event conditioned by a number of processes initiated just after NR↔RPE separation (Moriya et al., 1986).

2.3 Changes in vascular and immune systems

In the eye of vertebrates, RPE and NR represent a structural unit that acts only in case when two tissues are interactive. Other tissues of the eye back wall, namely Bruch membrane and choroidal coat underlying RPE, also endow retinal integrity and function (figure 1). It is known that vascular occlusion, thrombus formation, accumulation of fibrinopeptides and inflammatory associated cells and proteins all are participants of many eye diseases accompanying RPE↔NR separation. In our experiments on Urodela when eye surgery was applied for retinal removal the occlusion of choroidal small vessels, an inflammation, and a decrease of a tension of the eye back wall tissues represented the very first events that brought later to RPE cell-type conversion, cell proliferation, and withdrawal from the layer (Grigoryan & Mitashov, 1979). Recently it was shown that in newts the thrombin (a participant of hemostasis and other immediate responses to any damage) pretends to be a regulator of iris cell transdifferentiation (Imokawa & Brockes, 2003; Imokawa et al., 2004). It is known that thrombin derives from prothrombin when activated by coagulation factors and, in particular, by transmembrane protein TF (tissue factor). In the work of Godwin and co-authors (2010) it was found that TF expression correlates topologically and in the time course with lens regeneration. TF and other molecules responsible for clot formation are pretending now to be initiators of tissue regeneration in lower vertebrates. In urodelean amphibians the role of complement system was proposed also in limb and lens regeneration (Kimura et al., 2003) and recently in the chick in retinal regeneration (Haynes et al., 2010). It is not inconceivable that comparable mechanism participates in triggering of retinal rescue in mammals. On the other hand, activated leucocytes associated with TF/thrombin/fibrin system can be also important participants in the initiation of NR epimorphic regeneration in amphibians and NR rescue in mammals. It is proposed (Song et al., 2010) that soon after damage they can be a source of FGF, the key role of which in NR regeneration and rescue is discussed below.

In mammals similar changes in vascular and immune systems can be induced experimentally or come out from eye diseases. For instance, there are data obtained by proteomic analysis of subretinal fluid and vitreous body of patients suffered with retinopathy of different kind and NR detachment, in particular. Authors found an increase of the content of fibrinogenic and inflammatory associated proteins for all types of pathology (Shimata et al., 2008). There are data suggested tPA (tissue plasminogen activator) may be involved in remodeling of the extracellular milieu during eye development (Collinge et al., 2005). tPA was found at the apical interface between the developing RPE and NR and then began to down-regulate once the photoreceptors have differentiated. Therefore, tPA as well as other components of the fibrinolytic system can be involved in regulation of the processes subsequent to retinal tissue disintegration, and specifically ECM changes (see below).

2.4 Expression of growth factors and major signaling pathways

Anatomic and functional relationship between NR, RPE and RPE underlying tissues (Bruch membrane, choroidal coat) is consistent with the idea that signals pass between tissues for

coordinated processes in the eye back wall. The RPE secretes a variety of growth factors that support photoreceptor survival and ensure a structural basis for optimal circulation and nutrients' supply (Campochiaro, 1993). One of the signal molecules released by RPE is PEDF (pigment epithelium-derived factor) that plays a broad spectrum of developmental and neuroprotective roles (Tombran-Tink et al., 1995). In particular, it was shown that PEDF can act as an antiangiogenic factor that inhibits endothelial cell proliferation in the choriocapillaris. VEGF is another vasoactive factor of RPE known as preventing endothelial cell apoptosis (Saint-Geniez et al., 2009). In a healthy eye, PEDF and VEGF are secreted at opposite sides of the RPE cell. At the apical side PEDF acts on neurons and photoreceptors but the majority of VEGF is secreted to the basal side where it acts on the choroidal endothelium. It was found that the balance between PEDF and VEGF is disturbed in the early course of retinopathy. Thus, in subretinal fluid of patients suffered with early PVR the concentrations of both factors essentially increase changing a normal balance where PEDF counteracts to angiogenic potential of VEGF (Dieudonné et al., 2007). It is important to note that, as a rule, NR↔RPE disintegration is accompanying by oxidative stress that, in turn, induces a decrease of PEDF correct level (Ohno-Matsui et al., 2001).

