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Therapeutic Potentials of Mesenchymal and Induced Pluripotent Stem Cell Therapies for Glaucoma

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A B S T R A C T

Glaucoma is a neurodegenerative optic neuropathy and the leading cause of irreversible blindness worldwide. Current clinical treatments are only able to slow the progression of the disease, necessitating research for new, innovative treatment options than currently exist. This review describes the pre-clinically tested and stem cell based methods to treat glaucoma. We will critically discuss the translational prospects of two treatment paradigms:through cell replacement of the retinal ganglion cells (RGCs) or through neuroprotective mechanisms aimed at preventing further degeneration. In addition, this article will examine the intricate techniques employed to differentiate stem cells into RGCs; what researchers have learned about glaucoma through stem cells; and whether the potential for clinical treatment is within reach.

Keywords: Glaucoma, Induced pluripotent stem cells, Retinal ganglion cells, Mesenchymal stem cells, Stem cell therapies.

1. Introduction

Glaucoma is a group of neurodegenerative eye conditions that results in partial vision loss or blindness. It currently affects over 80 million people worldwide and by 2040, this number is expected to reach over 111 million [1]. This optic neuropathy is characterised by the progressive loss of retinal ganglion cells (RGCs), bridging neurons that connect the retinal input to the visual processing centres within the brain. Although the pathophysiology of glaucoma is not well understood, most cases are associated with fluid build-up in the anterior chamber of the eye [4]. Glaucoma's primary issue is associated with increased intraocular pressure (IOP), which causes compression and damage to the optic nerve. Increased intraocular pressure (IOP) is the major risk which happens when the aqueous fluid, responsible for delivering essential nutrients to the cornea and lens, accumulates and cannot drain naturally. In other words, there is a homeostatic imbalance in production and outflow of aqueous humour, which is the fluid produced by the eye. This leads to the death of cells and nerve ganglions in the delicate retina, known as retinal ganglion apoptosis. Moreover, the retina's small blood vessels are compressed, resulting in a lack of nutrients. Currently, hypotensive therapy through pharmacological reagents is the only clinically proven glaucoma therapy [2] however not all patients are responsive to these treatments [3]. Therefore the development and implementation of novel treatments to reverse vision loss due to glaucoma is essential. By developing this research we are guaranteed to learn more about neuronal development, stem cells, axon guidance, ocular immune responses, and visual perception. Our discussion will focus on evaluating the practical implications of two treatment methods that involve cell transplantation: neuroprotection and retinal ganglion cell replacement. In order to advance these approaches towards clinical use, certain obstacles need to be overcome and questions need to be addressed.

2. Stem Cells & Their Potential as Therapies to Treat Glaucoma

2.1 Background

Managing glaucoma can be challenging since each patient presents with different symptoms, causes, risk factors, demographics and prognosis. Presently, the damage caused by glaucoma is irreversible, but regular check-ups and treatment can slow or prevent vision loss, particularly during the early stages of the disease [5]. Lowering intraocular pressure is currently the main treatment strategy. Prescription eye drops, oral medication, laser therapy, surgery, or a combination of these treatments may be used [6]. Typically, the initial course of treatment involves prescribing eye drops that aim to reduce eye pressure by enhancing the drainage of fluid from the eye [6]. Others decrease the amount of fluid the eye makes [6]. Laser therapy and surgery can help drain fluid in the eye and reduce eye pressure, which is achieved through methods such as filtering surgery, drainage tubes and minimally invasive glaucoma surgery [6]. Patients are often prescribed drugs, particularly carbonic anhydrase inhibitors [6]. Selective laser trabeculoplasty (SLT) is gaining popularity as a form of first-line therapy. SLT uses photothermolysis (short pulses of low-energy light) to target pigmented cells of the trabecular meshwork, the drainage canals in the eye [7]. This leads to structural changes within it, causing the endogenous l healing mechanisms of the body to rebuild these cells and increase aqueous outflow. SLT has few postoperative complications, with the most common being ocular inflammation followed

by pain, redness, and an increase in IOP [7]. Currently, lowering IOP is currently the only proven treatment for glaucoma. Some patients, however, still experience progressive visual field loss and decreased quality of life, despite controlled IOP [8]. This indicates that other factors are implicated in glaucoma. Therefore, research into alternative approaches that could prevent and decrease the rate of progression, is gaining attention.

