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Review Article

The Interplay between Retinopathy and Senescence, Origin of a Possible Treatment of Retinal Diseases: Review of the Literature

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ABSTRACT

Retinopathy is a complex disease affecting the eye at different ages and whose etiological factors are multiple (diabetes, cardiovascular and nervous diseases, inflammation). The consequences of the latter are first of all difficulties in detecting light at the level of the eye and which can evolve until causing blindness. Recent studies have confirmed a direct relationship between retinopathy and senescence, these discoveries have opened up motivating perspectives to guide the lines of research in order to trace an effective treatment against this disease. The main supporting hypotheses aim to curb destructive angiogenesis in the retina first and foremost, while understanding the mechanisms involved and intervening appropriately to reverse them through the elimination of senescent cells and counteracting the inflammation triggered, one of the major characteristics of retinopathy.

Recent therapeutic trials for the evaluation of different possible treatments for retinopathy are based on experimental animal models.

Based on *in vivo* experimental studies (in mice or rats) reproducing retinopathy in humans, therapeutic trials testing various substances alone or in combination, and monitoring, in particular at the molecular and genetic level, the discoveries scientists could be to offer an effective cure for this disease affecting a large population across the world.

Moreover, working in this context would be beneficial even for other diseases such as diabetes, cardiovascular diseases, nervous diseases and all kinds of pathologies related to angiogenesis and senescence. Finally, achieving control of senescence is not only an objective of curing retinopathy, this physiological behavior is essential for all living beings, stopping aging is quite simply an extension of life at the cellular or the whole organism.

Keywords: Retinopathy; Diabetes; Angiogenesis; Senescence

INTRODUCTION

The primary issue hindering the eye's ability to perceive light and potentially leading to blindness is retinopathy (diabetic or premature). Once established, this retina's disease was characterized by a proliferation of blood vessels brought on by ischemia as a result of the death of blood capillaries in the eye, which would result in hypoxia and have effects on the neurological system [1].

A retinal detachment or even a reversal of neovascularization may result from these vascular structures stiffening and becoming fibrotic at an advanced stage [2].

The injured retina will naturally respond or behave in a way that stimulates the angiogenesis process, which is triggered and controlled by a number of different factors.

As a result, the retina, one of the tissues with the highest metabolic activity, receives an interruption in its normally flawless arrangement of ocular arteries, which provide it with nutrients and gas. Hypoxia in the tissue and intense inflammation characterize this injury [3].

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Recent experimental studies have shown a direct link between retinal ischemia and the Senescence Associated Secretory Phenotype that causes senescence (SASP). Several cytokines are also linked to the function of this trait (plasminogen activator inhibitor 1, IL6, IL8, Endothelial vascular growth factor) [4].

These complexes generate pathological damage that prompts pathological angiogenesis, which is what causes the early senescence of ischemic retinal cells mostly as a result of inflammatory cytokines. This incident worsens damaging angiogenesis, which prevents blood vessels from healing normally.

Understanding and managing this process (attempting to reverse it) promises a therapeutic approach to combating not just these retinal illnesses but also, on a larger scale, cell longevity and anti-aging.

LITERATURE REVIEW

Retinal pathologies

The preservation of healthy blood vessels in the eyes is crucial for maintaining proper vision. Guidance signals, angiogenic stimulators, and inhibitors all affect how many endothelial cells proliferate and create new blood vessels. Both sick and healthy neovascularization depend on angiogenesis.

Angiogenesis changes the flow of nutrients and oxygen, which in turn imbalances the demand and supply of metabolic energy. This change subsequently has an impact on brain and visual functioning. Cancer, cardiovascular disease, dementia, and proliferative retinopathy are only a few of the illnesses that have pathological angiogenesis as their underlying cause [5]. Leaky tuft-shaped arteries associated with hemorrhage and retinal exudates that result in retinal injury, retinal detachment, or both are signs of pathological retinal neovascularization [6].