In response to retinal damage or injury RPE also secretes the row of neuroprotective factors including those of FGF, CNTF, IGF, and TGF families, all of which are included in the regulative network of the eye and retina (for review: Strauss, 2005). For instance, many extracellular stimuli have been proposed to induce an increasing of VEGF secretion. This signaling exploits growth factors such as IGF-I that can contribute to a pathway in which photoreceptors can stimulate VEGF secretion by RPE cells. Fibroblast growth factor basic (FGF2) is one of several agents that elicits most profound effects in RPE and NR cells. Since 90s the role of FGF2 in RPE transdifferentiation and NR regeneration after RPE↔NR separation in adult amphibians and bird embryos is received the intensive study (Araki, 2007; Mitsuda et al., 2005; Park & Hollenberg, 1993). In accordance with the data including our own, FGF2 and FGF2R coupled with that of transcription factor Pax6 control urodelean RPE cell dedifferentiation and proliferation after NR removal (Avdonin, 2010; Chiba & Mitashov, 2007). FGF-FGFR-MEK cascade and Pax6 up-regulation depended on changes of the cell-ECM and/or cell-cell interaction are supposed important for realization of the first steps of NR regeneration (Avdonin, 2010; Susaki & Chiba, 2007). In the *in vitro – in vivo* like systems it was shown that cells of isolated RPE could be induced to faster dedifferentiation by additing of FGF2 to culture medium (Ikegami et al., 2001; Novikova et al. 2010b).

In mammals, soon after NR detachment FGF2 gene up-regulation also takes place in parallel with high expression of FGF receptors (FGFR) (Hackett et al., 1997; Ozaki et al., 2000). When the retina is perturbed, significant changes occur in the expression of FGFR1 by photoreceptors: FGFR1 immunoreactivity increases rapidly (in 24 hours after injury) and steadily (Ozaki et al., 2000). That appears to be accompanied by similar increase of FGF2 in the IPM. Ozaki and co-workers suggest that this describes a paracrine mechanism: FGF2 is released or activated after retinal injury and then binds to FGFR1 on photoreceptor target cells. The latter, in turn, initiates an intracellular cascade that "protects" the cells from further damage.

The study of the effect of light, various types of stress, neurotrophic factors, and cytokines on FGF2 levels in human RPE cultured *in vitro* showed that many agents of photoreceptor protection (for instance, BDNF, CNTF, IL-1β) can up regulate FGF2 mRNA in RPE cells. An

increase in FGF2 protein level was demonstrated by ELISA in RPE cell supernatants after incubation with BDNF or exposure to intense light or oxidizing agents. These data indicate that in RPE cells FGF2 is modulated by stress and by agents that provide protection from stress (Hackett et al., 1997). In addition, it was found that FGF2 immunoreactivity in the interphotoreceptor matrix tends to increase during first 24 hours after retinal detachment in the rat. It is proposed that the interphotoreceptor matrix has its own endogenous local source(s) of FGF2 (Ozaki et al., 2000). Therefore, it is possible to consider that in both cases, at the initiation of NR regeneration in amphibia and NR rescue in mammals, FGF2 signaling pathway participate in neuroprotection and regulation of RPE cell differentiation and proliferation.

Other signaling pathways, as like as IGF-1, CNTF, and TGFβ represent also a part of the molecular network, regulating RPE and NR cell behavior after separation of these tissues in mammals. However, for today there are only few data on their activity in NR regeneration in Urodela. There is the evidence that IGF-1 (as like as FGF2) can accelerate proliferation and proneuronal differentiation of amphibian RPE under *in vitro* conditions (Yoshii et al., 2007). Meanwhile, proapoptotic growth factor TGFβ more likely plays prohibitive role in RPE cell type conversion. Activin, a TGF-β family signaling protein has been shown to contribute to the loss in competence of the RPE to regenerate retina. Sakami and co-authors (2008) have found that additing of activin blocked regeneration from the RPE, even when the cells were competent. Conversely, a small molecule inhibitor of the activin/TGF-β/nodal receptors could delay and reverse the developmental restriction in FGF-stimulated NR regeneration in embryonic chicken (Sakami et al., 2008).

