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REVIEW ARTICLE

Vaccine development for glaucoma: From skepticism to certitude

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Abstract

Vaccines are conventionally thought to be a strategy to thwart the onset of any disease caused by pathogens. The elementary foundation for this concept is the ability of the immune system to discriminate between what is native to the body and what is foreign. This molecular xenophobia can, in principle, be exploited to prime the body to fight and neutralize any potentially disease-causing organism or moiety. For chronic disorders, preventive measures mediated through immune system modulation have been tried with little success yet the optimism for developing strategies of modulating the immune system is growing day by day as new techniques and animal models are being developed. Given the high prevalence of glaucoma and the ability of glaucoma experts to identify high-risk individuals, preventive regimens, and vaccine-like-substances can be developed to bring down the incidence. In this paper, we will discuss some preliminary efforts of vaccine development in glaucoma. We will also deliberate on the technical difficulties in developing effective vaccines for this disorder. In addition, we will try to identify measures with potential to transform the consistent toil of researchers in this field into an efficacious endeavor. We will attempt to recognize certain plausible methodologies that are likely to take the science of vaccine development for glaucoma (and other neurodegenerative disorders) somewhat nearer to the optimistic frontiers.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide[1] with around 80 million sufferers.[2] Around 10% of patients suffering from glaucoma are bilaterally blind.[3] More than 110 million people are estimated to be diagnosed with glaucoma by 2040.[4] The magnitude of the problem becomes manifest when we consider the fact that the majority of glaucoma cases are undetected/undiagnosed.[2,4,5-10] Lack of sufficient epidemiological studies intricates the problem further. This is particularly relevant to eastern countries. In addition, glaucoma comes with an additional caretaker burden which extends to family members of the patient often leading to stress, anxiety, and depression not only to the patient but also to the members of the family. Lifelong economic burden of expensive medication[11-13] and regular follow-ups[14,15] is an additional trouble further intensified by the side effects of the medication.[16-18] Moreover, despite regular follow-ups,[14,15] meticulous expensive medication,[16-18] high caregiver motivation, and repeated surgeries,[19-22] the disease may progress to blindness.[3,23-25] Hence, in effect, there is no cure for glaucoma though it can be prevented in many cases if early diagnosis is made.[26-30] In that backdrop, a hope and ardent need for preventive medication for glaucoma comes up as a potent, promising, and yet difficult option. Development of a vaccine,[31,32] may therefore, be a viable

option for high-risk populations and the patients who seem to have a genetic predisposition for this disease. However, what does a vaccine for glaucoma mean? After all, glaucoma is not a pathogen-related disease and hence a vaccine may seem to be an overstatement. While this argument holds some weight but vaccination now has gone beyond its traditional Edward Jenner's correlated definitions[33-36] and many chronic diseases are now being tackled with the development of vaccines[37] (or at least considered as candidates for vaccination). The success of such approaches has, however, been humble[38] but the conceptual hope is quite promising. Since almost double the number of patients suffers from glaucoma as compared to Alzheimer's disease (AD) and vision loss is one of the deadliest threats to patients, it would be worthwhile to consider the idea of a vaccine for glaucoma (be it mediated through neuroprotection or any other means). Here, we briefly touch on a few nuances that will give us an overview of the new vista of vaccine development in glaucoma.

Although a vaccine is generally understood in terms of a biological preparation that improves or modulates immunity/immunopotency of an organism (which contains a typical agent that resembles a disease-causing microorganism often referred to as antigen) against a particular disease and is often made from weakened or killed (attenuated) forms of the disease-causing organism (often a microbe) or its toxins (generally an active biological substance or protein). Such a biological/synthetic agent stimulates/modulates/activates/fine-tunes the body's immune system in such a way so as to recognize the agent as foreign, evoke a response to destroy/neutralize it and "remember" it so that the immune system can easily recognize any of these microorganisms (or their pathogenic products); it later encounters, neutralizes, and renders them harmless. In the light of present-day scientific literature, a paradigm shift of a sort has mushroomed in the understanding of the development and mechanisms of action of vaccines. Lately, investigators worldwide have started opening new frontiers of vaccines for various non-pathogen-based diseases (chronic diseases) and this idea is gaining recognition even among skeptics. In chronic diseases, the causative factor is not an infectious agent – a representative example of this scenario is cancer or Parkinson's disease (PD). Recently, many attempts to develop effective vaccines for various cancers have been reported and their efficacy tested with results generating significant enthusiasm.[39-45]

