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General review

Update of inflammatory proliferative retinopathy: Ischemia, hypoxia and angiogenesis

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ABSTRACT

Diabetic retinopathy (DR) and retinopathy of prematurity (ROP) present two examples of proliferative retinopathy, characterized by the same stages of progression; ischemia of the retinal vessels, leads to hypoxia and to correct the problem there is the setting up of uncontrolled angiogenesis, which subsequently causes blindness or even detachment of the retina. The difference is the following; that DR initiated by the metabolic complications that are due to hyperglycemia, and ROP is induced by overexposure of the neonatal retina to oxygen. In this review, we will demonstrate the physiopathological mechanism of the two forms of proliferative retinopathy DR and ROP, in particular the role of the CD40/CD40L axis and IL-1 on vascular complications and onset of inflammation of the retina, the implications of their effects on the onset of pathogenic angiogenesis, thus understanding the link between platelets and retinal ischemia. In addition, what are the therapeutic targets that could slow its progression?

Contents

Abbreviations: AGE, advanced glycation end products; ANG, angiopoietin; APCs, antigen-presenting cells; APJ, apelin receptors; ATP, adenosine triphosphate; CCL2, chemokine (C-C motif) ligand 2; DR, diabetic retinopathy; ECFC, human endothelial colony forming cells; EPO, erythropoietin; EPOR, erythropoietin receptor; FGF, fibroblast growth factor; gp39, cartilage glycoprotein 39; GPCR, receptor-coupled protein G; HIF, hypoxia inducible factor; HREC, human retinal endothelial cells; ICAM1, inter Cellular Adhesion Molecule; IGF-1, insulin-like growth factor-1; IL-1, interleukin-1; IL-1R, interleukin-1 receptor; Jak3, Janus 3 Kinase family; Mac-1, macrophage-1 antigen; MAPK, mitogen-activated protein kinases; MCC950, which is a potent and specific inhibitor of the inflammasome; MCP-1, mast cell protease 1; MiRNA-126, microRNAs 126; MMP, matrix metalloproteinases; MPV, mean platelet volume; MV, microvesicles; NFκB, nuclear factor-kappa B; NLRP3, inflammasome; NO, Nitric oxide; NOS, nitric oxide synthase; OIR, model of O2-induced retinopathy; P75NTR, neurotrophin receptor; PAF, platelet activating factors; PAR2/ F2RL1, the receptors activated by the proteinases; PCT, total mass of platelets; PDGF, platelet derived growth factor; PDW, indicator platelet size distribution; PHD, prolylhydroxylase; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLCR, ratio of newly produced platelets with the largest volume; PLCγ, phospholipase Cγ; PMV, platelet microvesicles; PSGL-1, p-selectin glycoprotein ligand-1; PTAFR, platelet activating factor receptor; REP, retinal pigment epithelium; ROP, retinopathy of prematurity; ROS, reactive oxygen species; RP, proliferative retinopathy; RPE, retinal pigment epithelium; RTK, tyrosine kinase receptors; sCD40L, soluble form of CD40L; Sema 3A, semaphorin-3A; SiRNA, small interfering RNA; STAT5, signal transducer and activator of transcription 5; TF, tissue factors; TIMPs, tissue inhibitor of metalloproteinase; TNFR, tumor necrosis factor receptor; TNFα, tumor necrosis factor-alpha; TRAF, TNF receptor-associated factor; VCAM-1, vascular cell adhesion protein; VEGF, vascular growth factor; VEGFR, vascular growth factor receptor; α5β1, alpha-5 beta-1; αIIbβ3, glycoprotein IIb/IIIa.

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Introduction

Proliferative retinopathy whether diabetic or premature are characterized by the same stages of progression, certainly the triggers differ from one form to another. Their development continues with a retinal microvascular degenerative phase, associated with a gradual cessation of peripheral vascularization, which leads to hypoxia, leading to retinal ischemia that predisposes to pathological vitreous angiogenesis, and consequently detachment of the retina or permanent loss of sight. Proliferative retinopathy is a multifactorial disease studied in humans and animals [1,2]. Today, with technological advances, it is useful to induce an animal model in the laboratory [2–5] representing the same characteristics in affected patients, which will facilitate the comprehension of the pathological mechanism involved, so think about correcting it.

Many studies aimed at validating the following hypothesis; Inflammation plays a crucial role in the pathogenesis of RP [1,6,7], remains to know its exact mechanism, which is currently the subject of intensive research. Several inflammatory factors intervene in the progression of the disease (1, 3)especially the CD40 receptor and its ligand. Since the discovery of CD40 two decades ago, the studies have shown that the CD40 / CD40 L axis plays a major role in the progression of inflammatory pathophysiology, including the retinopathy that interests us [8].

The second player being IL-1, defines as a potent central pleiotropic cytokine for many inflammatory processes, able to inducing an acute or even chronic inflammatory response after interaction with its ubiquitously receptor IL-1R [9]. In the next chapter, we detailed the physiopathological mechanism induced by these two actors.

In summary, this review is an update of published research on the pathophysiological mechanism of proliferative retinopathy. To illustrate the evolution of research conducted in this area, and what are the essential points that have not be studied so far. We will try to understand the inflammatory mechanism involved in the triggering and development of this proliferative form, in order to guide future therapeutic approaches towards more targeted points, for the recurrence or even the suppression of the disease.

The role of the CD40 / CD40 L axis and IL-1 in inflammation

Inflammation is an essential physiological mechanism, responding to various situations of oxidative stress, hypoxia, ischemia and senescence. Can thus become pathological depending on the intensity and chronicity of the response.

To date, several inflammatory mediators potentially involved in the development and progression of vascular diseases have been identified, in particular the CD40 /CD40 L axis, which is receiving increasing attention.

