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Cell technologies in retinitis pigmentosa treatment

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Abstract

The growing crucial problem in practical ophthalmology relates to growth of hereditary degenerative diseases of the retina, in particular retinitis, causing progressive loss of visual functions. According to international estimates, the incidence rate of hereditary dystrophy contains 1 case per 3000 population. With the development of biomedical cell technologies, transplantation of stem (autologous and allogeneic) cells is at the stage of active research.

The article reviewed literature sources on prevalence, risk factors, etiopathogenesis, diagnosis, clinical picture and treatment of retinitis pigmentosa.

Key words: retinitis pigmentosa, etiology, pathogenesis, diagnosis, clinic, treatment

Introduction

The growing crucial problem in practical ophthalmology relates to growth of hereditary degenerative diseases of the retina, in particular retinitis, causing progressive loss of visual functions [1]. According to international estimates, the incidence rate of hereditary dystrophy contains 1 case per 3000 population [2]. With the development of biomedical cell technologies, transplantation of stem (autologous and allogeneic) cells is at the stage of active research [3].

Recent publications have been devoted to issues revealed the perspectives of applied regenerative medicine, in particular, cell therapy in the treatment of a whole spectrum of ophthalmic pathologies of various etiology, especially in hereditary degenerative diseases of the retina [3].

Retinitis pigmentosa represents the heterogeneous group of hereditary retinal dystrophies resulted by variation of mutations in more than 150 identified causative genes and various types of inheritance (autosomal dominant, autosomal recessive, X-linked), with syndromic or non-syndromic manifestaion [4].

Loss of vision caused by retinitis pigmentosa occurs with initial impaired night vision corresponding with a gradual narrowing of peripheral vision up to blindness in patients of different age groups: infancy, adolescence and maturity [5].

However, pathogenetic mechanism of the development of retinal cell death still remains unexplored, that creates a barrier in the development of an algorithm for therapeutic measures to prevent the progression of visual impairment [6].

As a result, patients face the number of problems: low efficiency of existing treatment methods, disappointing outcome of the disease, forced financial costs for medical services and lifelong rehabilitation measures, issues in professional activity, as well as in psychosocial adaptation in conditions of low vision, which significantly affects the quality of life [7-8]. The issues of significant economic costs rise simultaneously with quality of life fall [5].

The aim is to conduct a literature review of the available international and local scientific sources on the use of cell technologies in the treatment of retinitis pigmentosa.

Genetic research

Significant advances have been made in identifying new genes responsible for retinitis pigmentosa, and further research work in screening patients for genetic mutations continues to this day [9].

Heterogeneity in mutation genetics in more than 60 and 30 genes can lead to the emergence of about 3000 of non-syndromic and 1200 syndromic variations of retinitis pigmentosa, respectively [10].

Despite the variety of genetic prerequisites, retinitis pigmentosa unites a group of diseases occurring with progressive loss of peripheral and subsequent loss of central vision, which is initially caused by dysfunction and loss of rod photoreceptors and secondary death of cone photoreceptors. The difference between syndromic (systemic) and non-syndromic forms of retinitis pigmentosa comes in combination with other neurosensory disorders, ontogenesis abnormalities and phenotypic manifestations: congenital deafness (Asher's syndrome), kidney pathology, obesity, physical retardation and polydactyly (Bardet-Biedl syndrome). Authors cannot reject the appearance of retinitis pigmentosa as a secondary disease against the background of systemic disorders: degenerative changes in the cerebellum, mitochondrial disorders [11]. That makes difficulties in diagnostics due to heterogeneity, both genetic and phenotypic, since a mutation of the same gene can have different clinical manifestations due to allelic mutations and the type of inheritance [1]. Clinically, the general picture manifests the heterogeneity of such mutations: the appearance of "bone bodies" in the peripheral retina, narrowing of blood vessels, and blanching of the optic nerve head [4].

Authors consider progressive loss of photoreceptors as a result of several possible ways of cell death. One is the sufficiently studied mechanisms of programmed cell death is apoptosis [12]. The initiation of apoptosis can be triggered both by internal (activation of the complex: cytoplasmic cytochrome C, activation factor for pesticide protease 1, caspase-9) and external (immune cells, tumor necrosis factor, caspase-8) factors. This mechanism leads to the isolation and elimination of damaged cellular elements with maximum minimization of damage to the surrounding tissue [13,14]. However, there is convincing evidence for the existence of an alternative molecular pathway of cell death without the involvement of caspases [14-16].

One more way referred to as regulated necrosis, involves the destruction of the cytoplasmic membrane. Activation can be due to either stimulation of cell death receptors (necroptosis) or an excess of intracellular iron (ferroptosis) or the activity of poly-ADP-ribose-polymerase (partanatos) [17-22].

Many authors also do not exclude the activation of autophagy against the background of oxidative and metabolic stress. Normally, the lysosome-mediated autophagy mechanism is designed to maintain intracellular homeostasis, thereby performing a protective function [23-25]. In other cases, with serious damage, excessive autophagy can lead to a decrease in cell survival [26].