2.2 Stem cells

Stem cells are cells that haven't yet differentiated into a specialised cell, which provides researchers with many possibilities to help patients through personalised medical treatments for glaucoma. The two key methods that are described in this review are cell replacement, used to replace the lost RGCs so they can regenerate nerves, and neuroprotection, which would mean the cells are protected from cell death, preventing the progression of the neurodegeneration. Researchers are interested in stem cells for glaucoma therapy because of their advantageous abilities to differentiate or be reprogrammed into many cell types, including retinal ganglion cells, and their neuroprotective and immunomodulatory properties. Stem cells have low immunogenicity [9], can secrete molecules that promote injury repair and immunomodulation [9], and can be used for intraocular delivery of neurotrophic agents [9]. Also there is the possibility of selective cell replacement of RGCs or other specialised cells within the eye; the neuroprotective and immunomodulatory properties of certain types of stem cells, such as mesenchymal stem cells (MSCs); the bioactivity of factors and molecules secreted by stem cells (the "secretome"); the presumably low immunogenicity, especially for pluripotent stem cells, with roles in injury repair and immunomodulation, with proven therapeutic benefits rather than the integration of stem cells into the host tissue; this prerequisite can be achieved by using extracellular vesicles (EV) or miRNA; the possibility of using transplanted stem cells as intraocular delivery devices for the release of neurotrophic agents, growth factors, survival/ anti-apoptotic factors with a prolonged and localised effect [10]. Preclinical studies using pluripotent stem cells, including embryonic stem cells (ECs), induced pluripotent stem cells (iPSCs) and adult stem cells derived from adult tissues were proposed for translation into human clinical research and application as they have shown promise for glaucoma treatment. Pluripotent stem cells, such as iPSCs, have the potential to differentiate into various cell types and can be maintained in an undifferentiated state for long periods [11]. Generating iPSCs from a patient's own cells can prevent immunological host response and reduce the need for immunosuppression therapy post-transplantation. However, a disadvantage is that genetic and epigenetic instability can lead to the risk of development of teratomas and immunogenicity [12]. MSCs, self-renewing multipotent and post-natal cells [13] found in placenta, foetal tissue, the umbilical cord and adult tissue (bone marrow, adipose tissue, dental tissues, peripheral blood, skin, limbal tissue [14], are capable of modulating the host immune system, express homing receptors, and produce bioactive molecules with trophic and survival roles. They have low immunogenicity, making them a good option for transplantation. [15,16] Stem cell therapy research is being heavily researched for ophthalmic diseases, due to the small number of cells required and the eye being surgically accessible [17]. Still, there are many safety concerns about stem cell transplantation, such as low engraftment, immunogenicity, and the risk of tumorigenesis, which must be properly addressed before human trials. Recent cases of severe vision loss and retinal detachment in patients with age-related macular degeneration who received stem-cell injections highlight the importance of pre-clinical testing that needs to be done before moving directly into human trials. Further in this review, the various stem cell based treatments such as neuroprotection and cell replacement for the treatment of glaucoma are evaluated and judged according to their advantages and disadvantages. [18,19]