The CD40 L protein consists of 261 amino acids with a C-terminal domain located in the extracellular region and an N-terminal domain in the intracellular region of the molecule [10,11]. This transmembrane form facilitates its interaction with its receptor CD40, thus the induction of intracellular signals. Apart from the membrane form, there is also a soluble form of CD40 L (sCD40 L) circulating in the blood, this form comes almost exclusively from enzymatic cleavage at the activated platelet membrane [12–14]. Moreover, sCD40 L is the most used form in research, firstly its intact functionality and on the other hand the close correlation, which exists between its plasma levels and the appearance of several vascular clinical syndromes [15]. Thus, sCD40 L is an important activator of platelets, which predisposes them to exacerbated thrombosis in response to vascular damage [15].

CD40 L so called, CD154, gp39, TBAM and TRAP, originally identified at the level of activated immune cells, play both pro-thrombotic and pro-inflammatory roles [8]. These two roles are explained as follows; CD40 L was detected on platelet surfaces within seconds after their activation [16] and proved to activate the endothelium, once it is activated by platelet, CD40 L in cooperation with TNFα and IL-1, it secretes chemokines and adhesion molecules thus recruiting leukocytes to the site of lesions [13,16]. Therefore, the CD40 / CD40 L axis and platelets contribute directly to inflammation of the vascular wall.

CD40, the high affinity CD40 L receptor, is a type I transmembrane protein. Contrary to CD40 L, the C-terminal domain of the receptor is located in the intracellular region and the N-terminal domain found on the extracellular side. The extracellular region has a typical rearrangement of proteins belonging to the TNF receptor family [14].

For a long time, the CD40 considered the only receiver for CD40 L. During the last few years, three other receptors have been identified, the αIIbβ3, Mac-1 and α5β1 integrin's [12,17–19]. Although, CD40 remains the main high affinity receptor for CD40 L, these new partners appear to perform a very specific function under different physiopathological conditions.

Thus expressed constitutively on APCs, CD40 can be present on non-hematopoietic cells [3,20]. José-Andrés C. Portillo team carried out the experiments in 2014 [3] in this sense, and they revealed that retinal endothelial cells, Muller cells, retinal ganglion neurons, microglia and REP cells (retinal pigment epithelium) they express CD40 at low levels [21]. At a given moment, following a triggering factor, for example, diabetes, the activated cells over-express CD40 on their surface, and thus contribute to inflammation. Proven recently by a study of Muller cells, which represent the glial cells of the retina; they indicated that the presence of CD40 in Muller cells is sufficient to increase inflammatory markers in the retina and promote retinopathy [22].

The CD40 / CD40L axis originally discovered on cells involved in immunity, such as B and T lymphocytes [23,24]. On the other hand, we know today the presence of this complex mainly in the cells of the vascular system; it has an important function in the inflammation, hence its role in the development of retinopathy. The increased importance of CD40 / CD40 L in vascular diseases are evidenced by the close relationship between circulating levels of sCD40L in patients and the appearance of pathophysiology [17,25]. In a model of experimental diabetic retinopathy, they used mice with limited CD40 expression in Müller cells and wild-type mice to identify the signaling pathways by which CD40 triggers pro-inflammatory responses in retinal cells. After incubation with peptides blocking the signaling pathway (CD40-TRAF2, 3 or CD40-TRAF6), they found as results: inhibition the expression of adhesion molecules ICAM1 and MCP-1 protein thus inhibiting prostaglandin and VEGF [3]. Blocking of a single signaling pathway was sufficient to inhibit the expression of major factors that contribute to the progression of retinopathy [3]. The discovery of a new TRAF-2 / Rac1 / p38 MAPK signaling pathway in response to soluble CD40 L (sCD40 L) by the Dr Merhi's Lab [26]. They were able to show the effect of the CD40 / sCD40 L axis on platelet aggregation, and thus a positive correlation between circulating sCD40 L levels and arterial thrombosis. Now the sCD40 L considered at an important biomarker that used in the future as a diagnostic and preventive tool in treatment, since its rate increases with the severity of diabetic retinopathy [26,27].

The union of CD40 by its ligand promotes the grouping of CD40 and induces the recruitment of known adapter proteins TNFR-associated factors (TRAF) to the cytoplasmic domain of CD40 [28]. The following proteins activate different signaling pathways, including canonical and non-canonical nuclear signaling pathways (NFκB), mitogen-activated protein kinases (MAPK),

phosphoinositide 3-kinase (PI3K), and phospholipase Cγ (PLCγ) [28]. Signaling can occur independently of TRAF proteins, with Janus 3 Kinase family (Jak3), which binds directly to the cytoplasmic domain of CD40. It has be shown that Jak3 binding induces phosphorylation of the signal transducer and transcription activator (STAT5) [29,30]. These complex pathways induce essential CD40-mediated signals by acting on the regulation of gene expression, for example the expression of pro-inflammatory cytokine genes in myeloid cells during diabetes [31] in particular the increase in the expression of TNF-α, IL-1β, inducible nitric oxide synthase 2 (NOS2) and CCL2 [11,32].

CD40 also leads to the upregulation of intracellular adhesion molecules I (ICAM-1) and (CCL2),which increases the nitration of proteins and the number of leukocytes adhering to blood vessel walls (leukostasis) in the retina of diabetic mice, leading to at vaso-obliteration continuation by capillary ischemia [22]. Will make it possible to control inflammatory disorders. The figure below (Fig. 1) shows that platelet activation by a stimulus such as hyperglycemia in diabetics, ROS in prematures neonates will lead to exocytosis of platelet granules containing CD40 L, which will remain at the surface of the cell or be excised by metalloproteases. Once bound to its receptor, the CD40 / CD40 L axis will activate signaling pathways leading to the activation of transcription of inflammatory genes and consequently activation of the retinal endothelium and amplification of the inflammatory phenomenon.