Earlier it was shown that TGFβ inhibits proliferation at the vitreoretinal interface after NR detachment in human (Esser et al., 1997). Nowadays the study of the role of TGFβ is carried out on the model of retinal detachment in experiments using mice null for Smad3, TGFβ functional cooperator, a key signaling intermediate downstream of TGFβ and activin receptors. Obtained results showed that Smad3 is essential for the epithelial-mesenchymal transition of RPE cells induced by NR detachment. *De novo* accumulation of fibrous tissue derived from multilayered RPE cells was seen in experimental NR detachment in eyes of wild type, but not in Smad3-null mice (Saika et al., 2004). Activation of several signaling pathways, particularly TGFβ /Smad, was also fixed by Zacks and coworkers (2006). Soon after NR detachment the interleukin-6/STAT, TGFβ-Smad, and stress response pathway (aryl hydrocarbon receptor) – all were transcriptionally and translationally upregulated, suggesting that retina produces survival factors after detachment and that there is a possible cross-talk between up-regulated pathways (Zacks et al., 2006). In sum, knowing of signaling pathways with proliferative and anti-proliferative as well as pro-apoptotic and anti-apoptotic effects is very important, because in both, retinal epimorphic regeneration in amphibian and proliferative retinopathy after detachment in mammals, changes of RPE cell phenotype, cell proliferation and apoptosis take place.

2.5 Up-regulation of heat shock proteins and immediate-early response genes

RPE↔NR disintegration results in the early activation of stress-response genes and specific signaling pathways which may enable retinal cells to survive at the most acute period of time. During NR detachment/regeneration in Urodela and detachment in mammals, heat shock proteins (HSPs) are involved in fast regenerative responses. Our preliminary

(unpublished) results show an accumulation and co-distribution of HSP70, 90 and FGF2 in the NR soon after its detachment in the newt. In the experiments we observed well correlated changes in the intensity of HSPs and FGF2 expression and in the localization of these proteins in the retina. These data preliminary show that besides well known role of HSPs in the protection of newly synthesizing proteins from degradation a regulative link between HSPs and FGF may play a role in triggering of early retinal cell death/survival events. It is interesting also when infected with MC29, a myc expressing virus, the RPE cells in developing eye can be induced to transdifferentiate to neuroretinal epithelium. Beside genes whose work is involved in regulating neuronal differentiation myc also induced a transient expression of Mitf, well-known regulator of the pigmented differentiation (Beche-Belsot et al., 2001). HSPs, growth factors, and mitogen-activated protein kinase (MAPK) signaling are capable of immediate-early response gene up-regulation in different systems. Retinal detachment in the rat results in early up-regulation of genes, coding HSPs, FGF, early emergency genes (c-Fos and c-Jun), and transcription factor AP-1 complex (Faktorovich et al., 1992; Geller et al., 2001). Authors hypothesize that NR detachment causes the rapid release of FGF2 from intra- and/or extra-cellular stores, leading to the activation of FGFR1 and ERK, and proximate induction of c-Fos and c-Jun protein expression in RPE. Up-regulation of these intracellular components linked with FGF expression [HSPs → FGF2→FGFR → ERK&MAPK (MEK) pathway → c-fos&c-jun (AP-I) →] pretends to be an important early step on the way to RPE cell type transformation, migration and proliferation in amphibian and mammals. It is likely that increased AP-1 expression besides entering to apoptosis can regulate a variety of genetic and cellular responses induced by NR↔RPE separation.