Abnormal ocular angiogenesis can be brought on by a variety of eye disorders, such as Retinopathy of Prematurity (ROP), Diabetic Retinopathy (DR), neovascular retinopathy, and others.

Eye abnormalities are primarily brought on by conditions that affect the eye directly, such as glaucoma and cataracts, or by conditions that affect the eye indirectly, such as hypertension, arteriosclerosis, and diabetes [7]. Reduced visual acuity, visual impairment, and even blindness can be caused by several disorders.

Diabetic retinopathy: Diabetes is a condition that is primarily characterized by an insulin and glucagon hormonal imbalance, while it can also be brought on by environmental and hereditary causes. Having an ongoing sugar surplus in the blood is one of its defining features. We are dealing with an epidemic since the prevalence of the latter disease grows every day throughout the world. Diabetes targets blood vessels, particularly those of the retina, which is noted for having a highly developed vascularization.

A major contributor to blindness and visual impairment is Diabetic Retinopathy (DR): For many years, this illness is not evident; symptoms only appear when complications have occurred. With adequate screening and care, vision loss can be prevented [8]. Treatment delay is the primary cause of vision loss. The only way to enable early diagnosis and treatment is through routine examination. Laser therapy, whose efficacy has long been established, can actually help to significantly reduce blindness and visual impairment associated with diabetic retinopathy.

Micro aneurysms, retinal hemorrhages, amirs (intraretinal microvascular abnormalities), venous abnormalities, retinal ischemia, exudates, cotton wool patches, and neovascularization are the chief clinical symptoms connected with diabetic retinopathy.

The mechanisms of diabetic retinopathy: In the retina (the layer of neurons lining the back of the eye that transmits visual information from light to the brain) of patients with diabetes, at an early stage there is a degeneration of the blood vessels that irrigate the eye, which results in oxygen and nutrient deprivation, triggering the second stage to grow uncontrolled and destructive blood vessels inside the eye. The most widely used therapeutic interventions at the level of the eye (sick blood vessels) are currently accompanied by undesirable effects, the first of which is the destruction of the retina itself. It is therefore essential to succeed in overcoming these therapeutic limits and to explore new pharmacological avenues [9].

Screening for DR and Age-related Macular Degeneration (AMD): The focus of DR and AMD prevention is on ongoing monitoring and early intervention. In addition to preventing blindness and lowering mortality rates, these preventative measures can slow or stop the advancement of certain diseases. Cost effective screening on large populations is required because there are no obvious symptoms in the early stages of DR and AMD, and the severity and number of symptoms fundamentally grow over time. The goal of screening, a secondary preventative measure, is to identify and treat problems that have previously manifested but have not yet progressed to the point where they necessitate medical treatment. According to studies, older individuals and those with more severe diabetes frequently attend screening sessions [10]. The progression of these disorders is also examined at least once every one to three years, which provides an increasing amount of data for the examination. For the purpose of DR and AMD screening, an image analysis system must be created.

Premature retinopathy: ROP, which affects over 16,000 infants annually in the United States, is a major contributor to childhood blindness [11]. Worldwide, preterm birth affects 10% of children, many of whom have lifelong visual impairment [12]. ROP is a biphasic disease, with the first phase characterized by vascular loss and the second by vessel multiplication. Infants born prematurely have incompletely vascularized retinas with an avascular area at birth because retinal blood vessels in humans start to form during the fourth month of pregnancy and reach the retinal periphery soon before birth.

After birth, the relative hyperoxic environment compared to in utero inhibits the normal secretion of angiogenic growth factors, which causes the vascular loss phase of ROP, or the regression of preexisting vessels. The retina becomes ischemic when there is

insufficient blood flow between birth and the gestational age of about 30-32 weeks, which causes tissue hypoxia and the release of hypoxia-induced angiogenic growth factors such Vascular Endothelial Growth Factor (VEGF). At around 32 to 34 weeks of gestation, the vascular proliferation phase of ROP starts. Retinal new vessels may result in retinal detachment and blindness in severe ROP.