The C40 / CD40 L axis thus leads to the synthesis of IL-1, which plays an important role in regulating the immune mechanism responsible for retinopathy.

Two genes that encode the cytokine of inflammation (IL-1); IL-1 A and IL-1B encode IL-1α and IL-1β respectively [33]. They bind to the same type 1 IL-1R cell surface receptor that is present almost on all cells, once bound, the IL-1 / IL-1R axis triggers a cascade of cellular events leading to the regulation of the expression of inflammatory mediators, chemokines and other cytokines [9,33,34].

IL-1α is present constitutively in the healthy cells of the individual, particularly the platelets, once activated following a stimulus; it allows cellular infiltration, including neutrophils in the inflammatory site, which leads to early ischemia [33,34].

Conversely, IL-1β is not present in the healthy cells of the individual, it requires a series of intracellular events before it can trigger inflammation, obviously hyperglycemia, TNF, IL-18, IL-1α, IL-1β itself will induce transcription of inactivated IL-1β. That will be activated by the action of caspase 1(33).

We will show IL-1 mediated inflammation in both forms of proliferative retinopathy. Kowlin Ra and his team [35] examined the role of IL-1β in retinal capillary cell and pericytes death in diabetic retinopathy. They found that exposure to high glucose concentrations (a model reflecting hyperglycemia) triggers an increase in the IL-1β level, leading to an increase in the level of NO. Which leads to the increased activation of NF-κB, within the same cells, they noticed the increase of the apoptotic activity with the acceleration of the phenomenon. Thus the activation of various genes involved in the inflammatory response, which will allow the amplification of inflammation, which makes possible the destruction of the blood-retinal barrier and the cellular infiltration and one will end up having not perfused capillaries. Consequently an ischemia leading to an uncontrolled neo-vascularization [35,36] as shown in Fig. 2 below. To control the effect of IL-1β, they added the IL-1ra receptor antagonist, all IL-1 mediated abnormalities were removed, so this approach can be effective in treatment [33,35].

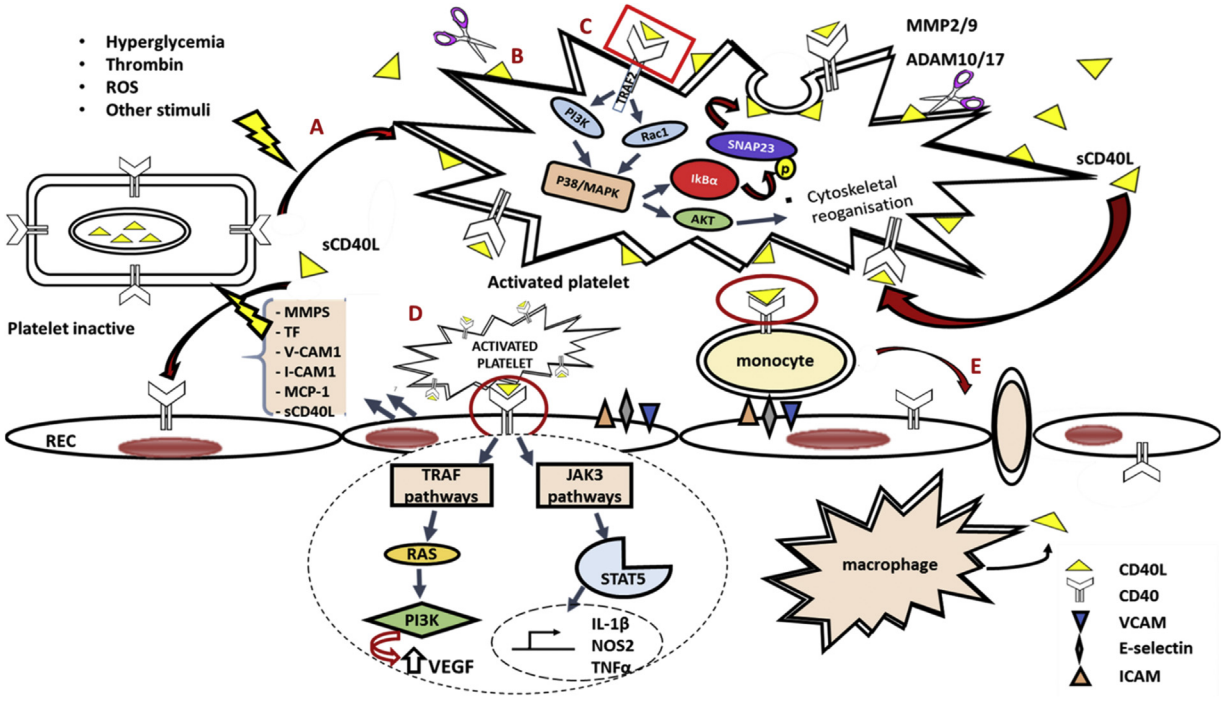

Fig. 1. Activation of the retinal endothelium and other immune cells by platelet CD40 / CD40L axis Hyperglycemia, and the oxygenated free radicals formed in premature newborns and other stimuli will allow activation of platelets **(A)**, resulting in exocytosis of platelet granules containing CD40 L, which will be translocated into the membrane or they will be excised by metalloproteinases such as MMP2, MMP9, ADAM10 and ADAM17 **(B)**. The union of the CD40 L and its platelet receptor CD40 will activate PI3K and RAC1 signaling pathways, which are initiated by the receptor-associated factors (TRAF), and the response will be the reorganization of the cellular cytoskeleton, and activation the factor SNAP23 by phosphorylation, which will reinforce the exocytosis of platelet granules containing the CD40 L **(C)**. The soluble or membrane CD40 L will activate retinal endothelium (REC) after interaction with their CD40 receptor, thus enabling the activation of TRAF-dependent and TRAF-independent signaling pathways thus called the JAK pathway. Leading to the transcription of pro-inflammatory genes such as IL-1β, NOS2 and TNFα, and angiogenic genes that encode vascular growth factors such as VEGF, and also overexpression of cell adhesion molecules such as ICAM, VCAM and E-selectin, will play an important role in cellular infiltration **(D)**. Monocytes expressing CD40 in their surface will be activated and differentiate into macrophage after infiltration **(E)**.

