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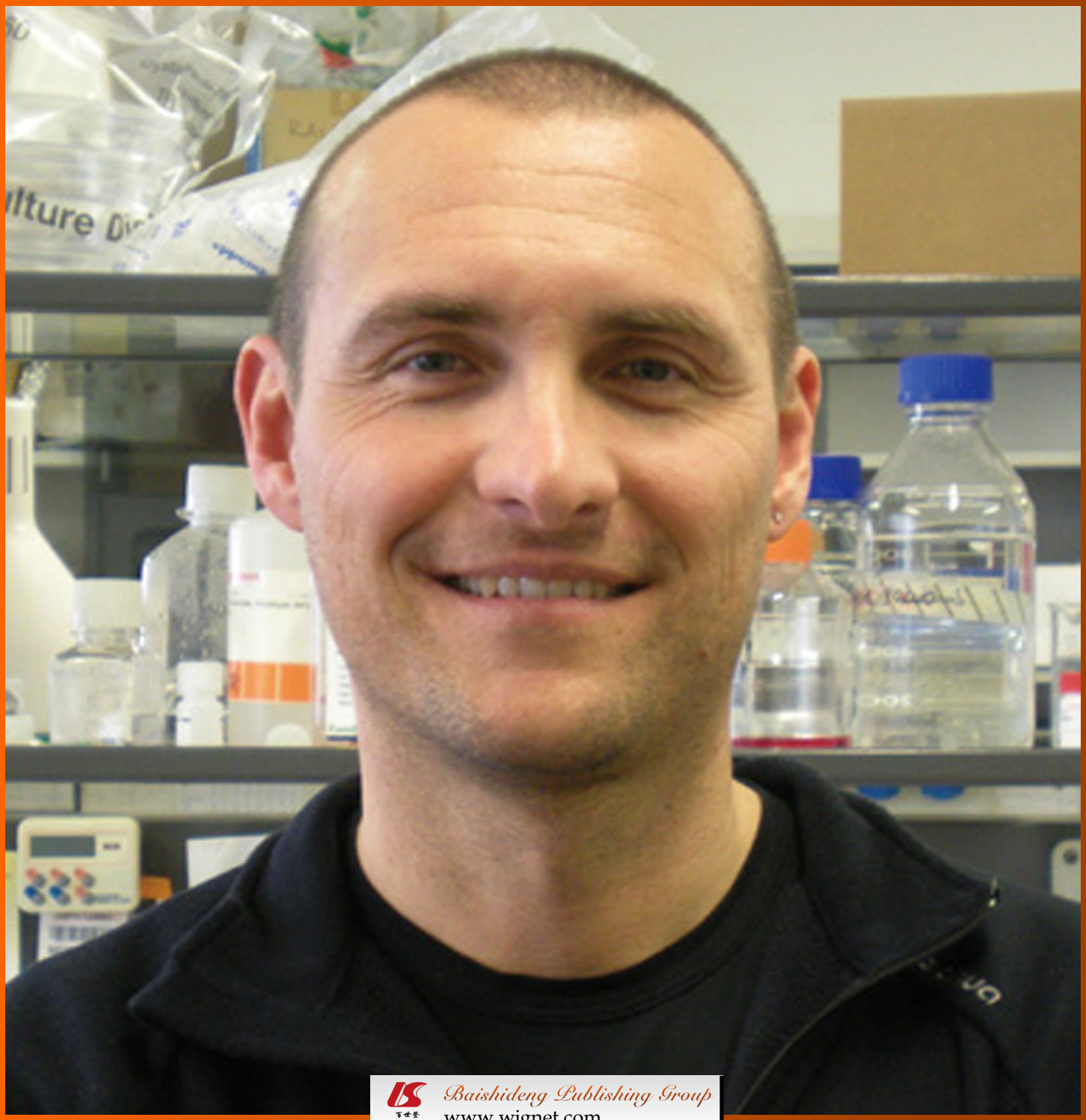

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EDITORIAL

Recent advances in cellular and molecular aspects of mammalian retinal ischemia

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Abstract

Retinal ischemia is a common clinical entity and, due to relatively ineffective treatment, remains a common cause of visual impairment and blindness. Generally, ischemic syndromes are initially characterized by low homeostatic responses which, with time, induce injury to the tissue due to cell loss by apoptosis. In this respect, retinal ischemia is a primary cause of neuronal death. It can be considered as a sort of final common pathway in retinal diseases and results in irreversible morphological and functional changes. This review summarizes the recent knowledge on the effects of ischemia in retinal tissue and points out experimental strategies/models performed to gain better comprehension of retinal ischemia diseases. In particular, the nature of the mechanisms leading to neuronal damage (i.e., excess of glutamate release, oxidative stress and inflammation) will be outlined as well as the potential and most intriguing retinoprotective approaches and the possible therapeutic use of naturally occurring molecules such as neuropeptides. There is a general agreement that a better understanding of the fundamental pathophysiology of retinal ischemia will lead to better management and improved clinical outcome. In this respect, to contrast this pathological state, specific pharmacological strategies need to be developed aimed at the many putative cascades generated during ischemia.

Key words: Cell death; Glutamate; Hypoxia; Inflammation; Neurodegeneration; Neuropeptides; Oxidative stress; Retinopathies

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INTRODUCTION

The mammalian retina is a very thin structure which obtains a limited amount of energy from the vitreous humour. When the retinal blood supply is completely blocked, the retina can still manage to survive longer than expected. However, as a system, the retina is highly vulnerable to diseases that affect the exquisitely balanced interplay of the neural retina and the vasculature that nourishes it. Visual loss occurs when this balance is disturbed. Generally, retinal diseases fall within the broad group of hypoxic ischemic disorders of neural tissue.

