Autoantibodies associated with glaucoma.

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Abstract

As a complicated chronic disease, glaucoma does damage to optic nerve and results in final blindness. However, its pathogenic mechanisms still remain ambiguous. Recently, the attractive reports have suggested that the immune system is involved in glaucoma. It is notable that the relationship between autoimmunity and open-angle glaucoma has become a hot point in the field of eye research. It is evidenced that glaucoma is associated with increased serum autoantibodies titers to heat shock proteins (hsps), retinal antigens, Gluthione S-Transferase (GST), a-fodrin, optic nerve head glycosaminoglycans, γ-enolase, vimentin, Phospholipid (PL), Neuron Specific Enolase (NEL), Myelin Basic Protein (MBP), ɣ-synuclein, Glial Fibrillary Acidic Protein (GFAP), 14-3-3 protein, homocysteine, hydroxyproline, solube CD44, erythropiotin and so on. In fact, these autoantibodies may be the pathogenic factors or indirectly induce the neural injury, on the other hand, they may protect eye against glaucoma. Thus, the fine regulations of immune system should be a potentially effective therapy strategy for glaucoma. Here, we summarize the reported autoantibodies associated with glaucoma and the underlying mechanisms involved in effects of these autoantibodies on the disease process.

Introduction

Glaucoma is a common kind of optic neurodegenerative disease, which is characterized by the loss of Retinal Ganglion Cells (RGC) that leads to visual field loss [1]. Most patients suffer the optic disease for over 10 years. It is estimated that more than 110 million people will bear glaucoma in the world by the year 2040 [2]. However, the underlying pathogenesis and involved molecular mechanisms of glaucoma remain to be elucidated. The pathogenic reports have been focusing on disordered blood circulation, cytotoxicity, neurodegenerative lesions and aberrant reactivity of immune system. Recently, there emergence compelling evidences demonstrating that immune system, especially autoimmune mechanism, is involved in the optic disease [3]. As is well known, blood-retinal and blood-aqueous barriers raise the specific immune microenvironment of eye, which pushes many groups to dissect the pathogenic mechanism of glaucoma through immune system. Thus, how autoimmune diseases lead to RGC loss or how the optic autoimmune diseases result in whole-body autoimmune responses becomes a hot point in clinic observation and studies. When the body is maintained in homeostasis, immune responses owing to damage of Central Nervous System (CNS) myelin can produce protective autoimmunity. It was reported that the self-antigens, which are produced by the active immunization due to the damages of retinal neurons, can reduce secondary and delayed neurodegenerative lesions [4]. On the other hand, the immune responses and the self-antibodies due to the responses will lead to many potential dangers to body health including eyes if the positive homeostasis is broken. The glaucoma is estimated to be the results of the broken homeostasis and autoantibodies produced by excessive immune responses. How to balance the homeostasis is very important for treating glaucoma effectively. Here, we summarized glaucoma-associated autoantibodies (Table 1) which are deposited or produced in blood serum and aqueous humor.

Antibodies against Heat Shock Proteins

Heat shock proteins (Hsps) are a kind of stress-response proteins. They are conservative in evolution and commonly present in prokaryotes such as bacteria through eukaryotes including human being. Additionally, their similarity between species reaches 80% in structure. It is because they express in all kinds of pathogenic microbes so predominantly that they bring up main challenges to immune system. Previously, Hsps were thought as "side products" or unrelated molecules when they were discovered in patients with glaucoma. With the development of technology and the deposit of knowledge, more and more evidences demonstrate that Hsps play a vital role in the development of glaucoma. In addition, these stress-response proteins supply a novel dimension and pave a new way for improving the treatment of glaucoma. Here, we focus on autoantibodies against three kinds of Hsps: small heat shock proteins, Hsp60 and Hsp70.

Hsp27, αA- and αB- crystallin are all small heat shock proteins. It was reported that the autoantibodies against α-

crystallins and hsp27 in the sera of patients with glaucoma, especially normal pressure glaucoma, were associated with the optic disease significantly [5]. In addition, Gruz group also reported that autoantibody against αB-crystallin showed a significant difference between patients with normal pressure glaucoma and people without the optic disease [6]. Further study performed by Tezel et al. disclosed the function mechanism of autoantibody against hsp27 in glaucoma. In the report, they found that the antibody against hsp27 prompted apoptotic cell death of retinal neuronal cells through the cleavages of caspase-8 and caspase-3 as well as actin microfilament breakdown following the internalization during the development of glaucoma [7]. Furthermore, the study on serum autoantibodies to hsp27, αB-crystallin of patients with glaucoma in Japan and America demonstrated that the serum antibodies against small heat shock proteins did not exhibit a significant difference between these two ethnic groups [8].