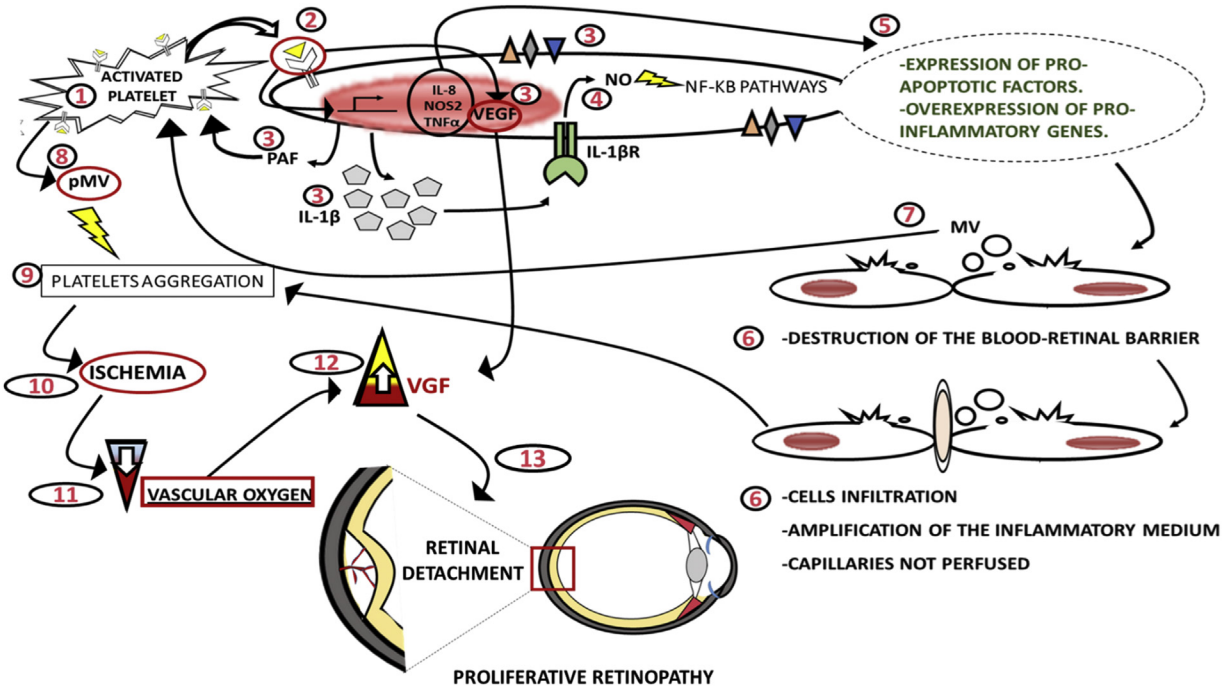

Fig. 2. The relationship between the CD40 / CD40L platelet axis and IL-1β in triggering proliferative retinopathy **1**. Activation of platelets by a stimulus. **2**. Activation of retinal endothelial cells (REC) through platelet CD40L. **3**. Activation of the CD40 receptor by its ligands will allow both the overexpression of inflammatory proteins such as IL-8, NOS2 and TNFα and vascular growth factors (VEGF), synthesis of platelet activation factors (PAF), and especially the overexpression of IL-1β. **4.** IL-1β will bind to its receptor (IL-1βR), it will induce the synthesis of nitric oxide (NO), which will in turn activate the NF-KB signaling pathway in an increased way. **5**. There will be overexpression of pro-apoptotic and inflammatory factors. **6**. The inflammatory medium will promote the destruction of the blood-retinal barrier and cellular infiltration, thus allowing the amplification of inflammation at this level, and consequently the capillaries will become uninfused. **7**. The debris of the apoptotic cells will give birth to microvesicles (MV), which will in turn activate the platelets. **8**. Activated platelets release their own vesicles (pMV). **9**. The activation of platelets by these various stimuli will allow their aggregation. **10**. Capillary occlusion by platelet aggregation and by cellular infiltration generate an ischemic environment. **11**. The ischemic retinal capillaries will be provided with oxygen and will become hypoxic. **12**. Variation in vascular oxygen level will be detected by molecular switches (HIFs), that regulate the synthesis and secretion of inflammatory mediators and growth factors (VGF). **13**. The vascular growth factors will allow the formation of neo-vessels in an uncontrolled manner, and they branch out towards the vitreous by exerting a strong pressure on the retina from where its detachment.

For the model of retinopathy of prematurity, the immune system of premature newborns remains immature, so it is always at risk. Following prenatal, perinatal and postnatal infection or other, they revealed the presence of the following inflammatory factors IL-1β, TNFα, and IL-6 as primary initiators of inflammation [37]. They can mediate activation of cytokine receptors, thus inducing upregulation downstream of effector molecules [1]: including IL-8, which plays a role in inflammation and angiogenesis [38]. RANTES that allows cellular infiltration into inflammatory sites [26]. MCP-1 that can attract a variety of immune cells that will contribute to the destruction of the blood-retinal barrier, growth factors VEGF, IGF-1 and MMP-1 and 9 that show the main actors of pathogenesis of ROP. The initiator cytokines of inflammation also activate proapoptotic factors, including Sema 3A, which allows vascular disintegration and forms a chemical barrier, thus pushing the neovessels into the vitreous [1]. All these events allow progression to retinopathy with all the steps previously described.