Ischemic condition

Ischemia means inadequate blood supply (circulation) to a local area due to impairment of the blood vessels to the area. Blood flow is either blocked, or the blood flowing

to the area has an extremely low oxygen saturation. Since all of the body's tissues need the supply of nutrients and drainage of metabolites to maintain function, ischemia can result in the shutdown of the area or significant damage to the area. Generally, ischemia causes a reduction of oxygen and glucose delivery, and, as a result, toxic metabolites, such as lactic acid, are unable to be removed. Even brief interruptions of blood flow can cause ischemia, and potentially result in a situation called an ischemic cascade, where cells with inadequate blood supply start dying and releasing toxins that damage neighbouring cells, causing them to rupture and release toxins of their own, creating a ripple effect across the area.

Ischemia should be distinguished from anoxia (a complete lack of oxygen) and hypoxia (a reduction in oxygen)[1]. Hypoxia refers to a reduction of either oxygen supply or utilisation. It may develop as a direct consequence of reduced oxygen supply, reduced ambient oxygen pO_2, low haemoglobin or impaired tissue utilisation following poisoning of the mitochondrial cytochrome enzymes. On the other hand, ischemia describes a reduction in blood supply leading to decreased oxygen delivery but, unlike hypoxia alone, there is also limited or no removal of damaging cellular metabolites. Although ischemia and hypoxia cause pathologically and clinically distinct patterns of injury, they usually coexist: ischemia always has a component of hypoxia/anoxia, but hypoxia/anoxia does not imply ischemia. Ischemia-related pathologies are central to many major diseases and pose a challenge for healthcare systems worldwide. Diseases such as myocardial infarction, angina, stroke and ischemic retinopathies are common and represent a major cause of morbidity and/or mortality worldwide.

Structure of the retina

The retina is composed of five principal neuronal cell types, including photoreceptors (the light sensitive cells in the retina), bipolar, horizontal, amacrine, and retinal ganglion cells (RGCs). A sixth type is that of interplexiform cells, that may be considered an amacrine cell variant. The basic circuitry within the retina directs the flow of visual information from photoreceptors, through bipolar cells, to RGCs, which are the only output neurons and with their axons constitute the retinofugal projections to the brain. Two horizontal pathways modulate this flow: one provided by horizontal cells in the outer retina, the other formed by amacrine cells in the inner retina. Horizontal cells are strongly electrically coupled and integrate light signals over a large retinal area. They feedback onto photoreceptors, and contact bipolar cells. Thus, inputs from a large surround region of the retina influence the response of photoreceptors and bipolar cells, providing the bipolar cell with a centre-surround organisation.

The retina is supplied by two arterial systems. While the photoreceptors of the outer retina are supplied by the high-flow blood vessels of the choriocapillaris, the inner retina has an additional intra-retinal circulation (central retinal artery)[2]. For instance, the human central retinal artery branches into a dense microvascular network with multiple capillary plexi that serve the inner retinal neurons and glia[3]. This retinal microvascular network is a true end-artery system and downstream from the precapillary arteriole the capillary beds form the key circulatory interface within the neuropile. Retinal capillary endothelia are non-fenestrated and each cell is linked by adherens and tight junctions that maintain the highly selective inner blood retinal barrier[4]. In the absence of a retinal lymphatic system, the retinal capillaries have a key role in clearing the neuropile of unwanted metabolites.

Ischemic retina

The retina is one of the most metabolically demanding tissues in the body. The rich capillary networks provide an excellent blood supply suiting the high energy demand of the retinal light processing events. When the retinal circulation does not meet the requirements of the retina, the retina suffers an ischemic damage. Since the retinal blood supply is complex, the reduction of blood flow in certain blood vessels may induce ischemia in certain parts of the retina and not in others. Thus, if either the choroidal or retinal blood flow are specifically reduced, then different parts of the retina will be affected in different way.

Retinal ischemia is a common clinical entity and, due to relatively ineffective treatment, remains a common cause of visual impairment and blindness[1,2]. Indeed, ischemia in the retina and optic nerve is assumed to be involved in the pathogenesis of major vision-threatening diseases, such as age-related macular degeneration, diabetic retinopathy and glaucoma. However, despite evidence from a substantial number of clinical and experimental studies, the role of retinal ischemia in these diseases is not understood in detail[5]. It should be noted that the cause of the symptoms in various retinal ischemic diseases is a mixture of hypoxia/anoxia rather than complete ischemia. Thus, it is tempting to speculate that hypoxia occurs in all "retinal ischemic diseases".

The pathways leading to retinal ischemia and the potential therapeutic strategies have been reviewed in several excellent papers[1,2,6]. Generally, ischemic syndromes are initially characterized by lower homeostatic responses which, with time, induce injury to the tissue due to cell loss by apoptosis. In this respect, retinal ischemia is a primary cause of neuronal death. It can be considered as a sort of final common pathway in retinal diseases and results in irreversible morphological and functional changes. Ischemia is also the driving force for new vessel formation in the retina. Retinal neovascularisation is a major cause of visual impairment. It is characterized by the development of sprouts from retinal vessels that in most cases penetrate the inner limiting membrane growing into the vitreous and leading to retinal detachment and blindness[7]. Retinal neovascularisation is observed in ischemic retinopathies such as proliferative diabetic retinopathy, retinopathy of prematurity, central vein occlusion and branch retinal vein occlusion[8].

The aim of this article is to present the recent advances on the effects of ischemia in retinal tissue and to point out experimental strategies/models performed to gain better comprehension of retinal ischemia diseases. In particular, we outline the nature of ischemic retinal damage leading to neuronal cell death and the potential and most intriguing retinoprotective approaches.

FEATURES OF ISCHEMIA AND EXPERIMENTAL MODELS

The morphological and functional changes occurring in retinal ischemia are the consequence of depleted adenosine triphosphate (ATP) stores, due to deprivation of both glucose and oxygen, though transient loss of these substrates is not immediately lethal[1,2,6]. Cell death is the result of an extremely complex cascade of biochemical responses initiated by energy failure. The main factors involved in ischemia-induced retinal degeneration are thought to be excitatory neurotransmitter release (i.e., glutamate), glial dysfunction, Ca^{2+} overload, formation of reactive oxygen species (ROS) and free radicals (oxidative stress), and release of potentially toxic mediators by activated inflammatory cells. These events finally lead to death (mostly by apoptosis) of certain cell populations or the entire retina depending on the strength and duration of the ischemic event.