Human and bacteria hsp60s share antigenic similarity and are high, mutually immunogenic. Thus, hsp60 has a protective role in elevating human immunity against microbes. In the meanwhile, it plays a vital role in many autoimmune diseases as a dangerous self-antigen [9-11]. Wax et al. reported that the antibody against hsp60 in the serum showed a significant increase in the patients with glaucoma, especially in the patients with normal pressure glaucoma, compared to control people. They deduced that the pathogenesis of glaucoma involved the autoimmune mechanism activated by hsp60 [10,12]. In addition, many patients with glaucoma also suffer from autoimmune diseases, accompanied by arterial stenosis and the bleeding of optic nerve fiber layer. For example, the deposit of hsp60 has been observed in the vessel of patients with Reiter's syndrome. These convincing evidences all lead to the conclusion that the normal pressure glaucoma should be associated with the bleeding of optic nerve fiber layer and vasospasm due to autoimmune diseases [13,14].

Hsp70 is the most conservative heat shock protein in evolution and ubiquitously participates in housekeeping activities of cells and organisms including stimulation of the innate and adaptive immune responses [15]. The activated immune cells release a serial of Reactive Oxygen Species (ROS) factors and cytokines, which further promote the synthesis of hsp70 in organism. In addition, hsp70 of pathogenic microbes can bind to MHC-I/II molecules as an epitope to form presenting complex and to be presented to T cells. This may cause augmented production of anti-Hsp70 antibodies owing to microbes infection and result in autoimmune diseases due to structural similarity between hsp70 molecules of pathogenic microbes and human hsp70 proteins [16-18]. Compared with control group of cataract, the patients with normal pressure glaucoma showed a significant elevation of anti-hsp70 antibody in aqueous humor [6]. As is mentioned above, the production of anti-hsp79 antibody has been observed in many autoimmune diseases including multiple sclerosis, rheumatoid arthritis and so on [17,19]. In addition, hsp70 autoantibodies have been also detected in cancer tissues [20] and in the aqueous humor of patient with Cancer-Associated Retinopathy

(CAR) [21]. Thus, it is estimated that hsp70 autoantibody should be an important cause for glaucoma procession.

Antibodies against Rhodopsin

Rhodopsin is a light-sensitive receptor pigment protein involved in photoelectric conversion as a vital component of retina. Romano et al. reported that the rhodopsin antibody was detected in a significantly high level in the patients with normal pressure glaucoma compared to those with high pressure glaucoma or age-matched control patients [22,23]. The authors further examined the epitope specificity of autoantibody to rhodopsin and found that binding of the patient antibodies to rhodopsin completely depended on the last two C-terminal amino acid of rhodopsin. Additionally, the C-terminal amino acid sequence of human rhodopsin was same to that of pathogenic microbes' rhodopsin protein, which may result in molecular mimicry and cause autoimmunity. However, how the autoantibody against rhodopsin lead to normal pressure glaucoma remains to be elucidated in detail [23].

Antibodies against Glutathione S-Transferase (GST)

Glutathione S-transferases are a kind important multigene family of isoenzymes involved in detoxification of electrophilic xenobiotics and metabolism of endogenous toxic products due to oxidative stress [24]. GSTs ubiquitously express in all organs including the glial cells and neurons of CNS, as well as retina. It was reported that specific antibodies against GST isoenzymes showed a selective cellular distribution or accessibility in rat and cow retina [24,25]. The high activity of GST isoenzymes in retina ganglion cells indicated that GSTs provided a protective effect on retinal nerve [26]. Retina is an important location involved in metabolism of Reactive Oxygen Species (ROS). The patients of glaucoma also showed a high level of ROS, which may result in retinal ganglion cell death and the optic neuropathy [27]. The roles of antibodies against GST in the development of glaucoma have been achieving a hot point in the research filed of the optic neuropathy.