Glaucoma recently attracted considerable attention as a potential candidate disease to be subjected to vaccine-based management.[46-50] To this effect, Schwartz group from Israel has reported initial testimony of this prospect.[46-50] This group has now been working for more than a decade to develop an effective vaccine against glaucoma. Schwartz *et al.* reported the development of vaccine called Cop-1 (also known as copolymer-1; Copaxone and glatiramer acetate; it is a synthetic polypeptide comprising of four amino acids: L-alanine, L-glutamic acid, L-lysine, and L-tyrosine in a fixed molar ratio of 6.0:1.9:4.7:1.0. The molecular weight ranges from 4.7 to 11 kDa), which is currently being evaluated through clinical trials. Although the efficacy of this vaccine is not yet fully explored and the results of the trials are yet to be published but it has given birth to a new domain of thought process in glaucoma management. Cop-1 is currently being tested as a vaccine for other neurodegenerative disorders and stroke.[51]

It is to be taken into consideration that the vaccine developed by the Schwartz team does not claim to prevent the onset of glaucoma.[46-50] It has been used to slow down the progression of the disease. Hence, the vaccine may not be quite fitting the widely accepted definition of an ideal vaccine. Cop-1 acts through enhancing the autoimmune defense and directing T-lymphocytes to the site of optic nerve injury (optic nerve head in this case) where they initiate the tissue repairing process. At the outset, this approach presents with an optimistic outlook and opens novel dimensions of investigations but there are some conceptual and technical intricacies that need to be noted. Cop-1 works on the premise that autoimmunity is good for health. This initiates a big debate and often coerces the tenets of immunology to revisit the dogmas. Considering autoimmunity beneficial may have some health-promoting and physiology ameliorating effects but such a phenomenon has not been reported in the peer-reviewed literature. Beneficial effects of autoimmune response present a radical outlook that needs to be acknowledged with a certain caveat. The whole conjecture is somewhat notional and conceptually incoherent. Bringing the lymphocytes to the site of injury might prove helpful in repairing the injured/degenerating nerve but slight excess of them concentrated at a fragile site like optic nerve head may cause inflammation and hence damage to the cellular integrity and viability in vicinity. This may lead to irreversible changes in the extracellular matrix and may even trigger the loss of surviving islands within the optic nerve and, consequently, additional damage. To bolster this further, neuroinflammation is one of the major mechanisms that contribute to retinal ganglion cell (RGC) loss and hence progress of glaucomatous optic neuropathy.[52-54] As an augmentation to this logic, our group also reported an increase in inflammatory and stress markers in glaucoma patients.[55-58] In addition, it is well established that peripheral blood leukocytic count increases as a defense mechanism for injury anywhere in the body. A noticeable example of such an observation would be myocardial infarction in which the number of macrophages substantially increases in the peripheral blood following myocardial injury.[59,60] Such a scenario has physiological significance as it prevents a multitude of infections and instigates tissue repair.[59,60] Due to this verity, many investigators undertook procedures involving injection of various colony-stimulating factors such as granulocyte colony-stimulating factor[61-63] (G-CSF) and granulocyte-monocyte CSF[65,66] (GM-CSF: Both bone marrow mobilizing factors that increase the count of precursor cells and other leukocytes in peripheral blood.[61,64] Although it could be viewed as an articulate prospect, not much success was seen by employing this approach and majority of such trials came up with humble results.[66] On this pretext, it can be argued that the conceptual basis of Cop-1 as a vaccine is not that thorough. However, we will have to wait for the results of the clinical trials to see how effective the vaccine will be and what safety concerns it proffers.