A search of the PubMed database yields more than 1000 papers published in the last 10 years related to ischemia in the retina of mammals, including humans, rats, mice, rabbits and pigs. Although caution is warranted in drawing general conclusions from any single methodological approach, the study of the ischemic insult might itself provide important insights in human pathophysiology of ischemia-related diseases. Besides the common clinical implications of understanding retinal ischemia, such a model is also considered a suitable and reliable experimental setting to study (neuro) apoptotic mechanisms as well as for predicting (neuro) cytotoxicity/(neuro) cytoprotection mechanisms in the nervous system.

In vivo ischemia-reperfusion injury

Acute and transient ischemia can be induced by elevating (40-120 min) the intraocular pressure to ca. 120 mmHg followed by a reperfusion ("return-to-control" conditions) period lasting between 2 h and 60 d. This is called ischemia-reperfusion injury, which causes an inflammatory and neurodegenerative response in the intact retina. This procedure models the neuronal damage observed in diseases with transient vessel occlusions and seems to replicate vascular abnormalities observed in the diabetic retinopathy and glaucoma[9]. Ischemia classically induces an increase of glutamate levels (see below) as well as the loss of retinal neurons indicated by decreased thicknesses of the ganglion cell layer (GCL) and inner nuclear layer (INL), while apoptotic neurons can be detected in all nuclear retinal layers[10-15]. In contrast, the thickness of the inner plexiform layer (IPL) to the inner limiting membrane results significantly increased due to edema[16]. RGCs show an elevated expression of growth associated protein 43 after ischemia-inflicted damage, thus suggesting a temporal window during which RGCs may remodel their neuronal network in the damaged retina[17]. The amounts of reduction in RGCs, visually evoked potentials, scotopic and photopic electroretinogram (ERG) functions differ as the duration of ischemia increases[18]. ERG experiments showed that a- and b-wave amplitudes are also reduced[11,12,15,19]. It has been suggested that Zn^{2+}, which is abundant in neurons, accumulates following an ischemic insult and may be responsible for retinal degeneration by the induction of abnormal cyclooxygenase (COX)-2 expression[20]. After ischemia-reperfusion injury, ROS production increases[21] as well as the levels of tumor necrosis factor (TNF)-α and its receptors (TNF-R1 and TNF-R2)[10,22-24]. The levels of protein kinase C (PKC) are reduced and the expression of phosphorilated extracellular-regulated kinase 1/2 are increased in the neuroretina, although other mitogen-activated protein kinases (protein and/or mRNA levels) were found to be differentially altered in both the neuroretina and retinal arteries[24,25]. In addition, increased levels of calcineurin or matrix metalloproteinases and decreased levels of phospho-Akt/PKB or phospho-Bad have been reported[23,26,27]. Interestingly, although both protein and mRNA levels of genes expressed by distinct subpopulations of amacrine cells are reduced, transcript levels are reported to be less attenuated than protein levels[28]. In addition, heterogeneous populations of resident microglia/macrophages in the inner retina result activated early after ischemia-reperfusion injury, even before dropout of the photoreceptor cells, and exhibit different antigenic expression which are further altered in the recovery phase[29,30]. The cytokine osteopontin is exclusively expressed by RGCs in the physiological retina, but in response to retinal ischemic neurodegeneration is synthesized *de novo* by endogenous, activated microglia[31]. Concerning the retinal glia, some Müller glial cells die by apoptosis, and clusterin produced and released by Müller cells may play an important pathogenetic role[14,32]. Interestingly, glial cells in the post-ischemic retina, but not in control retina, swell upon hypotonic stress. Swelling of control cells could be evoked when their K^+ channels are blocked. After transient ischemia, glial cells strongly downregulate their K^+ conductance and differentially modulate K^+ channel expression[33-35]. An involvement of water channel aquaporins has been also suggested[12,36].

Ischemic pre-conditioning, in which a brief (minutes) ischemic episode and recovery period precede the ischemia-reperfusion procedure, has been reported to effectively prevent subsequent retina neurodegeneration[11,37]. The ischemic pre-conditioning model has been recently used to demonstrate that neurodegeneration and vascular dysfunction in response to retinal ischemia-reperfusion may be functionally separated, thus suggesting that diseases that include an ischemic retinal response

may require combination therapies for protection of both vascular and neural function[11]. The activation of translational activity seems to be a mediator of ischemia-associated damage in the retina, and ischemic pre-conditioning may prevent activation of this mechanism[38,39]. In particular, an altered expression of genes implicated in the immune response and in apoptosis may be involved in ischemic pre-conditioning. Recently, neuroprotection by retinal ischemic post-conditioning, i.e., transient ischemia after more lengthy, damaging ischemia, has been also described[40-42]. Post-conditioning significantly protects retinal function and histology from ischemia-reperfusion injury through a mechanism that involves *de novo* synthesis of proteins[42]. One possible explanation of the effectiveness of ischemic post-conditioning is that it augments intrinsic neuroprotective mechanisms initiated during ischemia. Increasing duration of the damaging ischemic insult may therefore impact the effectiveness of ischemic post-conditioning. Ischemic pre-conditioning, in contrast, sets in motion a series of neuroprotective events prior to the onset of ischemia. Thus, ischemic pre-conditioning and ischemic post-conditioning may operate by different mechanisms. In this respect, many different factors have been shown to play a role in the neuroprotection and neural function of ischemic pre- and/or post-conditioning. Among them, adenosine A1 and A2a receptors, ROS, nitric oxide, p38α, mitogen-activated protein kinase phosphatase-1, PKC α and γ, Akt subtypes, iron and autophagic signals[43-54]. These reports indicate the presence of robust and redundant signalling systems which concur in the development of ischemic pre-/post-conditioning.