Antibodies against to α-Fodrin

Fodrin, consisting of α- and β-subunits, participates in the form of cytoskeleton as an important membrane-associated cytoskeletal protein. Alpha-fodrin is also involved in the apoptotic cascade as one of the primary targets cleaved by caspases. It was cleaved into two fragments with 120 kD and 150 kD, respectively, during proteolysis. 120-kD fragment further promoted the cleavage of caspase-3 and apoptosis [28,29]. Franz group found that the antibodies against 120-kD fragment were detected in a high level in German and American patients with normal pressure glaucoma. The authors thought that the caspase-associated apoptotic cascade was activated in normal pressure glaucoma. The results had been also demonstrated in rat models of high pressure glaucoma

[30,31]. In addition, the antibodies against α-fodrin are commonly present in other neurodegenerative diseases including Alzheimer's disease, which indicates that the antibodies against α-fodrin should play a role in the neurodegenerative changes during the process of glaucoma.

Antibodies against Glycosaminoglycans

Saccharides are a kind of important biological macromolecules as high-throughput information carriers, which are the extension and derivative of genetic information. Glycosaminoglycans (GAG), which are long unbranched polysaccharides chain with negative charge consisting of repeating disaccharide unit, are commonly present in extracellular matrix of mammals. They are highly hydrophilic and usually used as a lubricant or a shock absorber in body. Based on the core disaccharide structure and the modification of glycosylation, the GAG can be classified into four groups: heparin/heparan sulfate, chondroitin sulfate/dermatan sulfate, keratan sulfate, and hyaluronic acid [32]. These molecules, containing collagen, elastin, laminin, and fibronectin, possess high viscosity and favorable hydration. As macromolecular components of extracellular matrix of optic nerve head, they play vital roles in maintaining the stability of lamina cribrosa plate and viscosity of optic nerve head [33,34]. Tezel et al. reported that the serum content of antibodies against GAG in the patients with Normal Pressure Glaucoma (NPG) is 50% higher than that in the patient with open-angle glaucoma or 100% higher than that in matched control group. In addition, GAG immunostaining showed the augment of antibodies against GAG in the optic nerve head of patient with glaucoma compared with control group. Thus, it was deduced that GAG antibody should result in the change of lamina cribrosa and damage of retina, which finally cause glaucoma [35].

Antibodies against γ-Enolase

Enolase is an important glycolytic enzyme and commonly present in many organisms. In human, three subunits of enolase are observed, α, β, and γ, each is encoded by a separated gene. α-enolase is found in many tissues while β-enolase is muscle specific. γ-enolase, also called enolase 2, is only detected in neuron and neuroendocrine tissues [36]. It was reported that α-enolase was the one of self-antigens causing Cancer-Associated Retinopathy (CAR) [37]. Ikuyo et al. reported that antibodies against γ-enolase were detected in the sera of patients with Primary Open Angle Glaucoma (POAG) and Normal Pressure Glaucoma (NPG) [38]. In addition, the authors demonstrated that the damages due to antibodies against enolase in glaucoma and CAR occurred in different retinal cell layers. Damages in CAR were taken place in the photoreceptor layer while damages in glaucoma occurred in ganglion cell layer [39]. Yoko et al. found that 20% patients with open angle glaucoma had antibodies against γ-enolase in the serum. In addition, the visual field loss of patients with both Primary Open Angle Glaucoma (POAG) and the detectable γ-enolase antibodies was more serious than that of patient without the antibodies and with POAG only. In order to

further validate the roles of γ-enolase antibodies in glaucoma, the authors also injected the patient's serum containing the antibodies into the vitreous cavity of a Lewis rat, which caused the similar excitotoxicity induced by N-Methyl-D-Aspartate (NMDA) and finally resulted in the death of retinal ganglion cells [40]. The involved mechanism of γ-enolase antibodies towards glaucoma remains to be elucidated in the future.