Glaucoma: The eye condition glaucoma results in a permanent reduction in the field of vision. It is a side effect of harm to the optic nerve. It is related to elevated internal eye pressure (intraocular pressure). It ranks as the second major global cause of blindness [13].

Cataract: The crystalline lens, the converging lens inside the eye, can become partially or completely opaque in a cataract. The progressive loss of vision caused by this opacification is first accompanied by sensitivity to light (photophobia). Due to trauma, this loss of eyesight may occur quickly (within a few weeks) [14].

Age-related Macular Degeneration (AMD): Age-related Macular Degeneration (AMD) is the underlying condition, which has symptoms identical to those of diabetic retinopathy. It begins to manifest after the age of fifty and causes changes in the macular retina's function, which impacts central vision. After 50 years, there are 8% more people with the condition overall. Accordingly, it is roughly 1% to 2% between 50 and 65 years old, 10% between 65 and 75 years old, and 25% between 75 and 85 years old. The general prevalence rises steadily with age.

Atrophic and exudative age-related macular degeneration are the two clinically recognized subtypes (20% of cases) [15].

Other vascular diseases of the eye: Macular telangiectasia type 2 is characterized by anomalies of the retinal neurosensory system and the macular capillary network, although its etiology is unknown. The disease initially manifests in the fovea's center, yet it has the potential to spread to an oval area around the foveola [16]. Several uncommon human eye illnesses, such as familial exudative vitreoretinopathy and norrie disease, are characterized by incomplete peripheral retinal vasculature and a lack of deep retinal vascular layers. There have already been numerous different eye disorders with aberrant angiogenesis covered in other places [17,18].

Senescence

From childhood till the end of life, the eye senescence is a physiological condition that steadily advances.

In addition, aging is a complicated phenomenon, making it impossible to define and comprehend the entire process using a straightforward method. However, mounting evidence suggests that cellular senescence is a key factor in the emergence and advancement of numerous unfavorable characteristics of aging [19].

Senescence is marked by two notable events. First, the loss of physiological hypermetropia at age six as a result of the cessation of eye growth and the completion of the maturation of the visual pathways, and second, the onset of presbyopia at age 45 as a result of the lens's accommodative power decreasing to the point where it is now perceptible.

Furthermore, the development of a pathological condition, such as persistent glaucoma, diabetic or hypertensive retinopathy, cataract, or Age-related Macular Degeneration (AMD), may interfere with this physiological process.

Visual acuity, visual field, chromatic sense, contrast sensitivity, depth perception (binocular vision), but also all aspects of oculomotricity are factors that affect the sense of sight.

From both a physiological and pathological perspectives, the genetic element is crucial to senescence [20]. Since human aging is not uniform, prevention should play a more prominent part in aging management. This is based on screening by an organized ophthalmological exam, particularly in families at risk.

Biological markers of cellular senescence: Senescence detection is therefore based on a number of markers that are indirect of senescent cells, the best known of which is beta-galactosidase associated with the senescence (SA-β-gal). However, biological markers reflecting the direct proof of cellular senescence have not yet been fully identified. Lysosomal beta-galactosidase activity is often measured at low pH levels (typically around pH 4), but in senescent cells due to the growth of the lysosomal compartment, becomes detectable at higher pH levels (pH 6). High expression of p53, p16, p21, p38 mitogen-activated protein kinase (p38MAPK), and H2AX, which indicate activation of DNA damage responses, are additional recognized indicators of cellular senescence.

Otherwise, HMGA proteins or heterochromatin markers, such as HP1 and trimethylated histone H3 (H3K9me3), are acknowledged as molecular markers of heterochromatin foci connected to senescence and are regarded as cellular indicators of senescence.

Chronological aging is linked to the emergence of age-related clinical conditions such atherosclerosis, diabetes, and heart failure, which are defined by the buildup of senescent cells.

