Review

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Insights into Age-Related Macular Degeneration: A Concise Review of Emerging Therapeutic Approaches

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Abstract: Age related macular degeneration (AMD) as the name suggest is the timely degradation of the macular area of the eye which can lead to vision impairment, in particular the central vision. Macular is one of the important areas of the eye, present in the retina which controls our central vision. AMD is one of the most common types of irreversible blindness caused in older population of the society in developed countries. AMD is broadly classified as Dry AMD (Non Neovascular AMD) and Wet AMD (Neovascular AMD). Non Neovascular AMD more commonly known as Dry AMD is less aggressive and is very frequent type of AMD caused, it has three stages 1) Early dry AMD, 2) Intermediate Dry AMD, and 3) Late AMD. One the several therapies used to treat AMD is stem cells where Induced pluripotent stem cells (IPSC's) derived retinal pigment epithelium (RPE) cells was used to treat dry AMD. The use of siRNA that targets Vascular endothelial growth factor (VEGF-A) using different nanotechnology-based delivery system like the organic nanoparticles synthesized liposomes. An upcoming therapy used most widely in recent times is the photodynamic therapy where a photodynamic drug like verteporfin which a benzoporphyrin derivative is used, where the outcome shows great promise in reducing vision loss in wet AMD. This review discusses in details about age related macular degeneration and also its different novel therapies that is been currently used extensively.

Keywords: Age related macular degeneration (AMD); vision impairment; stem cells; nanotechnology; photodynamic therapy

Introduction

Age related macular degeneration (AMD) as the name suggest is the timely degradation of the macular area of the eye which can lead to vision impairment, in particular the central vision [1]. Macular is one of the important areas of the eye, present in the retina which controls our central vision. AMD is one of the most common types of irreversible blindness caused in older population of the society in developed countries [2,3].

AMD is broadly classified as Dry AMD (Non Neovascular AMD) and Wet AMD (Neovascular AMD). Non Neovascular AMD more commonly known as Dry AMD is less aggressive and is very frequent type of AMD caused, it has three stages 1) Early dry AMD, 2) Intermediate Dry AMD, and 3) Late AMD [4].

In Early AMD we find the bruch's membrane thickening and also drusen (made up of proteins and lipids) deposits which is characteristic of early AMD, they can be of various sizes like many small drusen which can be less than 63µm or intermediate sized drusen ranging from 63µm to less than 125µm.Intermediate AMD is mostly caused due to intermediate drusen or large deposits of drusen which can be more than 125µm. Both the Early and the intermediate AMD won't have any clinical evidence indicating AMD [4,5]. Late AMD also classified as the Advanced stage of AMD is mainly

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caused due to the atrophic lesions present in the outer retina which leads to irreversible visual loss [6,7]. This phenomenon is called as Geographic Atrophy. This type AMD is aggressive and lead to loss of the photoreceptors, Retinal Pigment epithelium (RPE) and choriocapillaris. Neovascular AMD (wet AMD) is characterized by the development of abnormal capillaries (choroidal neovascularization) which enters the sub RPE and sub retinal areas due to defects in the bruch's membrane, which can lead to fibrovascular disciform scarring, lipid deposition detachment of the RPE cells, fluid exudation, sub retinal haemorrhage leading to the severe vision loss due to the damage incurred by the photoreceptor [7]. Wet AMD is considered to be more serious and more aggressive due it poorly understood pathogenesis which has restricted the treatment options due to which this type of AMD is hard to treat and is considered to be the common cause of serve central visual loss. Many a times the intermediate and the late stage of Dry AMD can progress to Neovascular Form of AMD which is alternatively called as exudative AMD and is equally serve [5,7].

Early AMD and intermediate AMD isn't that serve comparatively to the other categories of AMD classifies above but it can show some mild symptoms like it blurry vision, need for bright light due to impaired dark adaptation may also need magnification to read, decreased sense in visualizing contrast also vision loss at a moderate level, it may also be asymptomatic. In Late dry AMD and Wet AMD people experience vision loss which starts gradually and later progress to complete loss of the central vision [8].

Retinal Pigment Epithelium (RPE) Cells

The RPE cells are a pigmented monolayer present in between the neuroretina and the choroids. The apical surface facing the photoreceptors and the basolateral surface facing the innermost layer of the choroid the vitreous lamina (Bruch's membrane) [9].