Antibodies against Vimentin

Vimentin is a type III intermediate filament and comprises cytoskeleton along with microtubules and microfilaments. It is down-regulated during the development of human lens and erythrocyte. Additionally, it is found in astrocytes and Müller cells. Stress response induces a progressive increase of antibodies against vimentin [41]. Vimentin antibodies have been observed in sera of patients with acute viral hepatitis, Systemic Lupus Erythematosus (SLE), and Idiopatic Pulmonary Fibrosis (IPF) [35,42,43]. Stephanie et al. found the antibodies against vimentin in the aqueous humor of patients with Normal Pressure Glaucoma (NPG) [6]. The authors collected the aqueous humors of patients with NPG at a series of time points before and after trabeculectomy or cataract surgery. They found that the antibodies against vimentin were increased gradually after surgery, which indicated that the continuous death the retinal ganglion cells and progressive loss of visual field were associated with autoimmune neuropathy. They thought that the antibodies against vimentin should be one cause which resulted in stress response and final damage of retinal tissues [6]. However, the underlying mechanisms of vimentin antibodies involved in the glaucoma processes need further research to be performed.

Antibodies against Phospholipids (APL)

Antibodies against phospholipids, also called Antiphospholipid Antibodies (APL), have three subgroups: Antiphosphatidylserine antibodies (APS), Anticardiolipin antibodies (ACL), and anti-β-2 Glycoprotein (β2AGP). These antibodies can bind to phosphatidylserine molecules specifically, which participate in apoptosis and thrombosis due to activation of coagulation cascade [44]. It has been demonstrated that glaucoma, especially open angle glaucoma is closely associated with retinal vein occlusion [45]. Here, the occlusion is induced by thrombosis which is associated with Antiphospholipid antibodies (APL). That is the cause why they are called antiphospholipid syndrome in clinic [46]. Kremmer et al. found that patients with Normal Pressure Glaucoma (NPG) showed the augment of APS antibodies (IgG and IgM) while patients with Primary Open Angle Glaucoma (POAG) had elevated β2AGP antibodies (IgM) concentration in the serum although they both showed identical antibody map. The authors further analysed the probability that the death of retinal ganglion cells leads to the augment of these antibodies. However, their data showed that this was the dominant cause because they found the death of ganglion cells in both NTG and POAG. Thus, they thought that these antibodies induced the apoptotic events which finally resulted in a systemic

autoimmune response [47]. In addition, different antibodies may play different roles in retinal vein during the process of glaucoma [35,48]. Further researches should be performed to establish and validate the relationship between these APL and glaucoma, especially NPG.

Antibodies against Myelin Basic Protein (MBP)

Myelin Basic Protein (MBP) is a kind of trans-membrane protein and functions in the central and peripheral nervous system through great contribution to myelination process. It was reported that anti-MBP antibodies increased in sera and in cerebrospinal fluid of patients with demyelination diseases. In the autoimmune diseases including multiple sclerosis, the augment of anti-MBP antibodies resulted in the demyelinating lesion of the optic nerve [49-51]. Stephanie and her colleague found that anti-MBP antibodies in the sera of patients with glaucoma were up-regulated compared to the control group. Especially in the sera of patients with open angle glaucoma, the antibodies against MBP showed a significant up-regulation [52].

Antibodies against γ-Synuclein

The synuclein family comprises three members: α-, β-, and γ-synuclein. These three proteins are all associated with neurodegenerative diseases including Parkinson's and Alzheimer's diseases. Among them, γ-synuclein related to the loss of retinal ganglion cells during the process of glaucoma [53]. Grus group found the down-regulations of antibodies against γ-synuclein in glaucoma patients [54]. They further demonstrated that γ-synuclein antibodies elevated the viability and oxidative stress response ability of retinal ganglion cell line RGC5. The down-regulation of the γ-synuclein in glaucoma patients may result in the protective effect loss of autoimmune [54]. More studies need to be carried out to disclose the roles of antibodies against γ-synuclein in glaucoma process.

Antibodies against Glial Fibrillary Acidic Protein (GFAP)

Glial Fibrillary Acidic Protein (GFAP) is a cytoskeletal protein and found in glial cells as well as astrocytes. It has been also found to be expressed in astrocytes and Müller cells of retina. GFAP can be up-regulated by the stress and injury in disease states. Glial scarring is considered to be the cause of neurodegenerative lesions [55,56]. It was reported that the antibodies against GFAP were found to be down-regulated in glaucoma patients including POAG and NPG compared to control group [52,57]. The antibodies against GFAP were considered to have protective effects on glaucoma patients through protecting retinal ganglion cells from oxidative stress, which is due to changed protein expressions of the actin cytoskeleton and a cross-reaction of the antibody against ERP57 on the cell membrane. The down-regulation of GFAP antibodies result in the loss of protective effect on glaucoma patients during the process of the optic disease [57].