3. Differentiation of RGCs from iPSCs Stem Cells

3.1. Current treatments

Currently, available treatments for glaucoma are only effective in slowing down the loss of retinal ganglion cells (RGCs) [20]. However, induced pluripotent stem cells (iPSCs) have the potential to form colonies that are similar morphologically to embryonic stem cells and can differentiate into all three germ layer cell lineages [21]. As somatic cells from a patient can be used to reprogram iPSCs, they can maintain the unique genomic information of that individual. Therefore, patient-derived iPSCs can serve as an excellent in vitro model for genetic disease research, with promising potential to develop personalised treatment. This has led to a plethora of studies aimed at improving the reprogramming efficiency of turning somatic cells in iPSCs and aiding clinical applications. Therefore, iPSCs offer promise as a candidate for cell replacement. This section focuses on the techniques employed to differentiate iPSCs into RGCs, given the limited availability of retinal progenitor cells and absence of self-regeneration in adult mammalian RGCs. iPSCs offer a widely available, ethical and almost infinite source of pluripotent cells, presenting a new approach to stem cell maintenance and differentiation for regenerative medicine. Recent studies demonstrate the potential for iPSCs to differentiate into fully functional RGCs, mimicking natural eye development [22,26]. For these RGCs to effectively function as projection neurons, they must integrate into the ganglion cell layer and form functional connections with the optic nerve and brain [23,24,25]. This section examines factors that influence RGC differentiation and emphasises the importance of these cells forming connections with central targets for effective function. The function of the RGCs as projection neurons of the retina is dependent on their ability to form contacts with central targets; A significant obstacle in the transplantation of iPSC-derived RGCs is their ability to integrate into the ganglion cell layer (GCL) and form functional axons that link with the optic nerve and establish connections with the brain [27]. To promote neural retina differentiation, it is typical to modify genes and use specific supplements and molecules that replicate in vivo signalling pathways during RGC differentiation; Combinations of N2, B27, and FGF2 are frequently included in the base culture medium [28]. FGF may play a role in optic vesicle domain patterning and the expression of Chx10 in the presumptive neural retina's form [28]. Dickkopf (Dkk), a Wnt antagonist, may be used in the RPC differentiation culture medium to promote iPSC neural differentiation [ref]. Various small molecules, including VPA [29], AZA [30], butyrate [31], vitamin C [32], TGF-β receptor inhibitor (A-83-01) [33,34], MEK inhibitor (PD325901) [33,34], GSK3β inhibitor (CHIR99021) [33,34], and ROCK inhibitor (HA-100) [33,34] have been shown to increase reprogramming efficiency and may even replace the use of certain transcription factors in iPSC generation protocols.

3.2 Alternative treatments

Alternatively, the 3D culture system is becoming more popular as it has the ability to organise itself, needs fewer external growth factors, and the intrinsic pattern appears to be similar to the normal eye development [35]. It also shows similar patterns to normal eye development. There are various techniques for 3D culture including suspension culture, cell encapsulation in gel and cell culture in scaffolds [36,37]. Hallam et al [38] demonstrated that retinal organoids derived from iPSC lines can be produced through 3D culture techniques on a large scale for pharmacology and drug screening. RGCs lie in the innermost layer of the neural retina, where the techniques may explore the functional axons [39]. Parameswaran et al [40] found that iPSC-derived RGCs were able to be transplanted into a rat model of ocular hypertension without producing tumours and they expressed RGC-specific markers. While the effects of cell transplantation therapy are not fully understood, it could be a possible strategy for neuroprotective and cell-replacement therapy. A major obstacle facing the transplantation of RGCs derived from iPSCs is their ability to integrate into the GCL and develop functional axons that connect to the optic nerve and potentially to the brain. Teotia et al [41] managed to overcome obstacles to produce functional axons derived from iPSC that were able to navigate the retina, optic chiasm, and central targets by expressing various guidance molecules. Ultimately, it should be simple to adapt the hiPSC-generated RGCs for use in living organisms, but it's crucial to ensure that a connection to the brain is established. However, further optimization of the process is needed for clinical applications. Firstly, the hiPSCs used for differentiation should be patient-specific and reprogrammed under feeder-free, xeno-free, and integration-free conditions to avoid graft rejection and genotoxicity [55]. Secondly, a medium without xenogeneic components should be used for differentiation [55]. Thirdly, high efficiency, simple and highly reproducible protocols should be established, where predictable variations should be minimised during each step [55]. Finally, there are still notable hurdles to overcome, including the danger of teratocarcinoma development as well as a dearth of reliable differentiation procedures and precise methods for directing axon growth [55]. In conclusion, some significant challenges still exist: a lack of robust and highly reproducible differentiation protocols and accurate axon guidance still exists. However, the potential for personalised treatment of glaucoma using iPSC-derived RGCs is a promising tool for the study of RGCs biology and the eventual treatment for glaucoma and other optic nerve diseases. The review's perspectives provide insight into the methods for differentiation and highlights the obstacles that must be overcome before iPSCs derived RGCs are used in medical applications, such as the methods of pathological understanding, identification of symptoms, drugs for treatment, and creation of cell-based and individualised therapies intended for the treatment of glaucoma and other optic nerve diseases.