Other in vivo models

Ischemic optic neuropathy is a common disorder caused by disruption of the arterial blood supply to the optic nerve which can result in significant loss of visual acuity and/or visual field. An ischemic optic nerve injury may be produced by intravenous injection of Rose Bengal dye followed by argon green laser application to the retinal arteries overlying the optic nerve, causing a coagulopathy within the blood vessels and disruption of optic nerve and retinal perfusion[55,56]. After this ischemic injury, oligodendrocytes, as well as RGCs, undergo progressive stress, with dysfunction and apoptosis. Similar results have been obtained by crushing one optic nerve for few seconds after a partial orbitotomy[57]. An endothelin-1 (ET-1)-induced chronic optic nerve ischemia model was obtained by delivering ET-1 at a constant rate for weeks[58]. In primates, chronic optic nerve ischemia causes demonstrable and localized damage of the optic nerve, without intraocular pressure elevation. There is preferential loss of large RGC axons in animals with significant axonal loss. These results suggest that ischemia-induced focal axonal loss is similar to human glaucoma and may represent a differential regional vulnerability[59].

Different approaches to induce retinal ischemia through the modulation of retinal blood flow have been also used. For instance, the occlusion of small retinal arteriolar branches by argon laser coagulation to induce focal ischemic insults induced protein changes in the cytoskeleton of RGCs, implying that the local environment plays an important role in modulating axonal structure and function[60]. In addition, typical signs of ischemia manifested in these retinas include development of stable retinal edema, decrease in the b/a ratio of the ERG b and a-wave amplitudes, pronounced disorders in the retinal microcirculation system, cell death of the inner layers[61]. Eyes under the experimental branch retinal vein occlusion display signs of retinal damage and ischemia on ophthalmoscopy, fundus photography, and fluorescence angiography[62]. In addition, after ischemic damage by permanent bilateral common carotid artery occlusion, a severe degeneration of all retinal layers has been reported. In particular, there is a reduction in retinal thickness and a robust loss of cells in the GCL[63]. In addition, the intensity of immunostaining for vesicular glutamate transporter 1, γ-aminobutyric acid transporter, and PKCα, but not that for glial fibrillary acidic protein, results dramatically decreased[64]. Recently, it has been reported that retinal ischemia induced by elevating intraocular pressure mostly affects Müller glial cells, whereas retinal ischemia induced by middle cerebral artery occlusion induces only a small-scaled axonal transport disturbance[65]. Another model of retinal ischemia has been obtained by clamping the ocular perfusion pressure in the left eye to 5 mmHg for few hours[66]. In these conditions, multifocal ERG shows a decrease in retinal functions and no signs of recovery were found within the 6-wk observation period. Quantitative histology reveals a highly significant reduction in the number of RGCs, amacrine cells and horizontal cells after the ischemic insult. Similarly, the transient ligature of the ophthalmic vessels has been shown to induce degeneration of the inner retinal layers and the retinotectal projection, 3 mo after the insult[67]. As expected, microarray analysis has revealed that the central retinal artery ligation-induced retinal ischemia, followed by reperfusion, is characterized by a time-dependent modulation of different gene families, as for instance transcription-related genes, protein kinase-related genes, and apoptosis-related genes[68].

Ex vivo models

The advantage of *ex vivo* models is the option to make direct observations and measurements of cellular responses to chemicals in a defined extracellular environment. In addition, in these models blood flow effects are excluded. Classically, an ischemic condition may be obtained in retinal slices by perfusion with oxygen deprived/low glucose solution. In these conditions, ischemic retinal damage has been found to be dependent on the Ca^{2+} concentration in the perfusion medium[69].

The first model of the ischemic mouse retina has been obtained by incubating retinas in N_2-saturated PBS containing iodoacetic acid[70]. These retinas showed a marked apoptotic cell death and immunohistochemical analyses

demonstrated that different retinal cell populations respond differently to the ischemic insult. Consistent with a role of glutamate excitotoxicity in ischemia-induced neuronal death, retinal glutamate release was observed to increase under ischemic conditions. In addition, among G protein-coupled receptor kinases (GRKs) and regulators of G protein signalling (RGSs), GRK1 and RGS1 expressions have been reported to increase in the *ex vivo* ischemic retina[71].

In rats, retinal explants have been subjected to chemical ischemia by incubation with PBS containing iodoacetic acid and sodium cyanide. In this model, ischemia has been shown to cause diffuse apoptotic cell death and to abolish choline acetyltransferase, tyrosine hydroxylase and neuronal nitric oxide synthase (nNOS) immunoreactivities in the INL, IPL and GCL. It also abolished PKC immunoreactivity in rod bipolar cells and terminals, but did not damage RGCs immunolabeled with antibodies directed to microtubule-associated protein-1[72].

PERSPECTIVES ON ANTI-ISCHEMIC TREATMENTS

As summarised above, several distinct factors are involved in the degenerative events promoted in the retina by an ischemic condition. The mechanisms leading to neuronal damage and the interplay among these factors are extremely complex. A comprehensive review by Osborne and colleagues[1] has elucidated the state of the art at the beginning of the new millennium. In the following paragraphs, we will consider the most recent advances in the research of agents that may interfere with the main events associated with retinal ischemia (i.e., excess of glutamate release, oxidative stress and inflammation), and in the possible therapeutic use of naturally occurring molecules such as neuropeptides.