Antibodies against 14-3-3 Proteins

14-3-3 proteins, a conserved family in evolution and a kind of proteinase inhibitor, participate in a series of cellular processes and are found to be associated with many neurodegenerative diseases [58]. It has been demonstrated that the functions of 14-3-3 proteins are mainly through MAPK/ERK pathway and calcium/calmodulin [59-63]. Bell et al. pre-incubated retinal ganglion cells with anti-14-3-3 antibody and found that the pre-incubation resulted in an increase in cell viability of up to 22 % and a decrease in Reactive Oxygen Species (ROS) of up to 31 %. They further demonstrated that the protective effect of 14-3-3 antibodies is *via* blocking mitochondrial apoptosis through MAPK/ERK pathway [63].

Antibodies against Homocysteine

Homocysteine is a homologous of cysteine. The elevated level of homocysteine in the peripheral blood can conduce to endothelial cell injury and subsequent ischemic injury [64]. Through retrospective cross-sectional study, Park group demonstrated that high homocysteine level in plasma is related to glaucomatous Retinal Nerve Fiber Layer (RNFL) defect [65]. However, some studies showed that the homocysteine level was not associated with the changes of IOP [66]. These studies indicate that the increased anti-homocyesteine antibodies may lead to glaucomatous damages without the elevated IOP.

Antibodies against Hydroxyproline

Hydroxyproline is generated through hydroxylation of the amino acid proline, comprising a major competent of collagen in mammals [67]. Arafa et al. examined the hydroxyproline level in aqueous humor samples of patients with Primary Open-Angle Glaucoma (POAG) and found that hydroxyproline level is dramatically higher in patients' samples than in those of control group with senile cataract. However, no significant augment of hydroxyproline in the plasma of POAG patients was detected. The discovery indicated that the augment of anti-hydroxyproline antibody in aqueous humor might be related to POAG. In addition, their further statistical analyses showed that the increase of anti-hydroxyproline antibody in aqueous humor was not associated with visual field loss [68]. Duman group found the augment of hydroxyproline in both aqueous humors and sera of patients with pseudoexfoliation. They concluded that the increased hydroxproline could promote the deposit of augmented collagen and lead to the augment of IOP in glaucoma [69].

Antibodies against Soluble CD44 (sCD44)

Soluble CD 44 (sCD44) is a soluble 32-KDa ectodomain fragment derived from transmembrane protein receptor CD44. It has been proved that sCD44 does damage to trabecular meshwork and RGC *in vitro* through triggering proapoptotic process as a cytotoxic protein [70]. Further reports demonstrated that the anti-sCD44 antibodies were significantly increased in aqueous humors of POAG patients compared to

control group of cataract patients. Additionally, statistical analysis showed that the augment of anti-sCD44 antibodies was associated with severity of visual field loss. However, no significant augment of anti-sCD44 antibodies were detected in the plasma samples of POAG patients [71]. These discoveries suggested that sCD44 should be related to glaucoma and may be increased in glaucoma as a result of glaucomatous damage. Anti-sCD44 antibodies can be explored as a potential biomarker in POAG patients.

Antibodies against Erythropiotin

Erythropiotin (EPO), a 165 amino acid sialoglycoprotein, is a kind of hormone to motivate erythrocyte formation. It is a well-known target gene of Hypoxia-Inducible Factor-1 (HIF-1) which has been demonstrated to play vital roles in retinal diseases including glaucoma [72]. EPO has been demonstrated to attenuate neuroinflatmmation as a neuroprotective agent in ocular diseases through inhibiting apoptosis, Reactive Oxygen Species (ROS), cytokines and so on [73-76]. However, EI-Baiomy group found that EPO concentration was significantly increased in aqueous humors of POAG patients compared to control group of cataract patients by use of Enzyme-Linked Immunosorbent Assay (ELISA) and anti-EPO antibodies. However, they did not detect the significant augment of EPO in plasma of POAG. In addition, they found a high positive correlation between EPO and a fore mentioned sCD44 in aqueous humors of POAG patients. Through statistical analysis, they also demonstrated that the augment of EPO was significantly associated with visual field loss in glaucoma [71]. Thus, the augment of EPO may be a result of glaucomatous damages rather than a reason. EOP and anti-EOP antibodies therapy would be a potential pharmaceutical strategy for glaucoma.