Recent studies have shown that vascular smooth muscle cells and senescent endothelium cells are present in atherosclerotic plaque. Senescent vascular endothelial cell buildup is also associated with diabetes, and endothelial cell senescence itself causes systemic glucose intolerance by impairing skeletal muscle metabolism. Cellular senescence and disruption of systemic metabolism are likewise well known to be closely related.

In numerous models, cellular senescence is suppressed or eliminated, and proof of concept studies have shown that preventing the growth of senescent cells may serve as a treatment for age-related diseases.

Vascular senescence in arterial disease: Two important factors that accelerate the development of age-related vascular dysfunction are ROS and persistent low-grade sterile inflammation. Ageing causes senescent cells to build up in arteries, whether or not a person develops vascular problems associated with old age. Increased levels of phosphorylated p16, p21, p38, and double-stranded DNA breaks, together with

increased SA-Gal activity, distinguish aging rodent and human vascular tissues. According to reports, aged people have higher levels of p53 and p21 expression as well as telomere decapsulation, a structural disintegration of telomeres. A recognized risk factor for atherosclerotic disease is hypertension, and hypertensive patients' arteries have been found to have higher levels of p53 binding to the p21 promoter.

Senescence of endothelial cells and VSMCs in the aorta was seen in a mouse model of genomic instability, accompanied with decreased vasodilation, increased vascular stiffness, and hypertension.

Endothelial cell senescence in arterial disease: Endothelial cells play numerous biological roles, including angiogenesis, blood pressure regulation, coagulation, and systemic metabolism. They are crucial for maintaining vascular homeostasis.

Reduced migration and proliferation, decreased expression of angiogenic molecules, and poor production of Nitric Oxide (NO), which is produced by NO Synthase (NOS) and promotes vasodilatation, are all characteristics of the dysfunctional phenotype that develops in aged endothelial cells. Low NOS activity in defective endothelial cells typically results in decreased NO generation.

Studies show that cellular senescence contributes pathologically to the pro-oxidant, pro-inflammatory, vasoconstrictor, and prothrombotic features that dysfunctional endothelium cells acquire. It was discovered through an autopsy investigation of ischemic heart disease patients that internal mammary arteries do not have a rise in SA-β-gal activity, but coronary arteries do. In cells at the luminal surface of coronary arteries, SA-β-gal activity is increased (probably endothelial cells). Human aortic endothelial cells that are senescent also have higher levels of ICAM-1, whereas youthful cells have lower levels of endothelial Nitric Oxide Synthase (eNOS) and NO activity.

Pro-inflammatory cytokines including interleukin-6, tumor necrosis factor alpha, and monocyte chemotactic protein-1 are expected to circulate at higher amounts as people age. It is very possible that the buildup of senescent endothelium cells increases the vulnerability to atherosclerotic illnesses by causing persistent sterile inflammation and vascular remodeling in the arteries of the elderly. Physical activity can lessen or reverse the alterations that aging and growing ROS levels cause in terms of NO bioavailability (lower levels of p53, p21 and p16 in endothelial cells of brachial arteries and antecubital veins).

Secretory products associated to senescence: Senescent endothelium cells affect nearby cells *via* their secretome, known as senescence-associated secretory products, which compromises the function of the endothelial lining of arteries (SASPs). TGF-β, galectin-3, IGFBP-3,-4, and-6, MIC-1, and other site-specific components make up SASP. Collagen XVIII and its C-terminal anti-angiogenic component, endostatin, are overproduced by dysfunctional senescent endothelial cells. A high-resolution mass spectrometric investigation of the secretome of endothelial progenitor cells identified 133 proteins, some of which were membrane-bound and others secreted (36). Particularly, soluble versions of VEGF receptors, adhesion molecules, semaphorin 3F and TGF- β, CD109, members of the Roundabout family, as well as endothelial indicators, were found. Colony-forming units are the progenitors of mature endothelial cells, and mass spectrometry screening of their secretome revealed 272 non-redundant proteins, of which 124 were also detected in cultivated EPCs.