Glutamate

Glutamate is the major excitatory neurotransmitter in the retina and it mediates the flow of visual information through the "vertical" retinal pathway, being released by photoreceptors, bipolar cells and RGCs, although it is also in a subset of amacrine cells. It has long been known that glutamate administration to retinal tissue *in vitro* leads to histological damage. A vast quantity of data demonstrates that the process of glutamate excitotoxicity occurs during retinal ischemia and that this process plays a fundamental role in the pathogenesis of ischemic retinopathy. Excitotoxicity in retinal ischemia is mainly mediated by metabotropic N-methyl-D-aspartate (NMDA) receptors and extensive evidence has established the protective role of different NMDA antagonists, as for instance, MK801, dextrometorphan, and sulfasalazine[1], in retinal ischemia. In addition, there is also a quantity of experimental data demonstrating a role for non-NMDA [2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (AMPA)/kainate] ionotropic receptor activation in retinal ischemic injury[1]. Therefore, activation of both NMDA and non-NMDA glutamate receptors is likely to occur during or subsequent to retinal ischemia, and over-stimulation of both receptor types can induce pathological changes[1].

Glutamate levels: In the ischemia-reperfusion *in vivo* rat model, glutamate levels have been directly measured using a microdialysis probe placed into the retinal tissue in conditions of high intraocular pressure. This method revealed a 90% increase of glutamate levels which was reversed by a pre-treatment with the NMDA antagonist MK801. In addition, the same antagonist as well as an antagonist of non-NMDA receptors (i.e., GYKI52466) significantly reduced RGC death, thus confirming the notion that retinal ischemia results in increased intraretinal levels of glutamate with consequent excessive activation of NMDA and non-NMDA receptors leading to excitotoxic, glutamate-mediated, RGC death[73]. Another study suggests that in the ischemic retina glutamate is released by both amacrine and bipolar cells in the inner nuclear layer[74].

Glutamate and apoptosis: One interesting question concerns the relationships between glutamate excitotoxicity and apoptotic cell death in the ischemic retina. Optic atrophy 1 (OPA1) is a mitochondrial inner membrane GTPase whose release participates in the rapid and complete release of cytochrome C in apoptotic cell death[75]. OPA1 has been shown to be released from mitochondria after ischemia induced by increased intraocular pressure. This event is inhibited by MK801, suggesting that NMDA over-activation leads to a distinct mitochondria-mediated cell death pathway in ischemic retinas[76]. In addition, it has been reported that the protective effect on RGCs in the ischemic retina exerted by an antagonist of the glycine site-specific NMDA receptor is concomitant with a reduction of the expressions of Bax, Ca^{2+}/calmodulin-dependent protein kinase Ⅱ, cytochrome C oxidase, caspase-3, and glutamate [NMDA] receptor subunit zeta-1 and with an increase of the Bcl-2/Bax ratio, suggesting that this antagonist might act through inhibition of apoptotic signalling[77].

Another link between ischemia-induced glutamate excitotoxicity and retinal cell death is provided by Ca^{2+} channel activation. Indeed, it has convincingly been shown that several blockers of Na^+/Ca^{2+} channels and intracellular Ca^{2+}-sensitive receptors exert neuroprotective effects on retinal ischemia[15,78,79]. In this line, calbindin D28k, calretinin, and parvalbumin, members of the EF-hand Ca^{2+}-binding protein family, may play important neuroprotective roles against ischemia due to their ability to buffer Ca^{2+}[80,81]. In addition, it has been reported that the Na^+/Ca^{2+} exchanger (NCX), which can cause Ca^{2+} overload in pathological conditions with consequent neuronal cell death, may play a role in retinal cell death induced by NMDA and ischemia-reperfusion. Indeed, NCX1(+/-) mice possess significant protection against retinal damage induced by intravitreal injection of

NMDA, while SEA0400, a selective NCX inhibitor, significantly reduces NMDA- or high intraocular pressure-induced retinal cell death in mice and cell damage in oxygen-glucose deprived RGCs[82]. Finally, spider toxins acting as Ca^{2+} channel blockers have been reported to reduce glutamate content and cell death in oxygen-glucose deprived retinal slices[83].

Glutamate receptor modulation and expression: Modulation of the NMDA receptor may result in important neuroprotective effects. This is the case of the α2-adrenergic receptor agonist brimonidine, which has been reported to modulate NMDA receptor function through a reduction of intracellular cyclic adenosine monophosphate production and to protect RGCs in rat glaucoma and rabbit retinal NMDA excitotoxicity models[84]. In addition, brimonidine has also been observed to reduce the effects of ischemic optic neuropathy[55] or of ischemia-reperfusion injury in rats[85].

AMPA-type glutamate receptor (GluR) subunits have been observed to be altered in the ischemic retina. In particular, retinal ischemia-reperfusion leads to differential changes in the expression of the different AMPA-type GluR subunits, which may affect excitatory synaptic transmission in the inner retina[86]. Shortly after ischemia-reperfusion, immunolabeling of GluR1, -2/3, and -4 is strongly decreased, whereas the corresponding mRNA levels are not affected, indicating degradation at the protein level. In contrast, the GluR2 protein appears to be relatively stable under post-ischemia conditions[87].

Glutamate transporters: Excess in extracellular glutamate leading to excitotoxicity in the ischemic retina is likely to be due to failure of glutamate transporters. It is well known that glutamate transport, mainly *via* glutamate aspartate transporter (GLAST) and glutamate transporter 1 (GLT-1), is a cardinal mechanism for maintaining glutamate homeostasis in normal and pathological conditions. A central question in retinal ischemia is therefore whether glutamate transporters can remove glutamate from the extracellular space under ischemic conditions. Concerning glutamate transporter localization, it is not altered after the insult, despite severe retinal degeneration[88]. In a rat glaucoma model, a significant increase of GLT-1 in the ischemic retina was reported, while GLAST, expressed in Müller cells, remained stable[89]. In any case, glutamate transporter function is severely impaired after ischemia, but a limited glutamate removal from the extracellular space has been shown to persist during simulated ischemia[90], suggesting that pharmacological enhancement of glutamate transporter activity may reduce tissue damage resulting from toxic extracellular glutamate concentrations. Trimetazidine, an anti-ischemic metabolic agent which is recognized as an efficient drug against ischemic injuries, was found to inhibit the extracellular glutamate accumulation in rat retina. It can also reverse the ischemia-induced inhibition of glutamate transport in rat Müller cells and, likely due to this positive action on the glial glutamate transporter, it protects the retina against excitotoxic damage[91].