In addition, Cop-1 based vaccine for glaucoma ensures repair of the site of injury,[45-50] indicating that the disease has to already set in before the vaccine is used. This, in turn, means that glaucoma has to already be diagnosed when the vaccination is considered. The vaccine is, hence, not preventive but a part of the treatment and management plan. Although this saves the vaccine from criticism of being dependent on predictive diagnosis, it cannot be considered as a true vaccine. Furthermore, there is significant apprehension about the efficacy of this vaccine in glaucoma cases where genetic etiology has been implicated. The fact that a majority of cases of glaucoma are etiologically rooted in mutations in CYP1B1, MYOC, FOXC1, LTBP2, and many other genes[67-72] and mitochondrial genome[73] further reinforces this line of thinking. If there are gene mutations underlying the etiology, the resultant functional deficit will continue and is likely to exacerbate the RGC apoptosis irrespective of the frequency and dosage of vaccines used to boost autoimmunity.

It is to be recognized that a vaccine for glaucoma, and any neurodegenerative disease for that matter, is not a non-conceivable enterprise neither is it a scientific taboo but the modus operandi needs to be coherent and, at least, the deliverable should be free of severe side effects (that might worsen the disease rather than ameliorating it). An effective vaccine system for glaucoma has to be effective in almost all case of glaucoma or there needs to be different vaccination approaches for different glaucoma based on the underlying etiology and arguably the pathogenic mechanisms involved. With this stance, two separate vaccine systems for glaucoma (one for cases with gene mutations and other without) can be conceived. In the following discussion, we describe a brief overview of the development of an effective vaccine system for glaucoma which is likely to aid in delaying the onset of the disease and also preventing the functional deficit precipitated by mutations/pathogenic alteration in the genes already implicated in the etiopathogenesis of glaucoma. From the above discussion, we learn that vaccines can be prophylactic (to prevent or ameliorate the effects of a future infection by any pathogen), or therapeutic effective in cases where the disease has already ensued. The case with chronic diseases is different. A two-fold vaccine system is likely to serve the purpose in preventing the onset of glaucoma where gene mutations are the etiological factor and slowing down (or stopping) progression in almost all cases where RGC apoptosis is the pathogenic hallmark.

Glaucoma where gene mutations are the etiogenic factors

For these cases, a vaccine can be preventive if the pathogenic gene alteration is corrected before the onset of the disease and therapeutic if the pathogenic genetic factor is corrected after the disease has started. It needs to be appreciated that correction of a gene deficit does not necessarily mean reversing a pathogenic mutation in the relevant gene. It can also indicate supplementation of the functional insufficiency precipitated by the pathogenic gene mutation underlying the etiology.[68] Use of an appropriate (non-pathogenic and non-toxic) genetically modified viral vector for the development of such a vaccine may be one of the imperative ways to tackle glaucoma.[74,75] Tagging the correct copy of the implicated gene to a suitable vector and delivery of the same to the relevant site where it will fine-tune the cellular metabolism and augment/improve the functional deficit of the implicated gene, is a scientifically consistent line of arguments. Such an approach may assist to develop a vaccine that holds some promise. With the development of gene-editing techniques such as CRISPR/Cas9 based genome editing technology, gene editing has become relatively easy, and vaccines based on these techniques are likely to have high precision and efficacy. We also reported CRISPR/Cas9 based gene editing in RGCs with CYP1B1 and MYOC genes recently.[76] One of the focuses of our team is to repair the genetic hitches observed in glaucoma. Our studies are yet based on cellular models which may soon lead to animal models followed by clinical trials.[76]