2.6 Remodeling of extracellular matrix (ECM) and RPE cytoskeleton

It is quite possible that RPE↔NR separation associated changes of cytoskeleton are involved in regulation of HSPs and AP-1 complex in RPE and NR cells. Our early studies showed fast down-regulation of epithelium-specific intermediate filament expression and up-regulation of pan-neuronal one in RPE soon after NR removal in the newt (Grigoryan & Anton, 1993, 1995; Grigoryan, 1995). Keratins of the cytoskeletal intermediate filaments have been identified immunohistochemically in RPE of the adult newt retina. In conditions of NR surgical removal or complete detachment the expression of keratins markedly decreased. Similar observation has been made immediately after dissociation of the RPE cells isolated from nonoperated newt eyes. The results obtained provide an evidence for the inhibition of cytokeratin expression just after destabilization of RPE cell phenotype. *In vivo* in RPE disappeared cytokeratins were replaced by NF-200 neurofilament proteins that testified an existence of the mechanism responsible for gradual change of cytoskeleton in modified RPE in amphibians.

Changes suggested cytoskeleton rearrangement were also registered in mammalian animal models simulating RPE epithelial-mesenchymal transition specific for NR detachment. It was found that RPE cells lost their initial phenotype, dedifferentiated and acquired mesenchymal migratory morphology and cytoskeleton proteins (Casaroli–Marano et al., 1999). Recently thrombin (see above) pretends to play a promoting role in actin stress fiber formation, an important determinant in eye diseases involving transformation and migration of RPE cells (Ruiz-Loredo et al., 2011). On the other hand cytoskeleton changes in

Kind of events	Prior NR epimorphic regeneration	Prior NR rescue
Disturbance of retinal cell contacts and change of RPE cell behavior	IPM disruption, weakening of RPE cell lateral contacts, RRE cell withdrawal from the layer, high proliferative activity of RPE cells, RPE cell conversion to macrophagal and proneuronal phenotypes	IPM disruption Weakening of RPE cell lateral contacts, RRE cell withdrawal from the layer, low proliferative activity of RPE cells, RPE cell conversion to macrophagal and fibroblast-like phenotypes
Visual cycle disturbance and cell apoptosis	Blockage of melanin synthesis in RPE cells, down regulation of visual cycle proteins, apoptosis of small set of RPE and photoreceptor cells	Up regulation of secreted proteins in RPE cells, down regulation of visual cycle proteins, apoptosis of small set of RPE and photoreceptor cells
Changes in vascular and immune systems in the eye back wall	Possible involvement of fibrinolytic (TF, thrombin) and complement systems in triggering of RPE cell transdifferentiation	Possible involvement of fibrinogenic (tPA), inflammatory associated proteins, and activated lymphocytes at the first stage of NR rescue
Participation of growth factors and major signaling pathways	FGF2, IGF1, TGFβ (activin)	PEDF, VEGF, FGF1,2, CNTF, BDNF, IGF1, IL-1β, and TGFβ
Up-regulation of heat shock proteins and immediate-early response genes	HSP70,90 proteins; *c-Myc* gene	HSPs, *c-Fos* and *c-Jun* genes, AP1-complex
Remodeling of extracellular matrix and RPE cytoskeleton.	Redistribution of fibronectin, laminin stimulating effect on RPE conversion, epithelial–neuronal transition of RPE cells: shift of specific intermediate filaments (cytokeratins → neurofilaments).	Role of laminin and integrins in modulation of RPE cells, epithelial-mesenchymal transition of RPE cells: change in composition of specific intermediate filaments (cytokeratins, vimentin, GFAP).

Table 1. A comparison of known NR detachment-induced cellular and molecular events preceding retinal regeneration in Urodelean amphibians and retinal rescue in mammals

RPE reflect an alteration of cell micro-surrounding. The latter, in turn, is a response for mechanical and chemical changes which are produced inevitably by RPE↔NR separation. Earlier we showed a decrease of fibronectin in Bruch membrane and its redistribution in RPE after NR detachment in the newt (Grigoryan et al., 1990). Similar results were obtained by Ortiz and co-authors (1992): at the beginning of RPE cell transdifferentiation in the eye of the adult newt, fibronectin was the first to appear in the cell border of the newforming neuroepithelium. A dependence of RPE phenotype on changes of ECM was also observed by Reh and co-authors in *in vitro* experiments (1987). They reported that RPE transdifferentiation is profoundly influenced by the substrate on which the cells are cultured. RPE cells plated on laminin-containing substrates frequently were conversed into neurons. Recently some data suggest that interaction of laminins and integrins in Bruch membrane leads to differential behavior of RPE cells in mammals (Aisenbrey et al., 2006).