RPE cells Functions include:

- Barrier function: The RPE are made up of blood-retina barriers. These blood-retina barriers are made up of endothelial cells. Tight junctions between these endothelial cells and the RPE cells are essential for control of fluids and solutes that pass through the blood-retina barrier. Also essential for the prevention of toxic molecules into the retina.
- Transport of nutrients such as glucose, ascorbic acid, fatty acids, retinol etc. to the photoreceptors from the blood. RPE also aids in the transportation of electrolytes and water from the subretinal space to the choroid.
- Retina is the only tissue that has persistent exposure to light, this condition aids in the photooxidation of lipids which is toxic to the retinal cells. To avoid such circumstances RPE cells are essential. RPE cells are pigmented cells, which help in the absorption of light and the filtration of specific wavelengths of light. RPE cells also contain antioxidants such as superoxide dismutase which can reduce the high oxidative stress in the retina.
- Various growth factors are produced and secreted by the RPE cells that are essential for the maintenance and integrity of the retina and the photoreceptors.
- To maintain the excitability of photoreceptors, RPE cells function by shedding the outer segment of the photoreceptors by phagocytosis.

Embryonic Stem Cells

(ES cells) are pluripotent cells, which can differentiate into almost all cell types except the placental tissue. Several studies have shown the scope of using ES cells, which can be differentiated into functional RPE cells, for the treatment of Age-related macular degeneration disease. Global gene expression revealed significant similarity between ES cells derived RPE and the RPE cells, such as potential to phagocytose [10,11].

The first clinical trial was performed by Advanced cell Technology (Santa Monica, California, USA) in 2011 , to understand the efficiency of ES cells derived RPE on dry AMD. The clinical trial suggested that ES cells derived RPE cells are safe to use, have no immune rejection and showed improvement in the vision of patients with dry AMD. Further studies on dosage escalation revealed increased vision acuity. Usage of immunosuppressants is considered one of the disadvantages [12].

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IPSCs into RPE Cells

Induced pluripotent stem cell (iPSC) was developed by Yamanka and colleagues in 2006. The combination of transcriptional regulators, octamer-binding transcription factors, kruppel like factor 4, had the ability to derive human or mouse somatic cells into pluripotent cells called iPSCs. Combination of these proteins is termed as the Yamanaka factor. Methods to generate iPSCs have evolved over time and these cells have now become a valuable resource in the area of regenerative medicine and disease modelling [12,13].

These iPSCs derived RPE cells can be used to treat dry AMD (loss of RPE, photoreceptors) as these cells are morphologically similar to native RPE cells and perform the same functions.

The use of iPSCs for cell replacement therapy in humans has several advantages, it presents an opportunity of using autologous cells, avoiding allogeneic cells and immunosuppressants, iPSCs has no ethical concerns like ES cells [12].

Clinical trials using iPSCs derived RPE have been limited. There has been only one clinical trial attempted for the treatment of wet AMD using autologous iPSCs derived RPE cells.

In 2014, a Japanese woman with wet AMD, was treated with autologous iPSCs derived RPE cells, was a success and had no adverse effects. Similarly, a second patient with the same condition when treated with autologous iPSCs derived RPE cells, genetic mutations were identified. However, it's not clear whether the genetic abnormalities were induced during the reprogramming process or from any somatic cells.

Sugita and colleagues worked with cells from Major Histocompatibility complex (MHC) homozygous donors which can be used for the treatment of histocompatible recipients with retinal disease. The goal was to use iPSCs from partially matched donors and to avoid usage of autologous cells for the treatment which could lead to genomic abnormalities. The study showed no immune response or graft rejection and there was no need of any immunosuppressants.

There are still studies going on understanding the tumorigenicity potential of iPSCs derived RPE cells [12,14].