The Roles of Antibodies in Glaucomatous Damage

Grus group demonstrated that the glaucoma-associated antibodies deposited in glaucomatous retinas when pro-inflammation occurred. They further showed that the deposition of antibodies took place in CD27+/IgG+ cells rather than microglia, accompanied by the augmented expression of cytokines including TNF-α, IL-6 and IL-8 [77]. More serious

evidences by the group have arrived at the result that increased antibodies were deposited in retinal structures and led to RGC loss [78-80]. However, anti-γ-enolase antibody showed the neuroprotective effect and decreased the IOP during the development of glaucoma through activating PI3/Akt and MAPK/ERK signaling pathways [81]. The anti-Hsp27 antibodies have been found to be increased and to result in RGC loss without augment of IOP in rat autoimmune glaucoma model [82]. Further studies suggested that anti-Hsp27 antibodies entered RGC cells and destructed the stabilizing effect of Hsp27, leading to apoptosis and subsequent neurodegeneration [7]. By use of autoantibodies profiling approach, Grus group studied the role of antibodies in glaucomatous damages and concluded that IOP mediated the changes of autoantibodies repertoire, in which the balance between potentially protective or destructive abs is considered as a key point for disturbing glaucomatous optic neuropathy after the rise of IOP [83].

Summary and prospective

Glaucoma is an optic neuropathy which afflicts 60 million people worldwide [2] and it is also a second leading cause of blindness in the world [84]. The pathogenic mechanisms and treatment strategies have been still on the way to be optimized. The aforementioned autoantibodies have been found in the sera and aqueous humors of glaucoma patients. The emerging evidences indicate that autoimmune reactions play vital roles in the pathophysiology and procession of glaucoma. However, the underlying mechanisms of autoantibodies involved in glaucoma still remain ambiguous. More studies are required to be performed to clarify the precise roles and exact mechanisms of autoantibodies in glaucoma. In addition, we can also explore specific antibodies as biomarkers of glaucoma if we can establish the specific relevance between the antibodies and the optic neuropathy. Thus, we can screen the specific antibodies in the sera or aqueous humors of patients to detect glaucoma early in clinic. Moreover, we also develop new therapeutic strategies to improve the treatment of glaucoma through the understanding of aforementioned autoantibodies in glaucoma. In all, the involvement of autoimmune system in glaucoma paves a new way for enhancing the diagnosis and treatment of the optic disease as well as improving life quality of patients.

Table 1. Autoantibodies associated with glaucoma.

Protein names [1]	Functions in glaucoma
Hsp27	RGC apoptosis [5]
Crystallin	Response to IOP [6,85]
Hsp60	Autoimmune response [10,12]
Hsp70	Stress-induced autoimmune response [16-18]
Rhodopsin	Molecular mimicry and autoimmunity [22,23]
Glutathione S-Transferase (GST)	Debating, protective effect on retinal nerve or RGC death [26,27]

A-fodrin	Activation of apoptotic cascade [30,31]
Glycosaminoglycans	The change of lamina cribrosa and damage of retina [33-35]
Γ-enolase	Damages in ganglion cell layer [38,39]
Vimentin	RGC death and damage of retinal tissues [6]
Phospholipids	Debating, RGC apoptosis and autoimmune response [35,47,48]
Myelin basic protein	Demyelinating lesion of the optic nerve [49-51]
Γ-Synuclein	The loss of RGC [53,54]
Glial Fibrillary Acidic Protein (GFAP)	Protective effect on RGC [52,57]
14-3-3 proteins	Protective effect on RGC through blocking apoptosis [63]
Homocysteine	Glaucomatous Retinal Nerve Fiber Layer (RNFL) defect [65]
Hydroxyproline	Deposit of augmented collagen and lead to the augment of IOP [68,69]
Soluble CD44 (sCD44)	Damage of trabecular meshwork and RGC [70,71]
Erythropiotin (EPO)	Debating, attenuation of neuroinflammation or visual field loss [71,73-76]

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Conflicts of Interests

The authors have declared no financial conflicts of interests.

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