Several effective approaches are available for gene delivery to tissues relevant for glaucoma. The critical constraint to development is to tag the correct (un-mutated/wild-type/normal) copy of the diseased gene to the appropriate vector and then successfully deliver the same to the relevant tissue site which may include as fragile a site as optic nerve head or as approachable an anatomical location as trabecular meshwork (TM). A good example can be tagging the CYP1B1 gene to an adenoviral vector/adeno-associated vector (modified in accordance with the needs such as δE1 and δE4) which has tendency to go to TM. If such a vector delivers the correct copy of the CYP1B1 gene to TM, TM dysgenesis can be reversed (due to the dynamic nature of the TM architecture), which in turn will restore the proper aqueous humor dynamics with lowering of the elevated intraocular pressure (IOP). Along with other cases of trabecular dysgenesis, this approach will be quite relevant to primary congenital glaucoma (in patients with loss of function mutations in CYP1B1 gene). The story goes like this: Myocilin (also known as TM inducible glucocorticoid receptor) is involved in the synthesis and maintenance of the beams of TM which determine the pore size and hence the rate of the flow and exit of aqueous humor. This has a direct effect on IOP. Myocilin/MYOC upregulation leads to thick trabecular beams leading to narrowing down the pores of TM which consequently hampers outflow and causes IOP elevation precipitating disease. CYP1B1 specifically hydroxylates 17β-estradiol at position 4 which then binds to the promoter region of MYOC gene leading to its downregulation and consequent lowering of IOP.[77] Events leading to RGC apoptosis can be targeted for genetic modulation if the gene underlying the etiology is known and if the correct gene delivery system is developed. Hauswirth and Beaufrere have proposed four prerequisites that should be met for any genetic therapy targeted to ophthalmic conditions.[78] They are (1) an efficient and nontoxic gene delivery technique, (2) sufficient characterization of the genetic basis of the disease to select an appropriately matched therapeutic approach, (3) proper control of the expression of the therapeutic gene, and (4) the availability of an animal model of the disease for preclinical testing. Any investigative endeavor should ideally exercise these simple but essential criteria. Additional issues that need to be taken care of include (1) tissue tropism of the gene

vehicle, (2) time course of gene expression, (3) intracellular viability of the gene and the vehicle, (4) gene carrying capacity of the vector, (5) potential for integration into the host genome or at least ability to replicate episomally using the host replication machinery, (6) immunogenicity, and (7) toxicity. Appropriate target structures or cell types for glaucoma gene delivery include TM, ciliary epithelium, ciliary muscle, RGCs, Muller cells, optic nerve, and subarachnoid space around optic nerve.

Glaucoma where no gene is known to be mutated

Glaucoma involves the loss of RGCs in a characteristic hourglass pattern.[79-85] Progressive loss of RGCs in a predictable sequential apoptotic manner[86] leads to loss of vision (currently considered to be an irreversible condition). A vaccine aimed at targeting this pathogenic hallmark can be conceptualized (at least theoretically). Such a system seems to be arduous at the outset but may need experimental rigor to metamorphize into reality. Recent advances have, in a way, prompted researchers and clinicians to revisit the definitions of glaucoma and call it a kind of optic neuropathy (if not a frank neurodegenerative disease, though the evidence of glaucoma being a neurodegenerative disease is quite ripe[87]), so it is apt to think that if neuronal death is the issue, we need to look for modalities that will enhance the neuron viability. Such an approach will be applicable to AD, PD, and other neurodegenerative conditions due to the fact that glaucomatous damage has also been reported in the central nervous system.[87,88] RGCs are typical neurons and eye as such is also an extension of diencephalon.[87-89] TM is of neural crest origin. Investigators argue that there are many brain degenerative changes that take place in glaucoma.[87-89] Hence, glaucoma is essentially a neurodegenerative disorder. A Janus-faceted vaccine can be conceptualized against such conditions. Since the hallmark of glaucoma is RGC apoptosis, two important issues need to be addressed including enhancing the survival of RGCs and preventing the onset of apoptosis. The development of such a vaccine will include the important steps of identifying factors (substance) that are neurotrophic in nature and likely to enhance the survival of RGCs. A comprehensive list of neurotrophic factors can be prepared by bioinformatics approaches and data mining and then tested on RGC cultures using high throughput screening. Leads taken from cultures can then be tested on animal models for efficacy and safety. Subsequent steps may then give birth to clinical trials. However, it is important to note that predictive diagnosis of glaucoma is not yet a reality so this approach may be realistic in the high-risk individuals (such as the ocular hypertensives and near relatives of the glaucoma patients). A few candidate analytes for vaccine have already been indicated in literature for AD. The notion that AD is etiopathogenically similar to glaucoma[90-93] bolsters the aim of testing the same list on RGCs as well. Factors such as brain-derived neurotrophic factor and ciliary neurotrophic factor are potential candidates for this approach. Moieties like Citicoline and Quercetin might also fall within this category with effective neuroprotective properties and minimal-to-no side effects. Since RGC apoptosis is central to glaucoma pathogenesis, it will be worthwhile to identify (therapeutic) analytes that prevent the onset of apoptosis in many cells in general and neurons in particular. A list of such substances can be prepared bioinformatically and screened experimentally. An example of such a substance is GM1 – ganglioside (a glycosphingolipid-ceramide and oligosaccharide – also called oligoglycosylceramide containing one or more sialic acid residues linked to the sugar chain. It is a cell membrane component which plays a role in modulating signal transduction). Once a shortlist of possibly effective substances for the prevention of RGC apoptosis is generated, it can be combined with the previous list and the two lists could then be used to make a combination and permutation of substances likely to (1) prevent RGC apoptosis and (2) enhance RGC survival.