MMP-9, IL-8, MIF, different cathepsin and protease inhibitors, S100 proteins A11, A8 and A4, PAI-2, apolipoprotein E, as well as proangiogenic and pro-survival factor, thymidine phosphorylase, were among the secretion products. In many ways, the variety of functional consequences that normal and dysfunctional secretomes may offer are still unclear.

Senescence has traditionally been linked to an accelerated aging process of neurons, blood vessels, and retinal immune cells in regions where blood vessels have been injured. It has been demonstrated that retinal cells are resilient and do not perish when their main source of oxygen and nutrients is cut off due to illness. Instead, they go into a state of cellular senescence (or aging) where they are dormant but start a complicated or multifactorial process that makes blindness more likely.

The activated chemicals during this accelerated aging process have been listed and identified thanks to this exciting research.

Better retinal blood vessel regeneration and lessened retinal damage have been seen in mice with retinopathy treated for early cellular aging using currently available medicines and new medications under development.

"The current treatments for diabetic retinopathy may be intrusive or, if used long-term, may have unwanted side effects. No cure leading to a cure is discovered by our research. We may now imagine novel therapeutic strategies to halt the disease process and so preserve vision, however, because we have identified the chain of molecular occurrences that results in premature senescence linked to retinopathy, according to Mike Sapieha.

Therapeutic trials: Inhibition of one of the three main cellular aging pathways-sirtuins, Target of Rapamycin (mTOR), or insulin-like growth factor is the foundation of emerging approaches in rejuvenation pharmacology. The restoration of stem cell competency in aged animals was revealed by groundbreaking investigations on heterochronic parabiosis (the sharing of the circulatory system between young and old mice), which led to the prospect of rejuvenation therapy. Growth Differentiation Factor 11 (GDF 11), a member of the activator/TGF-superfamily, has been discovered using modified aptamer-based proteomic technology as one of the substances present in the serum of young mice, diminished in aged animals, and capable of restoring cardiac function when supplementing old mice.

A variety of small molecules SIRT1 activators have been created and are currently being investigated in light of prior research on SIRT1 and the activation of this enzyme by resveratrol. Sirtuin-Activating Compounds (STACs) exert their effect by allosteric activation of this deacetylase. In addition to resveratrol, quercetin, and butein (first generation), there are three generations of STAC: SRT 1720, 1460, and 2183 (second generation), and STAC-5, -9, and -10 (third generation), all of which extend service life or both. Clinical trials for these

substances are currently being conducted. In reality, dietary restriction functions *via* mTOR signaling and NAD dependent pathways together with a shift towards oxidative metabolism, both of which constitute novel mechanisms of rejuvenation therapy, and may promote SIRT1.

The cofactor NAD^+ is required for the activation of a number of sirtuins. Disease conditions and aging limit the bioavailability of NAD^+. Nicotinamide, a precursor to NAD^+, is paving the way as a treatment for NAD^+ insufficiency.

Based on a series of discoveries involving mTOR activation and the ensuing autophagy deficiency in senescence, rejuvenation therapy has found another target. Even when used at advanced age, the mTOR inhibitor rapamycin has been found to have rejuvenating effects.

Animal models of retinal diseases

All retinopathy diseases have been reproduced experimentally by almost similar models of these in humans,

- OIR model in cat, mouse, rat, dog, and fish.
- Animal models of DR are generated through surgical injury, laser or chemical damage, drugs, or diet. Genetic models are created with selective gene editing in rodents.
- Animal models of neovascular age-related macular degeneration.
- Genetic models include transgenic mouse models with intraretinal angiogenesis, subretinal angiogenesis, and deficient intraretinal angiogenesis.

RESULTS AND DISCUSSION

Recent research has proven that vascular senescence plays a harmful function, particularly in cardiovascular illnesses, all metabolic disorders, and retinopathies. In order to maintain physiological function, nutrients and oxygen had to be transported to the organs and tissues by the circulatory system. Vascular homeostasis is greatly influenced by the roles performed by blood vessels, particularly vascular endothelial cells and VSMCs.