SiRNA Therapy

As discussed earlier that choroidal neovascularization is the characteristic feature of the wet AMD. The choroidal neovascularization and retinal neovascularization are highly dependent on the Vascular endothelial growth factor (VEGF-A), this is what makes VEGF-A a potential target for therapeutics. As per a study done in 2004 [15] it was seen that targeting the VEGF also gives us an added advantage of suppressing the other sub types of the VEGF-B all the way to VEGF- E including the Placental growth factor (PIGF) family which is very crucial. Hence J. *shen and R. Samul and co-workers* [16] used a siRNA path to silence these Growth factors where they used siRNA027 one of the first chemically modified short interfering RNA that was used in targeting VEGF-1 receptors also the Placental growth factors (PIGF) [18]. There were various modifications and enhancement also done to the siRNA to make it stable and to increase its half-life in-vivo of the vitreous and ocular tissues, modifications such as the inversion of the abasic moieties at the 5′ and 3′ end of the sense strand and a 3′ end linkage of the two last nucleotides via a single phosphonothioate linkage of the antisense strand [16,17,19]. The potential of Sirna-027 was evaluated using a luciferase reporter assay which was cultured in HeLa cells [16]. The results concluded that Sirna-027 works by the RNAi mechanism to cleave the vegfr1 sequence also it is highly effective at even low concentrations which lead to the understanding that [16,19]. Now there is a need for an effective and safe delivery systems for these Si RNA with the upcoming development in nanotechnology and novel methods of delivery systems made using organic nanoparticles like lipids (cholesterol) to form liposomes led to the lipid based nanotherapeutics for siRNA delivery. The pros of these lipids-based drug delivery system is that many of these are self-assembled via the electrostatic interactions with the siRNA. The use of Cholesterol based liposomes comes with many other advantages such as it provides protection for, the degradative enzymes such as the RNAses, it increases the Si RNA uptake into the cell as cholesterol play a vital role in the internalization and this has been studied by *James j lu and colleagues*

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which resulted in depleting cholesterol form cells and then transfecting the cells with Si RNA, showed no uptake as compared to the other cells that had cholesterol in them [20].

Photodynamic Therapy

The photodynamic therapy which started long before from the 1960's is still widely been used as a treatment option for various diseases including Neovascular AMD or abnormal proliferation of the endothelia tissue in the back of the eye [23]. This therapy makes use of a photosensitizer (drug), which gets activated when exposed to a light of a specific wavelength, typically used source of light is a laser. After the exposure to the light the photosensitizer becomes toxic to the tissue it is targeted to leading to cell death by apoptosis or the destruction of the cell by necrosis. Earlier this therapy was extensively used for the treatment of cancer but it was seen that it has some effects on the vascular cells hence this led to a series of investigation and research on animal models for the treatment of sub foveal choroidal neovascularization [21]. In the early 2000's the photodynamic drug verteporfin (trade name Visudyne), a benzoporphyrin derivative drug is been approved by the FDA and also been widely hence since. The main ingredient in the in the drug is the benzoporphyrin derivative mono acid ring-A. The drug is a green coloured lyophilized liposome powder which is administered intravenously after infusing it with sterile water for injection. This photosensitizer requires a non-thermal red light to activate it. This type of therapy is considered targeted therapy as the liposomes are selectively localized at the neovascular regions of the eye [23]. The therapy showed great promise in reducing the vision loss caused by wet AMD.

Mitochondrial Dysfunction as a Target

Different mitochondrial drugs like the MTP-131 were used to treat mitochondrial dysfunction in mouse models [24]. It was seen that mitochondrial dysfunction is directly related to the increased subRPE deposit formation which leads to the formation of dry AMD. The use of the MTP-131 drug had a promising response by showing a reversible effect on the signal activating system and biochemical mediator of deposits. Another clinical phase study done showed that elamipretide a small tetrapeptide that targets the mitochondria and reduces the production of toxic reactive oxygen species, proved to be beneficial as out of the patients in the study had intermediate AMD, results was assessed after 24 weeks of treating the patients with elamipretide ophthalmic solution and the outcome showed a mean increase in low luminance visual acuity of 5.4 ± 7.9 letters [25,26]. Even patience with high risk of drusen showed improvements in low luminance.

Conclusion

In conclusion, Age-Related Macular Degeneration (AMD) stands as a formidable challenge confronted by a substantial population of older individuals within our society, leading to consequential vision impairment. While the pathogenic mechanisms underlying AMD are subjects of ongoing extensive study, the diverse pathways involved continue to present a formidable challenge for therapeutic interventions. Early detection emerges as pivotal, particularly in the case of dry AMD, where timely recognition of visual impairment plays a central role in diagnosis and prognosis. Lifestyle factors significantly contribute to the development of AMD, emphasizing the importance of proactive adjustments in this regard. This article has elucidated various therapeutic modalities, offering promising avenues for novel and efficacious interventions in the reduction or potential cure of AMD. However, the translation of these therapeutic strategies from experimental settings to practical clinical applications necessitates rigorous phases of clinical trials and human testing. While the positive outcomes observed in animal models serve as encouraging indicators, there remains a crucial imperative for continued advancements in research. The journey towards bringing these therapies to market for societal benefit requires unwavering dedication to conducting thorough clinical trials. Despite the existing challenges, the optimistic outlook is grounded in the rapid progress witnessed within the scientific community. As we advance in our research

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endeavours, there is a legitimate hope for a better future for patients grappling with Age-Related Macular Degeneration.

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