Recently, the axon severance hypothesis of glaucoma was proposed[86] which says that glaucoma is more of a mechanical problem where the axons die due to physical pressure at the neuroretinal rim. While this theory may not take the neurodegenerative, molecular, and genetic aspects into consideration, ocular hypertension is one of the major risk factors and the only modifiable factor for glaucoma.[94] Hence, exploitation of IOP lowering can be used as a starting point for vaccination. Low dose ocular hypotensive medication could be given as a potential vaccination to high-risk patients before they develop the disease. Such an approach is, however, not without drawbacks given the side effects of ocular hypotensives in addition to the economic burden. Furthermore, such a vaccination is not long lived, an individual will have to take the medication lifelong to keep the onset of the disease at bay. While this approach may generate skepticism as to the fact that we do not know which ocular hypertensive patients will develop glaucoma and which would not, but it will surely help a majority of potential future glaucoma sufferers in preventing blindness and preserving vision. This may help a great proportion of high-risk patients from developing the disease. Normotensive individuals who develop glaucoma may not benefit from this approach.

Another interesting area to consider will be stress-based etiology of glaucoma. One of our recently published papers gives a detailed account of how mental stress can initiate and exacerbate events leading to vision loss in glaucoma.[58] This includes elevation in IOP, vascular dysregulation, endothelial dysfunction, and neurodegenerative processes.[58,88,89] Stress reduction may, therefore, be thought to be as one of the promising non-invasive and relatively inexpensive techniques to delay the onset of glaucoma and to bring down the severity. In a clinical trial, we recently reported that mindfulness/meditation-based stress reduction techniques lead to lowering of IOP and improve quality of life in glaucoma patients.[56] Hence, mindfulness-based practices could ideally be used in ocular hypertensive patients and those at higher risk to delay the onset and bring down the severity of the disease. Moreover, stress reduction leads to improvement in insulin signaling,[95-97] thereby providing justification as a method of vaccination in the light of brain diabetes theory of glaucoma.[98,99]

Conclusion

Although vaccine development for glaucoma is a difficult notion to realize, the goal is not absolutely out of question. In the backdrop of current literature, the development of any vaccine in near future is unlikely but the hope is growing day by day. Our understanding of glaucoma mechanisms is poor and hence most of the approaches to tackle this disorder are based on treating the only modifiable risk factor IOP pharmacologically/surgically. The recent brain diabetes theory for glaucoma has opened a new molecular vista for investigations into this disorder and initial evidence of our theory has been reported by some groups.[100,101] Results of our experiment are currently in communication. As we know more about the molecular mechanisms of glaucoma, we may identify novel targets to aim the vaccines at.

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