The role of platelets in the development of RP and angiogenesis

Inflammation and angiogenesis are mainly involved in the progression of proliferative retinopathy. During retinal vasobliteration either by metabolic complications in diabetic subjects DR or by free radicals overproduced in premature neonates ROP, an inflammatory microenvironment is present, including platelet activation and cellular infiltration and their adherence to this level, resulting in ischemia, and therefore a hypoxic microenvironment. Which will stimulate the production of pro-inflammatory cytokines and especially the pro-angiogenic factors necessary for uncontrolled angiogenesis. What role does platelets play in the development and progression of proliferative retinopathy?

Uncontrolled activation of platelets contributes to ischemia and thus the onset of angiogenesis that characterizes proliferative retinopathy as shown in the two previous figures. Recent studies have identified biomarkers that reflect morphology and platelet activation; they have found a close relationship between them and the progression of the disease [39–44]. Under normal conditions insulin is a natural antagonist of platelet hyper-activation, but any defect in the action of insulin in a diabetic subject, Platelet activity remains disordered and therefore the onset of retinal microvascular event [39,44]. In a diabetic subject, there is an increase in the size and function of activated platelets with denser granules containing a significant amount of serotonin, β-thromboglobulin and thromboxane A2. That will be secreted into the media, thus generating increased activation other platelets, we will have a microenvironment with a very large number of activated platelet with a larger size and consequently the increase in platelet aggregation and retinal vascular complications observed in diabetic retinopathy [42,45]. Mean Platelet Volume (MPV), a measure of platelet size, reflects changes in platelet stimulation level or platelet production rate, when the mean platelet volume (MPV) is large, the probability of having retinal vascular complications and ischemia is higher, so there is a positive correlation between MPV and diabetic retinopathy [41]. As mentioned above, there are other markers that reflect platelet morphology [43]. Such as PDW, which is an indicator of the platelet size distribution, it is a more specific marker [46].The second marker PLCR, tells us about the ratio of newly produced platelets with the largest volume, when the value is important, this is a

significant platelet aggregation. The last markers being PCT that tells us the total mass of platelets [41,43]. The studies have already approved the relationship between the stage of retinopathy and the MPV, PDW, PCT values that tell us about the morphology and alteration of platelet function.

When the endothelial cells are activated (thrombin, IL-1β . . .), they release platelet activating factors (PAF) shown in figure2 [47]. PAF are pleiotropic phospholipids, having a powerful role in platelet aggregation, vascular permeability, microvascular leakage, thrombus formation, leukocyte adhesion to endothelial cells pro-inflammatory cytokine releases by activated platelets, they participate in several physiopathological cases including the initiation and progression of ischemia [47–49]. PAF are founding with a small portion in the bloodstream, this is the neo-synthesized form, and most commonly, PAF are intracellular [47]. They activate a single receptor-coupled protein G (GPCR), the platelet activating factor receptor (PTAFR), expressed in several cell types, in particular platelets [47,50]. Recent studies have determined that there are functional intracellular GPCR receptors such as PTAFR [51].Different functions for PTAFR are observed, depending on their location, cell-surface PTAFR has been shown to positively control the regulation of pro-inflammatory vasodegenerative cytokines such as IL-1β, leading to vaso-obliteration and endothelial cytotoxicity in vivo [47]. While intracellular PTAFRs contribute to the increased expression of pro-angiogenic vascular factors such as VEGFa and NOS3 in micro-vessels and thus the onset of pathogenesis angiogenesis uncontrolled in vivo [47]. In a model of O2-induced retinopathy (OIR), they confirm that cell surface receptors are mainly involved in retinal vaso-obliteration, and intracellular receptors mainly nuclear are involved in neo-vascularization [47].

Platelets lead to ischemia, after interaction with circular microvesicles (MV), they are membrane fragments, released from activated blood cells or apoptotic cells [52,53], MVs have tissue factors (TF) on their surface that are involved in the coagulation cascade and increase the adhesion of leukocyte and endothelial cells [54]. The interaction of platelet P-selectin and PSGL-1 at the level of the MVs, will lead to the initiation of a blood coagulation pathway [55], and activation of platelets, which in turn will release platelet microvesicles pMV, and therefore additional thrombin formation and hyper-coagulation phenomenon [54,55]. Leading to ischemia and subsequent predisposition to abnormal intravitreal neovascularization. All changes in numbers and compositions of MVs regardless of origin of monocytes, endothelial or platelet cells, they reflect diabetic retinopathy [56].

Among the most important pro-angiogenic factors that play a role in the development of pathological retinal neovascularization are erythropoietin, platelet derived growth factor (PDGF), FGF, and VEGF. Until now, VEGF is recognized as one of the major factors involved in the pathophysiology, it is a therapeutic target of proliferative retinopathy [57,58].

The variation in oxygen level will detected by molecular switches, which regulate the synthesis and secretion of growth factors and inflammatory mediators [59]. Hypoxia Inducible Factor (HIF) is a transcription factor that transacts the genes that code for angiogenic factors, including vascular endothelial growth factor (VEGF), which is one of the major target genes. It should note that intracellular levels of HIF and its location depend on oxygen levels [60,61].

In hypoxic stress induced after platelet activation and vaso-bliteration, three major ligand-receptor systems are upregulated, such as VEGF-VEGFR, Angiopoietin-Tie-1 / Tie-2 and Delta-Notch [62]. In ischemic retinal tissues, the HIF-1 factor induces the expression of vascular growth factor VEGF, once bound to its receptor, a signaling pathway is activated which then lead to intraocular neovascularization associated with severe consequences, of where the physiopathology [58,63].