3.3 Figure 1

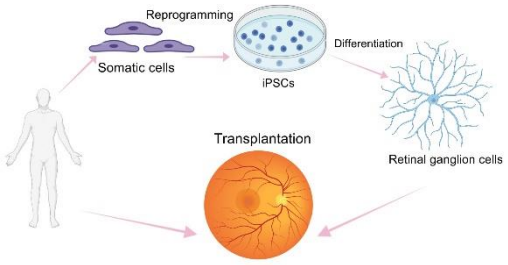

Fig. 1 - Somatic cells are reprogrammed into iPSCs, then differentiated into RGCs for transplantation into the optic nerve.

4. Cell Based Neuroprotection / Neuroenhancement Therapy

4.1 Therapeutic Potential

This section of the review discusses potential cell sources and strategies for stem cell-based RGC regeneration and protection, and the challenges that need to be overcome before stem cell-based therapy can be translated into clinical settings. Stem cells or altered cell lines can secrete neurotrophic factors that can be administered into the eye through direct injection or a partially permeable capsule. These factors may have the ability to protect and enhance the function of RGCs, which can help preserve vision and possibly improve cellular performance. These neurotrophic factors may have neuroprotective and/or neuroenhancing effects on RGCs, preserving vision and perhaps improving cellular function [56]. Replacing RGCs that have degenerated due to glaucoma is a challenging task as several barriers need to be overcome for the functional replacement of the optic nerve. Stem cell-based RGC regeneration and replacement for glaucoma treatment is being studied, but faces challenges such as the migration of stem cells to the ganglion cell layer, axon extension, and synaptic integration with appropriate targets in the brain [56]. While it may not be achieved soon, efforts are being made in preclinical investigations on stem cells for cell replacement therapy in treating glaucoma and restoring optic nerve function. This aims to replace damaged RGCs. Progress of photoreceptor cell replacement is expected to come sooner as photoreceptors can directly sense external light signal input, and their target sites are located in inner retinal neurons, within a short distance [42,56]. However RGC regeneration requires sufficient synaptic integration of stem cells in the inner layer of the host retina and the development of and long-distance axon projection to the brain [56], and that accurately form effective synaptic connections with their appropriate targets , such as dorsal lateral geniculate nucleus, suprachiasmatic nucleus and superior colliculus, thereby completing the signal transmission. Due to its difficulty, this procedure has been referred to as the final step in utilising stem cells for visual neuro-regeneration. In addition to replacement, intraocular transplantation of certain stem cells provides great potential for the treatment of glaucoma [56]. Mesenchymal stem

cells (MSCs) have been found to have neuroprotective effects on surviving retinal ganglion cells (RGCs) [43] and are a promising source of autologous cells for therapeutic applications. Scientists have developed MSCs that express elevated levels of BDNF (brain-derived neurotrophic factor) and utilised them in experiments involving the transplantation of these cells into the eyes of animals with glaucoma [44,45]. This led to a considerable improvement in the ability of MSCs to protect damaged RGCs [46,47]. In 2006, Yu S. et al. [48] transplanted bone marrow MSCs into the eyes of glaucoma animal models and found that these cells can integrate into the ganglion cell layer and the inner plexiform layer, reducing the loss of RGCs and demonstrating the potential of MSCs for the treatment of glaucoma. MSCs from different sources, such as dental pulp, have also been found to have a protective effect on glaucomatous optic nerve damage [49]. This demonstrates the protective role of MSCs in glaucomatous optic nerve damage. Given the goals of this treatment, stem cell transplantation is advantageous due to long-term release of multiple therapeutic factors through a single injection, reducing the risk of infection and bleeding caused by intraocular injection, and patient compliance burden [50]. However, researchers noted that despite transplanted MSCs ability to integrate into the GCL layer, they do not readily differentiate into RGCs [51], indicating that their therapeutic effect primarily derives from their neuroprotective effect of neurotrophic factors secreted by MSCs on neurons and their regulatory effect on the microenvironment [51]. Further research is needed to fully understand their mechanism of action and optimal delivery methods. Mesenchymal stem cells (MSCs) have the ability to produce various types of cytokines, such as BDNF, CNTF, GDNF, and BFGF [50]. Among them, BDNF has been demonstrated to be a crucial and efficacious protective element in terms of glaucoma-induced damage to the optic nerve [50]. In recent years, exosomes secreted by MSCs have gained attention in MSC-mediated neuroprotection. Exosomes are endocytic structures composed of proteins, lipids, and mRNA, and can regulate protein translation of proteins in target cells when delivered to target cells. Exosomes taken from in vitro BMSC cultures and transplanted into the eyes can effectively safeguard RGCs and improve the visual abilities in animal models of glaucoma [52]. In the further study of the effective components of exosomes, miRNAs were found to be key components for neuroprotection [53,54], which provides a new approach for the neuroprotective treatment of glaucoma.