Oxidative stress

Glucose/oxygen deprivation and excessive glutamate release result in the formation of free radicals, which have been proposed as important mediators in retinal damage caused by ischemia. The detrimental effects of ROS can be appreciated by considering the retinal injury following reperfusion after ischemia. It may appear paradoxical that recovery of blood flow results in retinal damage, however a quantity of oxygen-derived and other free radicals are formed when reduced compounds, which accumulate during ischemia, are reoxidized. A free radical burst then characterises the early stage of reperfusion, and it overwhelms normal cellular antioxidant defence mechanisms, causing oxidative stress and retinal injury. Not only the mitochondria of neuronal cells generate free radicals, but also activation of glial cells and infiltrating leukocytes release inflammatory mediators, such as arachidonic acid, nitric oxide and cytokines, which all play major roles in the formation of free radicals following ischemia[1]. However, the question as to whether the post-ischemia increase in nitric oxide production is beneficial or detrimental to the retina has proved difficult to answer. In this respect, increased nitric oxide levels are reported to participate in protective effects of some compounds but also to induce retinal damage [mainly trough inducible nitric oxide synthase (iNOS) activation][1] (see also below), suggesting that activation of nitric oxide synthase (NOS) causes cell death or the opposite. This is partly due to the lack of specificity of the majority of pharmacological tools employed to date, partly due to the variety of different experimental protocols, and partly to the complexity of the nitric oxide system in the retina[1]. Thus, a critical evaluation of the role of nitric oxide in retinal ischemical damage is still to come and further work is clearly necessary to sort this out.

Antioxidant enzymes: An evaluation of the expression and protein levels of antioxidant enzymes in the rat retina exposed to oxidative stress induced by ischemia-reperfusion injury indicated a very modest, if any, response to oxidative stress[92]. However, delivery of antioxidant enzyme genes through administration of plasmids encoding superoxide dismutase 2 or chloramphenicol acetyltransferase significantly reduced levels of superoxide ion, H_2O_2, and 4-hydroxynonenal as well as the ischemia-reperfusion-induced apoptosis of retinal vascular cell and retinal capillary degeneration[93].

Antioxidant molecules: Ischemia-reperfusion induces a decrease in glutathione levels[94]. Not surprisingly, the administration of antioxidant agents has been found to significantly protect retinal neuronal elements from the effects of ischemia-induced oxidative stress. This is the case of lutein, which has been reported to inhibit the increase of nNOS and COX-2 expression levels[95] and

to protect both outer and inner retinal neurons from ischemic damage[96]. Together with lutein, three other commonly used antioxidants (vitamin E or α tocopherol, fenugreek or *Trigonella foenum-graecum* and germander or *Teucrium multicaule*) have been reported to exert protection against *in vivo* retinal ischemia-reperfusion injury in rats[97]. In general, multiple vitamin E forms have been demonstrated to be effective in preventing retinal injury following ischemia-reperfusion[94,98]. Recent data show that nicotinamide attenuates injury to the retina caused by ischemia-reperfusion probably acting as a an antioxidant[99]. Similarly, antioxidant protective mechanisms may underlie the protection against ischemia-reperfusion induced morphological changes and lipid peroxidation provided by fibroblast growth factor whose biostability is improved by modification with polyethylene glycol[100].

An important group of antioxidant molecules with a positive effect against retinal ischemia is that of flavonoids[101,102]. The antioxidant epigallocatechin gallate (EGCG), a catechin-based flavonoid derived from green tea, stimulates glutathione (GSH) levels[103] and protects retinal neurons *in vivo* from ischemia-reperfusion and *in vitro* from oxidative stress by H_2O_2[103,104]. It has been reported that EGCG is effective in protecting RGCs from ischemia-reperfusion challenge by ameliorating retinal nitrosative stress and by regulating cell death through apoptotic pathways[105]. In addition, orally administered EGCG attenuates injury to the retina caused by ischemia-reperfusion where caspases are activated[106]. Finally, the isoflavone genistein has been reported to blunt the effects of ischemia to the retina[107], while the flavonoid baicalin counteracts ischemic and oxidative insults to retinal cells and lipid peroxidation to membranes of nerve cells[108].

Radical scavengers: In addition to antioxidant molecules, agents acting as radical scavengers exert important protective actions against ischemia. Ferulic acid significantly attenuates retinal ischemia-reperfusion induced alterations by acting as a hydroxyl radical scavenger[109], while edaravone protects the retina from ischemia-reperfusion injury in rats by reducing oxidative stress and inhibiting apoptosis of retinal neurons[110]. The radical-scavenging activity of docosahexaenoic acid may also be protective against oxidative stress-induced cell damage in RGCs[111].