Therapeutic approaches

Since proliferative retinopathy remains one of the leading causes of blindness worldwide, several researches have started in this field, to alleviate this problem. Proliferative retinopathies, whether diabetic or premature, are characterized by an range of events, first a vaso-obliterative phase leading to ischemia, thus generating a hypoxic microenvironment, and consequently the induction of a neovascularization that drag to the vitreous, involving multiple mechanisms that act synergistically. The success of therapeutic research lies in the understanding of the different physiopathological mechanisms involved, the relationship between them, to find the target, and therefore the development of new and more effective treatments. Another problem that may arise is the ability of researchers to induce adequate animal models that illustrate the pathogenesis of human proliferative retinopathy. In this work, we will go back in time, to follow the evolution of the treatment of proliferative retinopathy during the previous years until today, in focus on the targets that will correct the physiopathology effectively and without side effects.

Treatment that control vascular biochemical complications

A few years ago, studies were focused mainly on systemic treatments that target hyperglycemia, in the case of diabetic retinopathy [64,65]. These therapeutic approaches control blood sugar, which can have beneficial or deleterious effects directly or indirectly on the progression of the DR [64]. Hyperglycemia leads to biochemical metabolic complications, altered cellular, enzymatic, circulatory, vascular and molecular mechanisms. Including the sorbitol pathway [66], presence of advanced glycation end products (AGE), activation of PKC [67], oxidative stress [68], presence of inflammatory markers [69] and the presence of vascular endothelial growth factors (VEGF) [70]. All of these cooperate to trigger and advance the DR. To avoid all these metabolic complications due to hyperglycemia, they thought about insulin therapy, which causes long-term reduction in the risk of development and progression of DR in people with diabetes [71]. While they have proven in a rodent model (in vivo and in vitro); Incubation of cultured retinal pigment epithelial cells, and intensive insulin administration, increase retinal gene expression of angiogenic vascular factor VEGF and the onset of pathophysiology [72]. Insulin therapy is a non-targeted systemic therapeutic approach that can have pathogenic effects after exceeding physiological doses [65]. There are other hypoglycemic agents that reduce microvascular complications by mechanisms other than their effect on glycemic control, such as Rosiglitazone and Pioglitazone [65], but studies have shown that the use of the latter increases the incidence of diabetic macular edema that characterizes DR [73]. Other systemic therapeutic approaches that control DR include antiplatelet agents that decrease their activation and aggregation [74], anticoagulants [75], anti-inflammatory agents [76,77] and anti-angiogenic [78]. These therapies can have deleterious effects following their systemic mode of action, non-targeted, knowing that several pathophysiological mechanisms are involved in the phatogenesis DR, there are those that was removed due to an increased risk of triggering or progression of the disease.

Aside from systemic treatments, more recently, new therapeutic approaches have been put into experimentation, more targeted, more specific than those just mentioned. Niaspan is a treatment that allows vascular restoration in the DR, it is a sustained-release formulation of Niacin (Vitamin B3 or nicotinic acid) [79], this treatment aims at stimulating the synthesis of microRNAs 126 (miRNA-126) which negatively regulate the expression of adhesion molecules (VCAM-1) and the expression of vascular growth factor

(VEGF), thus slowing neovascularization. induced by hypoxia [80,81], miRNA-126 causes increased expression of angiopoietin 1 (ANG-1) in the retina [82], thus promoting vascular remodeling [83]. Studies have shown that the decrease in the level of miRNA-126 has been accompanied by retinal endothelial lesions that allow the development and progression of diabetic vascular complications [82,84].

Hyperglycemia also leads to the accumulation of advanced glycation products (AGE), which are among the major triggers of inflammation in the DR [85]. They induce the expression of Il-1β which in turn causes the overexpression of galectin1, an angiogenic factor, which interacts with the N-glycans of the vascular growth factor receptor VEGFR2, thus increasing their phosphorylation, which leads to the increase in signal transduction mediated by the VEGF / VERGFR2 axis [86,87]. In a diabetic model induced in mice, they found that the inhibition of AGE products in vivo by aminoguanidine and by anti-IL-1β antibodies of the retina, lead to the inhibition of the expression of galectin 1 [87].

Inflammation treatments in RP

Inflammation characterizes the two forms of proliferative retinopathy DR and ROP, the main inflammatory cytokine being Il-1β whose pathophysiological mechanism described previously. The limitation of inflammatory processes triggered by the latter constitutes a new therapeutic strategy to limit the progression of several physiopathology's, notably the retinopathy in the pre-ischemic stage [33,36]. They found three ways to block Il-1β; target IL-1R receptors either by antagonists analogous to IL-1β [88] or by antibodies blocking the receptor, since the signaling induced by the Il-1β / Il-1R axis can play a key role in the development of retinopathy [36,89]. Or the neutralization of Il-1β by trapping it with soluble receptors or monoclonal anti-IL-1β antibodies [90]. Internal signaling pathways can be targeted by using endogenous antibodies that block caspases [91]. Recent studies have shown that inflammation causes activation of the proteases that form the vascular system, and that the receptors activated by these proteinases (PAR2 OR F2RL1) could modulate the deleterious effects of Il-1β by the decrease of expression of its receptor Il-1R [92]. We can said that IL-1 regulates its own endothelial cytotoxic actions.

Recently, they thought to block the activity of the inflammasome NLRP3, a critical innate immune pathway responsible for the production of active interleukin IL-1β, and thus the progression of the pro-inflammatory effects of retinopathy [93], by MCC950 which is a potent and specific inhibitor of the inflammasome [94]. The anti-NLRP3 effect of MCC950 has be described in studies for macrophages, dendritic cells and myoblasts [95], remains to know its effect on human retinal endothelial cells (HREC). This was the goal of a study conducted by [94]. They stimulated the HRECs with high doses of glucose, there was after the high production of NLRP3 inflammasome, and apoptosis, but all this was suppressed after treatment with MCC950, either by acting directly on the NLRP3 protein or by interaction with the pathways related to the activation of the inflammasome (Fig. 3) [94,96,97]. This approach seems more targeted because it inhibits the trigger of inflammation that characterizes retinopathy in the pre-ischemic phase.