In several experimental models, the reduction of vascular cell senescence improves the phenotypic aspects of aging, whereas vascular cell senescence increases the development of age-related illnesses such as diabetes, atherosclerosis, and heart failure.

Even though their metabolic input was significantly reduced, hypoxic areas of the retina in one of the mouse animal models of ischemia retinopathy revealed relatively mild rates of apoptosis.

The involvement of the enzyme Inositol-Requiring 1a (IRE1a), through its endoribonuclease activity, promotes a state of senescence in which cells take on a Senescence Associated Secretory Phenotype, according to transcriptome and genomic study of inducible loss of function (SASP). In the vitreous fluid of patients with proliferative diabetic retinopathy, its effect is combined with that of additional substances such cytokines linked with SASP (plasminogen activator inhibitor 1, interleukin-6, interleukin-8, and vascular endothelial growth factor). Inhibiting SASP with intravitreal metformin injection or blocking senescence effectors (semaphoring 3A or IRE1a) in mice reduced harmful retinal neovascularization *in vivo*. These findings demonstrate the role of SASP in the pathological development of arteries, senescent prematurity of ischemic retinal cells, aberrant inflammatory cytokine release, impaired destructive angiogenesis, and obstruction of reparative vascular regeneration.

This process' reversal might be therapeutically advantageous. Additionally, recent research has shown that age-related alterations can be reversed by specifically removing senescent cells. For instance, demaria and colleagues discovered that genetic removal of senescent cells prevented mice's wounds from healing. Senolytic agents are currently being tested in a number of clinical trials with the aim of determining whether the combination of specific predefined treatments may prevent premature aging in hematopoietic stem cell transplant recipients (clinical trials. gov identifier: NCT02652052), decrease pro-inflammatory cells found in skin biopsies taken from patients with idiopathic pulmonary fibrosis (clinical trials. gov identifier: NCT02874989), or reduce (clinical trials. gov id: NCT02848131).

Senescent cell depletion has been demonstrated to inhibit the pathological development of atherosclerotic plaque in rodents, indicating that senolytic medicines may one day serve as a new type of treatment for vascular-related diseases.

In the same context, Oubaha, et al. asserted that activation of NETose would result in a decline in senescent endothelial cells and a decrease in pathogenic neovascular clusters in proliferative diabetic retinopathy, but that the adverse effects on vascularization would still be considerable.

Therefore, any therapeutic action must be taken prior to neutrophil granulocyte recruitment utilizing "senolytic" medicines to remove senescent cells and thereby lessen inflammation. The revascularization of retinal tissue would also be accelerated by such an approach, which would further aid in the speedy recovery of vision.

CONCLUSION

In the healthy body, the retina is irrigated by two vascular sources of blood: The central retinal artery transporting blood to the inner retina and the choriocapillaris which irrigate the retinal pigment epithelium and the outer retina.

Pathologic causes of vision threatening neovascularization will arise from either vascular bed.

The nervous system and more specifically the neurons control vision by receiving and executing the signals received from the eye, the slightest deficit in nutrients and respiratory gases transported by the blood vessels for these neurons can disrupt visual functions or even trigger neovascularization pathological. In addition, neuronal and vascular interactions involving glial cells are important in modulating angiogenesis in the retina, of which this physiological phenomenon is intimately dependent on the state of general homeostasis, in particular: The phenomenon of vasomotion managing the pressure systemic

and arteriolar arterial, oxidative stress and lipid peroxidation, genetic factors are also confirmed involved and influencing retinal angiogenesis, immune reactions related to inflammation, immune cell motility, cytokines, hemostasis, apoptosis, and without forgetting senescence, which once controlled, offers an efficient alternative to stop or control all the physio pathogenesis pathways of diseases causing retinopathy such as diabetes.

AUTHOR CONTRIBUTIONS

A. A: Consulted, analyzed and summarized the literatures, designed the study, revised and drafted the manuscript; H.S: Revised the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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