4.2 Figure 2

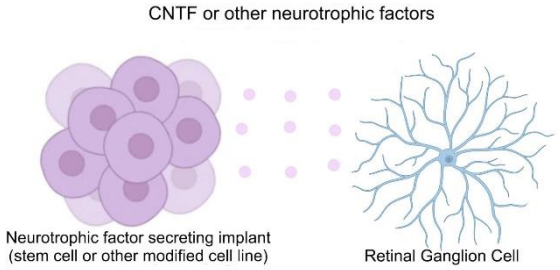

Fig. 2 - Cells secrete specific molecules, promoting the growth, survival and differentiation of neurons.

5. Stem Cell Derived Exosomes

The majority of the outcomes achieved through the use of stem cell transplants are influenced by the exosomes they produce. Starting from this idea, it is understandable that exosomes could be a viable alternative to cell therapies, especially for avoiding some worrying aspects such as immunogenicity. Exosomes were discovered in the late 1980s [57] and were initially considered as a manner through which the cells dispose of debris. Since then they were discovered to contain a wide variety of molecular species such as proteins [58], lipids [59], nucleic aids [58,60,61], and metabolites, making them important biomarkers for diagnosis and prognosis in different diseases. Exosomes are small entities ranging between 40 and 150 nanometers in diameter, generated through the inward budding of late endosomes, thus producing multivesicular bodies (MVBs). Then, MVBs fuse with the cell membrane, releasing the exosomes in the extracellular space. During biogenesis, exosomes are loaded with several bioactive molecules from the donor cells, such as nucleic acids (miRNAs, lncRNAs, DNA), lipids, metabolites and specific proteins from the donor cells, which can be delivered to a target cell, exhibiting different biological functions depending on their cell origin [65,66]. They play an important role in intercellular communication and discharge of excess molecules and have potential to be able to modulate a wide range of biological processes in different diseases as cancer prognostic markers and anticancer drug carriers: in many cellular processes, such as immune response [62], signal transduction [63], antigen presentation [64]. Therefore exosomes could be a viable alternative to cell therapies, avoiding immunogenicity. In addition to the cargo specific for the donor cell, exosomes also have markers that are usually constant between different donor cells, being termed as “exosomal marker proteins” Exosomes have markers that reflect the mechanism of exosome formation and are specific to endosomes, membrane proteins needed for fusion and cell transport, and phospholipases. Markers found in exosomes typically indicate the process of its creation, such as ESCRT proteins in addition to complimentary proteins like Alix, HSC70, HSP90β, and TSG101 [67, 68, 69, 70, 71] . Furthermore, exosomes also include particular markers that are exclusive to endosomes (CD9, CD63, CD81, CD82) and necessary membrane proteins for fusion and cellular transport (annexins, flotillin, GTPase), as well as phospholipases [72, 73]. Conversely, certain markers are scarcely observed or completely absent in exosomes: Proteins associated with mitochondria or the nuclear membrane are not seen in exosomes, while proteins associated with the endoplasmic reticulum and the Golgi apparatus are present in low levels. MSCs produce more exosomes compared to other cells, which express surface proteins common for all exosomes and adhesion molecules specific to MSC membranes, like CD29, CD44 and CD73 [74]. Due to their small size, MSC-derived exosomes are excellent vectors for drugs or DNA constructs and are potential resources for cell and gene therapy [75].