Treatments by inhibition of angiogenesis

When we can not control the pre-angiogenic events of proliferative retinopathy, we resort to stopping the angiogenesis that characterizes the physiopathology.

In a murine model with retinal neovascularization induced by ischemia, they transfected the retina with HIV lentivirus expressing angiostatin [98]. Angiostatin is known as an endogenous anti-angiogenic factor that negatively regulates the expression of vascular growth factor (VEGF) [99], it allowed a decrease in neovascularization in vivo without toxicity, because this vector achieves gene transfer and stable expression of angiostatin in retinal cells [98]. It is a more targeted and localized approach because the HIV vector integrates into the retina, and no expression of angiostatin has be detected in nearby organs examined [98].

In other experiments, they worked on deguelin, an extract of the plants of the family of Mundulea Sericea, which has an antiproliferative effect, studied in a model of oxygen-induced retinopathy (OIR) [100]. Deguelin acts either by inhibiting phosphatidylinositol-3-Kinase (PI3K / AKT), mediated signaling pathways and thus an antiproliferative effect [101], or by reducing the expression of the HIF-1α protein or its degradation, involved in angiogenesis [102], in a way independent of the ROS and PI3K/AKT pathways [100]. We can said that degueline may have a therapeutic potential in the treatment of proliferative retinopathy.

It possible to control angiogenesis in ischemic retinopathy by inhibiting prolylhydroxylase (PHD), an oxygen scavenger and stabilizing hypoxia-inducible factors such as HIF-1α [103]. This has be established in a study in a model of ischemia-induced

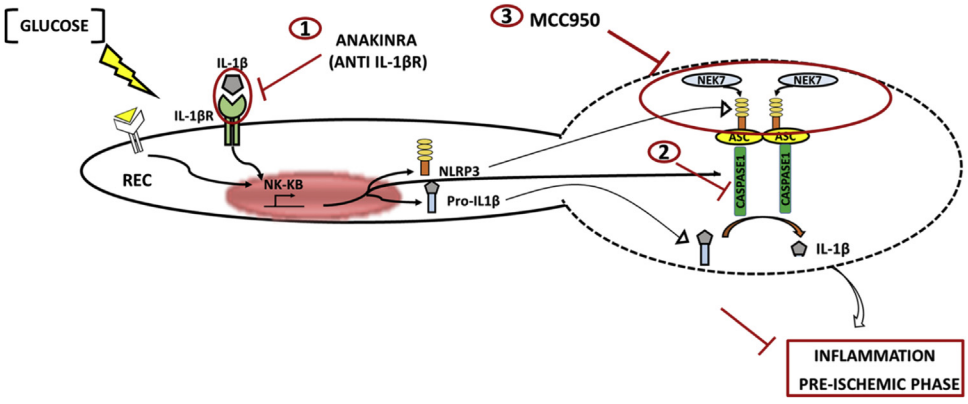

Fig. 3. Therapies targeting the pre-ischemic phase of retinopathy. After exposing retinal endothelial cells to high glucose concentrations, they revealed that there was overexpression of pro-IL1β, pro-caspase 1 and NLRP3, which play a major role in the induction of inflammation, characterizes the early stages of the onset of retinopathy. Studies have been shown to suppress inflammation by suppressing the interaction of IL1β with its IL1βR receptor [1]. Or by targeting internal signaling pathways using endogenous antibodies that block caspases [2]. Or by using Mcc950, a potent and specific inhibitor of the NLRP3 inflammasome, which is part of the more specific and targeted therapy, it works by inhibiting the interaction between the NEK7 protein and NLRP3, thus inhibiting the activation of the inflammasone, which plays a crucial role in the maturation of IL-1β, the cytokine most involved in pathogenesis [3].

neovascularization [104], however, when they inhibit PHD, there is a decrease in retinal neovascularization by preventing the degradation of HIF-1α in the case of hypoxia and therefore the inhibition of VEGF. This inhibition was accompanied by the decrease in apoptosis and retinal vascular permeability [104,105].

They managed to control angiogenesis by acting on the neurotrophin receptor ($p75^{NTR}$) [106], which is strongly expressed in human neo-vessels [107,108]. The retinal pigment epithelium (RPE) maintains the good functioning of the retina, all dysfunction in the retinal pigment epithelium leads to neovascularization at this level [109]. In vitro, they exposed RPE to hypoxia conditions to induce neovascularization, with the invalidation of the gene that encodes the $p75^{NTR}$ receptor. The results showed that there was an under-expression of the pro factors -angiogenic secreted by RPE (vascular and platelet-derived endothelial growth factors), inflammatory factors such as IL-1β, IL-18 and stromal cell-derived factor 1, and matalloproteases (MMP3 and MMP9) in hypoxia [106]. Conversely, the induction of the expression of anti-angiogenic factors derived from RPE, angiostatin and the tissue inhibitor of metalloproteinases (TIMPs) after invalidating the $P75^{NTR}$ gene [106]. These data indicate that $p75^{NTR}$ might act as a potential therapeutic target in ischemic retinopathy.

The mechanism of pathological neovascularization characterizing proliferative retinopathy is complex, since there is the involvement of several pro-angiogenic factors. VEGF-targeting therapy can not completely eliminate angiogenesis [110,111]. These pro-angiogenic factors are associated with tyrosine kinase receptors (RTK), such as VEGF/VEGFR, FGF/FGFR, PDGF/PDGFR [112,113]. A recent study has highlighted an effective and powerful therapeutic approach to control ocular angiogenic diseases, targeting triple angiokinases at a time (VEGFR, FGFR, PDGFR) by BIBF1120 (vargatef) (57), its mode of action is to bind competitively to the ATP binding site, thereby inhibiting downstream intracellular signaling [57,114].