Degradation of ECM is one more important stimulus for the initiation of RPE cell migration and phenotype transformation. Metalloproteases are known molecules for ECM changes and, vice versa, metalloprotease inhibitors (TIMPs) are factors that stabilize ECM. Mechanical trauma induced by NR↔RPE separation is associated with an increased activity of proteolytic enzymes. To ascertain whether RPE cells release proteases due to mechanical stress special tests *in vitro* were performed by Kain and Reuter (1995). In traction conditions created *in vitro* RPE might release proteases to cut intercellular adhesions in order to escape mechanical strain. Authors suggest that release of proteases from RPE may be involved in the pathology of traction detachment, facilitating the disconnection between RPE and photoreceptor outer segments. In human RPE cultured *in vitro* stromelysin which degrades important constituents of the ECM was found (Schönfeld, 1997). Therefore, the action of lysosomal proteases may change the surrounding that, in turn, can induce further detachment of RPE cells from the basement membrane and initiate RPE proliferation and dedifferentiation under conditions of RPE↔NR separation.

3. Conclusion

In the review we summarized our own and literature data on the early cellular and molecular events taking place after separation of neural retina (NR) from the retinal pigmented epithelium (RPE) in the eyes of vertebrates (Table 1). In amphibians RPE↔NR disintegration leads to the formation of the new NR by means of RPE cell transdifferentiation into retinal cells, while in mammals NR detachment triggers a retinal pathology. A comparison of these two opposite phenomena unexpectedly reveals a similarity of early cell and molecular processes induced by RPE↔NR separation (figure 4). In both cases alterations of RPE cell contacts, changes in cytoskeleton and ECM composition as well as perturbations in blood circulation and immune system can be found. These alterations lead to RPE cell type destabilization, phenotypic transformation, cell withdrawal from the layer, and migration. In parallel, down-regulation of the expression of visual cycle molecules takes place. In contrast heat shock proteins, FGF signaling, immediate-early response genes, and AP-1 complex demonstrate up-regulation. In all animals and in human these, NR detachment associated events represent a limited, universal range of retinal cell responses to the stress. Among them RPE dedifferentiation, proliferation and migration seems most important for both, subsequent NR epimorphic regeneration in amphibians and a progress of detachment induced eye diseases in mammals.