Other molecules: A variety of other molecules displaying protective effects against ischemia-induced oxidative stress in the retina, but which cannot be classified as known antioxidants or radical scavengers has been investigated in recent years. For instance, retinal lipid peroxidation, induced by ischemia-reperfusion[94], may be attenuated by the anti-ischemic metabolic agent trimetazidine[112]. Aldose reductase, the first and rate-limiting enzyme in the polyol pathway, contributes to retinal ischemic injury through increased edema and free radical accumulation[113]. The aldose reductase inhibitor fidarestat significantly counteracts cell death and sorbitol pathway intermediate accumulation in ischemic retinas[114]. Coenzyme Q10, an essential cofactor of the electron transport chain, affords neuroprotection[115] probably preventing the formation of the mitochondrial permeability transition pore[116]. D-allose, a rare sugar, may protect neurons in the ischemic retina by decreasing extracellular glutamate and attenuating oxidative stress[117]. The transcription factor nuclear factor (erythroid-derived 2)-like 2 is a master regulator of the antioxidant response, and it is implicated in cytoprotective mechanisms in the retina in response to ischemia-reperfusion injury[118]. Agmatine is an endogenous polyamine that is widely distributed in the brain and other tissues. It binds with high affinity to α2-adrenoceptors and inhibits NMDA receptors and NOS in the brain. Agmatine exerts a significant neuroprotective effect on guinea pig retinas after transient ischemia-reperfusion insult[119]. H_2S at low concentration is neuroprotective against oxidative stress. ACS67, a hydrogen sulfide-releasing derivative of latanoprost acid, acts as an H_2S donor and stimulates GSH levels and significantly attenuates H_2O_2-induced toxicity to RGCs in culture[103]. Plant derivatives have also been shown to blunt the effects of retinal ischemia. Recent data report that *Polygonum Bistorta L*. n-butyl Alcohol has a therapeutic effect on retinal ischemia-reperfusion injury by increasing the activities of NOS terminator and endothelial NOS, decreasing the activity of iNOS, elevating the content of nitric oxide and enhancing retinal anti-oxidative activity[120]. In addition, *Lycium barbarum* polysaccharides, extracted from wolfberries, are good for "eye health" according to Chinese medicine. Pre-treatment with polysaccharides for 1 wk effectively protected the retina from neuronal death, apoptosis, glial cell activation, aquaporin water channel up-regulation, disruption of the blood-retina barrier and oxidative stress[121]. Finally, caffeic acid phenethyl ester can protect the rat retina from ischemia-reperfusion injury by enhancing the anti-oxidative ability and inhibiting the apoptosis of retinal cells[122].

Inflammation

It is widely accepted that acute inflammatory responses contribute to ischemic brain injury, especially following reperfusion. In retinal ischemia, potentially toxic mediators are released by activated inflammatory cells, by glial elements, and by injured neurones. Different roles of arachidonic acid, NOS (especially iNOS), cytokines such as interleukin-1, and TNF-α have been described[1]. In addition, the importance of inhibiting adhesion molecules involved in leukocyte-endothelium interactions in retinal ischemia has been demonstrated. Indeed, reduction of intercellular adhesion molecule 1 (ICAM-1) mRNA expression in the ischemic rat retina obtained with pitavastatin is associated with attenuation of ischemia-induced leukocyte-endothelial interactions[123]. Further, triamcinolone acetonide, an anti-inflammatory drug constituted of a corticosteroid suspension that downregulates adhesion molecules of retinal vascular endothelium, inhibits

leukocyte-endothelium interactions in the retina after ischemia and effectively decreases retinal thickness due to edema[124].

Inhibition of COX-2 and iNOS: Concerning the arachidonic acid pathway, it has been reported recently that COX-2 blockade with celecoxib, a selective COX-2 inhibitor, rescues RGCs from death after ischemic injury, while in COX-2 knockout mice RGCs are resistant to ischemia-reperfusion injury[125]. On the other hand, it has been demonstrated that phenylbutyrate, which inhibits iNOS levels, can play a role as an effective retinal protector against the damaging effects of ischemia in rats[126].

TNF-α: Retinal ischemia results in increased expression of TNF-α and its receptors[127]. A study investigating the role of CD40, a member of the TNF-receptor superfamily, in the pathogenesis of retinal injury identified CD40 as a regulator of retinal inflammation and neurovascular degeneration. The observations support a model in which CD40 stimulation of endothelial and Müller cells triggers adhesion molecule up-regulation and chemokine production, promoting the recruitment of leukocytes that express iNOS/COX-2[128].

TNF-α plays a largely deleterious role in ischemia-reperfusion injury, and direct neutralization of this cytokine partially preserves retinal function[22]. Indeed, it has been reported that the histone deacetylase inhibitor trichostatin A protects the retina from ischemic injury and that its neuroprotective effect is associated with the suppression of retinal TNF-α expression and signalling[129]. In addition, thalidomide treatment has also been found to reduce the effects of retinal ischemia-reperfusion through a decrease of TNF-α synthesis[130].

Combined effects on inflammation mediators: A number of recent studies have revealed a variety of factors that may reduce the effects of retinal ischemia acting on the expression of cytokines, chemokines, cell adhesion molecules or TNF-α, or on NOS activity or expression. For instance, nuclear factor-κB (NF-κB) is an essential transcription factor that controls the gene expression of cytokines, chemokines, growth factors, and cell adhesion molecules. Pentoxiphylline, an antioxidant, has been found to decrease the up-regulated activation of NF-κB and the expression of proinflammatory cytokines, TNF-α and interleukin (IL)-1β in rat retinas following ischemia-reperfusion[131]. Certain NF-κB-regulated proinflammatory and redox-active pathways are central to glial neurotoxicity induced by ischemic injury. In retinas of transgenic mice in which NF-κB pathway was suppressed specifically in astrocytes, neuroprotection was associated with significantly reduced expression of proinflammatory genes, encoding TNF-α, chemokine (C-C motif) ligand 2 (CCL2), C-X-C motif chemokine 10 (CXCL10), IL-1β, vascular cell adhesion molecule 1, several subunits of NADPH oxidase and NOS[132].

Byproducts of heme degradation (bilirubin, ferritin, and CO) have been proven to confer cellular protection through their anti-inflammatory, antiapoptotic, antiproliferating, and antithrombotic effects. In a rat model of ischemia-reperfusion injury, overexpression of heme oxygenase (HO)-1 obtained with cobalt protoporphyrin (a potent HO-1 inducer) was associated with inhibition of caspase-3, p53, NF-κB, and iNOS and with increased expression of Bcl-xL. At the same time, the anti-inflammatory effect of HO-1 was related to reduction in the recruitment of macrophage infiltration in the retina through the suppression of monocyte chemoattractant protein[133].

The protein encoded by the toll-like receptor 4 (Tlr4) gene plays a fundamental role in pathogen recognition and activation of innate immunity. Tlr4 deficiency has been linked with reduced neuronal death and lowered levels of proinflammatory cytokine expression in the hippocampus in models of global cerebral ischemia-reperfusion[134]. In a model of retinal ischemia-reperfusion, Tlr4 deficiency was associated with significantly increased survival of neurons and with significantly reduced expression of proinflammatory genes, including TNF-α, IL-6, CCL2, CCL5, CXCl10, iNOS, and ICAM-1[135]. Similar effects have been reported in ischemic retinas treated with phosphatidylserine-liposomes[136] or with ATP-liposomes[137].