Another recent therapeutic approach is targeting apelin receptors is a G protein-coupled (APJ) [115,116], which have pro-angiogenic activity [117] induced by hypoxia [118], and is overexpressed in terminal endothelial cells located at the edge of growing capillaries [119]. In a murine model of oxygen-induced retinopathy, they tested the ML221 antagonist of the APJ receptor, in vitro they found the following results, inhibition of proliferation of endothelial cells in culture; it depends on the ML221 dose added in the culture medium. While they obtained the same results in vivo, after intraperitoneal injection of ML221, they found that there was inhibition of pathological angiogenesis and improved recovery of normal vasculature in the ischemic region of the retina [115]. Another study is added targeting this time the ligand apeline by a small interfering RNA (siRNA), there was a suppression of pathological angiogenesis in a model OIR [120]. Selective inhibition of retinal pathologic angiogenesis by blocking the APJ receptor or its ligand apelin could be new candidates for the treatment of ischemic retinopathy.

While another pathway was followed to control the progression of proliferative retinopathy of prematurity, targeting microRNAs (miRNAs) that target the mRNAs that code for VEGF and its receptor VEGFR [121]. Van Mil team revealed increased retinal vascularization and VEGF levels when there is a decrease in the expression of miRNA-214 [122]. MiRNAs could considered as biomarkers in retinopathy of prematurity, but first we need to clarify the relationship between miRNA and angiogenesis that characterizes retinopathy and pro-angiogenic factor VEGF, this is a prospective for future research.

The anti-VEGF therapy has shown efficacy, but given their systemic mode of action, over time patients suffer a progressive loss of vision as previously mentioned, they totally block the VEGF factor thus inhibiting its pathological and physiological effect [111,123]. For this, they have combined this approach with drugs that target the angiopoietin (ANG) pathway and its TIE receptor, which plays a necessary role in the development of blood vessels [124,125]. The endothelial ANG / TIE axis, in particular the ANG1 isoform, regulates patency and pathological vascular remodeling during inflammation [126–128]. While there are some isoforms such ANG2, has an opposite effect and promotes vascular permeability in synergy with inflammatory cytokines [129,130], ANG2 may behave as an antagonist by inhibiting the ANG1 / TIE2 mediated signaling pathway during inflammation [131–134]. However, they correlated the level of ANG2 induced by hyperglycemia and hypoxia and the progression of ocular vascular diseases including retinopathy [135–138]. The blocking of the response mediated by the ANG2, can be done either by neutralizing it [139,140], or by antibodies which induce their regrouping [141] thus allowing the improvement of the functioning of the retinal vascular barriers and the reduced vascular permeability [139]. In contrast, activation of the ANG1 / TIE2 pathway in an OIR model normalizes the retinal vascular system by inhibiting vascular leakage and abnormal angiogenesis [142]. An anti-VEGF treatment in combination with inhibition of ANG2 allows avoid the consequences of blocking VEGF on healthy vessels [124].

Today, thanks to the regenerative medicine, studies conducted in search of a therapy against retinopathy have evolved, they have been able to incorporate human endothelial colony forming cells (ECFC) in avascular areas caused by hypoxia [143]. In diabetic and OIR mouse models [144], they obtained as results, a decrease of the avascular zones with the increase of the normovascular zone, their implantation also makes it possible to prevent the pathological retinal neovascularization which characterizes the proliferative retinopathy [143,145]. For better therapeutic effects, they chose a subset of ECFCs with a high level of expression of CD44 to facilitate regeneration of the vascular system and decrease abnormal angiogenesis [146]. In order to obtain human ECFCs, they must be isolated from the peripheral blood or umbilical cord; firstly, the surface markers that distinguish ECFCs must defined.

Treatment of eye disorders in retinopathy

Diabetic patients and premature newborns are prone to microangiopathy and damage to the basement membranes responsible for retinal complications. These degenerative complications are also sources of alterations of the ocular surface. Recent studies have assessed the effect of erythropoietin (EPO) in the treatment of eye disorders [147]. It was said that EPO is solely responsible for the production of erythrocytes, but recently they have identified the presence of EPO and its receptor in the retinal layers [148,149] having anti-apoptotic activity [150], anti-oxidant [151], and anti-inflammatory [152]. They specified the mode of administration of recombinant EPO so that it could cross the blood-retinal barrier and interact with its receptor EPOR expressed on the damaged cells to prevent apoptosis by inhibiting caspase activity in retinopathy diabetic [153], and that of the premature [154]. Among the recombinant EPOs, they have developed a carbonyl form, more targeted it does not bind to conventional receptors, so it does not induce erythropoiesis [155,156].

In recent years, great advances in understanding the pathogenesis of proliferative retinopathy have led to the development of more effective therapies for the early and late stages of the disease.

Conclusion

Proliferative retinopathies are eye diseases of vasoproliferative origin. Excessive and pathological vascular growth is the main cause of these pathologies. This neovascularization can lead to detachment of the retina and blindness. More specifically,

retinopathy of prematurity (ROP) and diabetic retinopathy DR, two examples of proliferative retinopathy, are the two leading causes of blindness in the 50 s and under in industrialized countries. In this work, we have reviewed the pathophysiological mechanisms of proliferative retinopathy, which have be described so far, for its two forms namely DR and ROP. Some therapies that have be highlighted to address this pathophysiology have be cited, and grouped according to a chronological order of evolution and specificity, from the systemic to the most targeted. The good mastery of the pathogenesis of this disease will solve many problems that characterize these severe forms.

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