Authors supported arguments in the development of cell apoptosis in favor of oxidative damage, which may serve as evidence of the effectiveness of further development of antioxidant therapy [24]. Oxidative stress implies state of dysregulation of the balance between reactive oxygen species and the antioxidant defense complex [27-30]. Normally, such oxygen saturation is associated with an active blood supply to the retina, which requires high metabolic and energy costs to perform visual functions. However, with degenerative changes in the retinal cells, oxygen consumption decreases with a constant level of blood supply, which in the future can serve as a supersaturation of oxygen concentration in the interstitial space and cause an increase in oxidative stress in the tissue [31,32].

There are also other assumptions about the impact of other biological dysfunctions that affect the progressive death of photoreceptors, such as metabolic stress, inflammation [33,34].

Thus, the study of possible biological mechanisms of retinal cell degeneration remains unexplored, that requires further researches to develop effective methods of therapy for retinitis pigmentosa [35].

Diagnostic measures carried out to identify genomic abnormalities and the nature of the mutation, are the following: molecular methods, linkage mapping and DNA sequencing [33]. In recent years, the linkage mapping method based on the identification of more than 10 thousand informative markers and related genes linked became worldwide popular. This method allows you to test more than 1 million genetic markers and identify chromosomal mutations. Additional retesting required in case of variants of random "coincidences" of linkage possible due to large number of independent tests [36]. Sanger sequencing and ultra-high throughput (next generation sequencing) are considered the gold standard in detecting mutations at the DNA level [37,38].

Ophthalmology examination of retinitis pigmentosa is based on detecting the causes of genetic mutation, the nature of inheritance of phenotypic traits, with potential detailed study of the patient's family history. Diagnostics examination is performed for registration and subsequent monitoring of progressive visual disturbances: the presence of nyctalopia, pigment "bone cells" along the periphery of the fundus, a decrease in the amplitude of the electroretinogram. In order to record changes in visual functions, instrumental research methods are used: fundus photography, Goldman visual field testing, fundus autofluorescence, optical coherence tomography in the spectral region, electroretinogram [39].

Currently, ophthalmological care for these groups of patients is represented by a limited list of treatment methods with minimal effect, and is mainly aimed at slowing the deterioration of the disease and saving vision, since they do not eliminate the main molecular defect [39].

Significant advances have been made in the study of gene therapy carried out at the stage of preclinical trials: models of induced pluripotent stem cells, experiments on restoration of vision on a natural model of retinal dystrophy in dogs, which have a promising scientific future for further scientific developments [40-42]

At the same time, this direction meets certain complications in the process of implementation of gene therapy for patients. The process registration and approval by the European Commission requires long time together with significant financial costs for both researchers and patients, since the expected cost of treatment can exceed more than 1.5 million US dollars [5].

From one hand, some researchers stated the model of induced pluripotent stem cells has a number of advantages, due to the relatively low cost and potential in detecting retinitis pigmentosa gene mutations in vitro, as well as providing experiments in search of effective drugs. From the other hand, the recreation of the real conditions of biochemical interaction of drugs as on animal or a human model remains uncertain [42-45].

Another promising direction is the use of the model of induced pluripotent stem cells as a source of an unlimited number of cells for the treatment of damaged retina through their transplantation, since the use of embryonic stem cells, photoreceptor precursors, has limitations in matters of ethics and dietology [46,47]. Experimental models of transplantation of induced pluripotent stem cells carried out in animals have demonstrated the presence of similar characteristics with embryonic stem cells in the case of therapeutic use [48].

Overall, gene therapy for retinitis pigmentosa comes as promising innovative area for further study.

Current medical interventions are aimed at slowing the progression of vision loss leading to legal and functional blindness [49]. In general, medical care is implemented by prescribing vitamins with a trophic and antioxidant effect (vitamins A, E), food additives (omega-3 fatty acid, lutein, docosahexanic acid, gangliosides), drugs with a neuroprotective effect (0.2% bromonidine tartrate, ciliary neurotrophic factor), which have a protective effect on photoreceptors [50,51]. Systematic review analized traditional symptomatic treatment and revealed a certain efficacy of therapeutic interventions on indicators of visual function in patients with retinitis pigmentosa [52]. However, the presented methods of treatment, despite the proven safety of their use, have limitations due to their weak effect on a significant improvement in visual functions.

Thus, the search for effective pathogenetically grounded therapeutic interventions remains relevant and requires further consideration the existing genetic heterogeneity of retinitis pigmentosa.

Conclusion

Hereditary degenerative diseases of the retina, including retinitis pigmentosa, lead to progressive visual function. The search for effective methods of treatment remains relevant in view of the insufficient knowledge of the pathogenesis of retinal cell death, and the low effectiveness of treatment methods. The use of cellular and technologies for the treatment of groups of eye diseases is promising and promising.

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