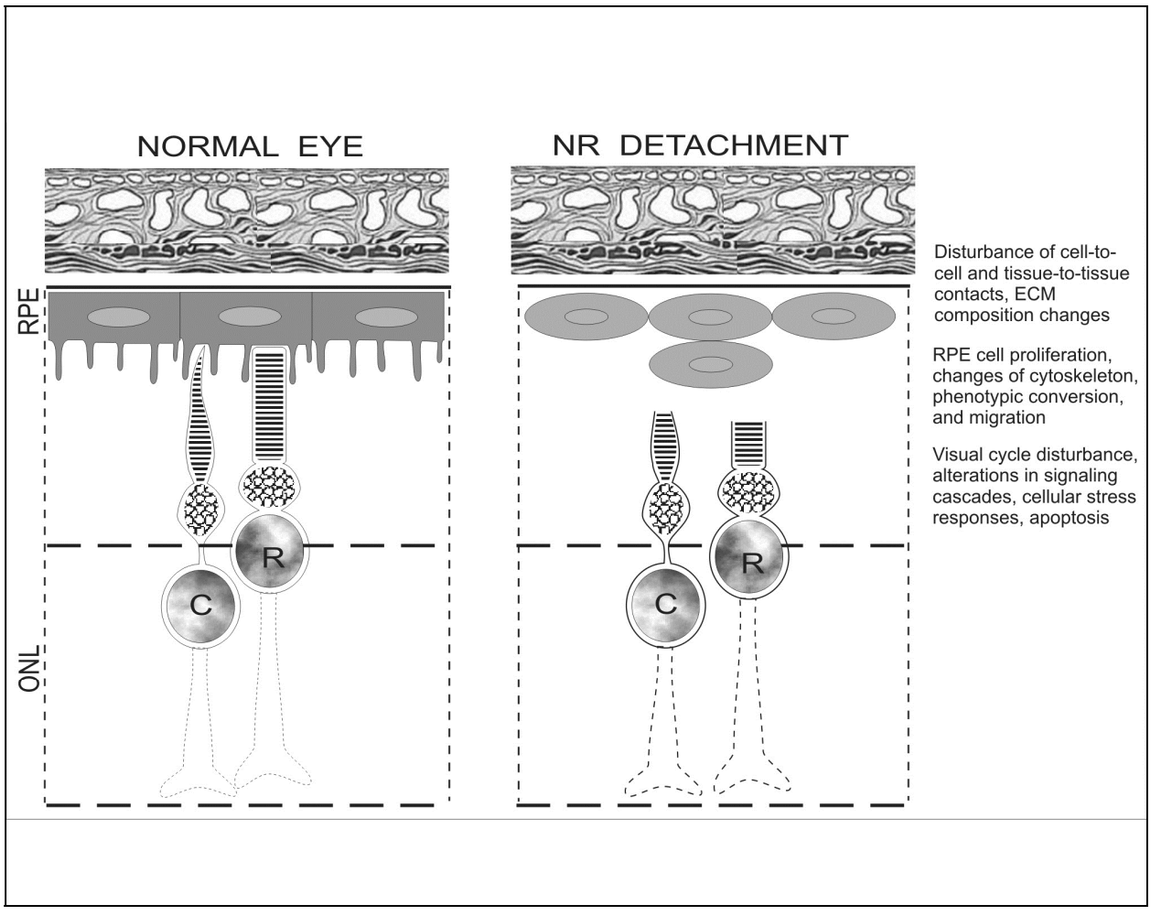

Fig. 4. Main shared processes taking place in the eye back wall soon after neural retina detachment in amphibians (NR epimorphic regeneration) and mammals (NR rescue/pathology). ONL – outer nuclear layer, R – rod, C – cone photoreceptors.

A comparison of initial mechanisms triggering retinal regeneration and retinal rescue/pathology seems efficient. It could be very helpful for understanding why quite similar intrinsic protective responses, occurring at early stages of NR regeneration in amphibians and NR detachment in mammals, give such contrast final results. In regards of this, being based on the accumulated data we can make several suppositions. The first one is the difference in the level of RPE cell differentiation. In Urodela it has some developmental traits whose expression in permissive conditions *in vivo* leads to acquiring of neuronal phenotype. Contrast to amphibians, in adult mammals changes of RPE differentiation *in vivo* imply the epithelial-mesenchymal transition and cell transformation into migrated macrophages, the processes resembling an inflammation and scarring. The second assumption is a difference in the external molecular network, its signals, and cross-talks which regulate RPE cell differentiation in amphibians and mammals. The search of key factors which distinguish detachment induced signaling for amphibian RPE from that for mammalian and human RPE is rather difficult though also necessary step for future work. Finally and more likely, both: RPE cell intrinsic competence (including epigenetic features) and molecular regulation by microsurrounding are different in lower

and higher vertebrates. This difference can be proved in only some characteristics, even epigenetic ones, meanwhile crucial for RPE conversion into neuroepithelium. We can also speculate that cellular and molecular mechanisms which adult amphibians use for initiating of NR regeneration, in evolution have been recruited by higher animals for NR rescue attempts. Answers for these fundamental questions should improve our ability to elucidate the maintaining and pathogenic mechanisms triggered by NR detachment and to facilitate a development of therapies for different types of detachment associated diseases of the eye.

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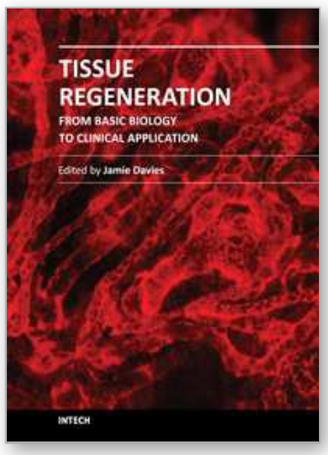

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