Retinal ischemia-reperfusion induces the expression and deposition of complement components. In these conditions, injured RGCs may be targeted and actively destroyed through complement mediated processes. Complement component 3 gene deficient mice clearly exhibited reduced optic nerve damage and substantial preservation of RGCs, suggesting that inhibition of the complement cascade delays optic nerve axonal and RGC degeneration in retinal ischemia[138].

Aldose reductase activity plays an important role in ischemia-reperfusion injury in the retina. In addition to oxidative stress (see above) the mechanisms involving this enzyme may be linked to inflammation. Indeed, the aldose reductase inhibitor fidarestat has been shown to partially suppress the inflammatory response associated with retinal ischemia and manifested by increased gene expression of TNF-α and ICAM-1 as well as elevated protein levels of soluble ICAM-1[139].

Protective effects of neuropeptides

Neuropeptides and their receptors are widely expressed in mammalian retinas, where they exert multifaceted functions both during development and in the mature animal[140]. Some of these neuropeptides have also been found to play important neuroprotective actions. In particular, in recent years somatotropin release inhibitory factor (somatostatin) (SRIF) and pituitary adenylate cyclase activating peptide (PACAP) have been reported to be highly protective against retinal cell death caused by ischemia, while data on opioid peptides, corticotropin-releasing factor (CRF), endocannabinoids, angiotensin Ⅱ, and a peptide derived from the activity-dependent neuro-

protective protein have also been published.

Using an *ex vivo* rat retinal model, SRIF analogues have been described to protect the retina from ischemic damage[72]. These observations have been confirmed and expanded in an *ex vivo* mouse retinal model, showing that the neuroprotective effect of SRIF in ischemic retinas is mediated by the SRIF subtype receptor 2 (sst_2). These studies showed that an increased expression of functional sst_2[70] or the use of SRIF or SRIF receptor agonists, such as the multireceptor ligand pasireotide and the sst_2 agonist octreotide[71], protect against retinal ischemia reducing the number of apoptotic neurons, the expression of apoptotic markers, such as caspase-3 mRNA, and the release of glutamate. In contrast, cell death was increased by blocking sst_2 with the sst_2 antagonist cyanamide[71]. In addition, SRIF as well as sst_2 agonists, administered intravitreally, have been shown to protect the retina from AMPA-induced neurotoxicity *in vivo*[141].

An over-expression of functional sst_2 characterises the retinas of mice carrying genetic deletion of another SRIF receptor, sst_1[142-145]. One would expect that sst_2 agonist administration to these retinas results in greater protection from ischemic damage. However, in contrast to this expectation, in sst_2 over-expressing ischemic retinas SRIF analogues increased cell death, and octreotide also increased glutamate release. This apparent contradiction has been clarified by experimental data at pharmacological and molecular level showing that over-expressed sst_2 are likely to be rapidly desensitized by agonists (i.e., octreotide), thus resulting in a decrease of their functional activity[71].

The mechanisms by which the somatostatin analogues prevent the damage produced by chemical ischemia require further elucidation. However, a role of nitric oxide and cyclic guanosine monophosphate has been proposed as mediators of SRIF protective action against retinal ischemia[146].

PACAP is known to protect the retina against a variety of insults[147]. In particular, a neuroprotective effect of PACAP against RGC loss induced by ischemia following high intraocular pressure in the rat has been reported recently[148]. In general, PACAP acts by activating anti-apoptotic and inhibiting proapoptotic signalling pathways in the retina[147]. Indeed, the retinoprotective effects of PACAP are not phenotype-specific, but it rather influences general cytoprotective pathways irrespective of the neuronal subtypes in the retina subjected to the effects of ischemia[64].

Concerning opioid peptides, recent evidence demonstrates that activation of one or more opioid receptors can reduce the effects of ischemia-reperfusion injury by the suppression of TNF-α production[10]. In addition, intravitreal administration of morphine immediately after reperfusion blunts the effects of ischemia-reperfusion injury, and pharmacologic evidence suggests that this protective action may be mediated, at least in part, by opioid receptors[16,149]. Possible protective effects of CRF are suggested by a study showing that intraocular administration of urocortin 2, a paralog of CRF that preferentially activates CRF2 receptors, may preserve the thickness of retinal layers and reduce RGC loss in ischemic retinas[63]. Retinal ischemia has also been found to induce modifications in the retinal endocannabinoid metabolism and there is evidence that drugs that interfere with the endocannabinoid system may prevent retinal damage due to ischemic insult[150]. Further, a recent study reports that ischemia promotes the expression of angiotensin Ⅱ type 1 receptor in the inner retina and that blocking this receptor may attenuate the retinal ischemic damage[21]. Finally, NAP, a synthetic 8-amino acid peptide (NAPVSIPQ) derived from activity-dependent neuroprotective protein and playing important roles in neuronal differentiation and survival, has been found to exert a neuroprotective action *in vivo* after retinal ischemia and optic nerve crush[57].

CONCLUSION

At present, a working hypothesis to comprehensively explain the causes and the detrimental effects of retinal ischemia is still lacking. As outlined above, the cascade of events leading to cell death and their prevention may be similar in retinal ischemia and hypoxia. However, in basic sciences such a distinction could be important to develop and study experimental models which may simulate the human retinal ischemic disease in a more precise way and so provide valuable information for future treatments. On the other hand, to contrast this pathological state, specific pharmacological strategies need to be developed aimed at the many putative cascades generated during ischemia. In this respect, a better understanding of the fundamental pathophysiology of retinal ischemia will lead to better management and an improved clinical outcome.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

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Both personal authors and an organization as author

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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Conference paper

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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