6. Cell Replacement Therapy

6.1 Therapeutic Potential

Cell replacement therapy using stem cells shows promise in treating glaucoma. This involves differentiating stem cells (such as human embryonic [hESCs] or iPSCs) directly into ocular cells for transplantation. In the image below, stem cells are directed to either TM cells or RGCs to develop treatments that would help to restore damaged retinal ganglion cells or enhance drainage of aqueous outflow by replacing trabecular meshwork cells. Replacing trabecular meshwork (TM) cells may be a more immediate solution and translation for clinical use. Recently, investigators used human anterior segments stem cells to transplant them into an ex vivo perfused outflow pathway organ culture model to see if stem cells could restore homeostatic function after saponin-induced TM cell loss. 8 Human iPSCs were differentiated into TM-like cells and transplanted into the organ culture model, restoring aqueous outflow [76]. The notion that patient-derived TM-like cells could potentially replace TM cells and assist doctors in treating patients with elevated IOP caused by a loss of functional cells in the aqueous outflow tract is a thrilling prospect. Stem cell transplantation has been shown to ameliorate neurodegenerative disease processes without overt functional cell replacement, and neuroprotection of endogenous host tissue has been offered as one possible explanation for this effect, possibly through activating multiple neuroprotective pathways via secretion of various factors [77]. Stem cells that are transplanted could be used as a tool to transfer bioactive factors in the eye to achieve RGC neuroprotection in patients with glaucoma [78]. This method would have the benefit of providing a sustained and localised impact, which could be the result of multiple bioactive factors working together, and derived from a single treatment. Additionally, it would eliminate the issue of patient noncompliance with medication because it would only require one treatment.

6.2 Figure 3

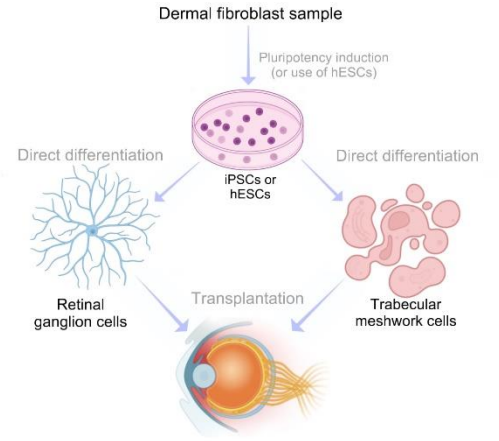

Fig. 3 - Somatic cells are reprogrammed into iPSCs, then differentiated into either RGCs or trabecular meshwork cells, then transplanted into the eye.

7. Conclusion

The neurodegeneration of the visual system caused by glaucoma goes beyond the retina and optic nerve, as the death of retinal ganglion cells leads to further degeneration in the rest of the visual pathway. Research in primates [79] and human [80] patients has demonstrated this effect on the lateral geniculate nucleus as a result of glaucoma. However, the impact on other parts of the visual pathway on upstream neurons, such as photoreceptors and bipolar cells, is not clear. While some studies have observed degenerative changes in some postmortem human glaucoma eyes' outer retina [81], as well as in monkeys and rodents with experimental glaucoma[81,82], others report limited photoreceptor loss [82,83]. If retinal ganglion cell replacement is to be effective, the rest of the visual pathway must remain functional, as upstream or downstream deficits in the glaucomatous visual pathway could limit overall functional recovery. Chronic neurodegeneration and gliotic scarring may also impede therapeutic regeneration over time. It is important to explore whether changes occur in the retina and optic nerve after retinal ganglion cell death, as this may affect the window of opportunity for therapeutic intervention. Subretinal transplants are more invasive and may cause retinal detachment. Intravitreal transplantation is less invasive and provides direct access to the inner retina, making it a more suitable option for glaucoma treatment. Nonetheless, both transplantation techniques have potential barriers to cell integration, so further research is needed to determine which method is most effective for treating glaucoma. It is essential to note that even if RGC replacement is fully achieved through transplantation, additional therapies, including ocular hypotensive and neuroprotective treatments, would still be necessary to ensure the survival of the newly generated RGCs. Although it may take several decades until RGC replacement can be practically implemented in clinical settings, it is evident that research should persist. In recent years, significant advancements have been achieved in various interrelated branches of neuroscience, including stem cell biology, cell movement and distribution, axon regeneration, materials science, and more. These advancements can be useful in numerous phases of RGC replacement, regeneration, possibly eventually providing patients with a cure to glaucoma.

Indicate references by (Van der Geer, Hanraads, & Lupton, 2000) or (Strunk& White, 1979) in the text.

1.1 File naming and delivery

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