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Mini Review

Role of chronic inflammation in diabetic retinopathy

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During inflammation, leukocytes undergo a series of consecutive adhesive interactions orchestrated by leukocyte adhesion molecules expressed on the cell surface of leukocytes and the vascular endothelium and migrate to the inflamed tissues. Also, inflammatory cytokines secreted by recruited leukocytes and resident cells regulate the inflammatory response in inflamed tissues. Under proper conditions, inflammation contributes to clear away invading agents, degrade necrotized tissue components and promote tissue regeneration. However, if inflammation becomes chronic, it can turn out to be detrimental by prolonged and excessive tissue damages.

One of the major microvascular complications of diabetes is diabetic retinopathy (DR), a leading cause of blindness in developed countries. The mechanisms underlying the development of DR are not fully understood; however, recent studies have implicated chronic inflammation in the pathophysiology of DR. In this review, we focus on the role of leukocyte adhesion molecules and inflammatory cytokines in the pathophysiology of DR.

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Introduction

The prevalence of diabetes is increasing worldwide[1], and diabetic retinopathy (DR), one of the microvascular complications in diabetes, is a leading cause of acquired blindness among the people of occupational age[2]. The pathophysiology of DR is closely correlated with chronic hyperglycemia. Under hyperglycemic conditions, retinal vascular endothelial cells are directly damaged and subsequent obliteration of retinal microvasculature causes ischemia-mediated pathology such as pathologic neovascularization originated from retinal vessels. The pathologic neovascularization due to retinal ischemia causes the formation of fibrovascular tis-

sues at vitreoretinal surface, which is a hallmark of proliferative diabetic retinopathy (PDR) and leads to severe complications such as vitreous hemorrhage and tractional retinal detachment. In addition, diabetic change compromises the blood-retinal barrier (BRB) and results in fluid accumulation in the center of the diabetic retina, *i.e.*, diabetic macular edema (DME). So far, preclinical and clinical studies have revealed that vascular endothelial growth factor (VEGF), a potent angiogenic factor, predominantly plays a role in the development of two major manifestations in DR, formation of fibrovascular tissue and DME. Since the first report of off-label use of anti-VEGF agents for PDR in 2006[3], anti-VEGF therapy has emerged as a part of first line treatment in DR and recently the U.S. Food and Drug Administration approved anti-VEGF agents for the treatment of DME. The treatment of DR is being revolutionized by intravitreal therapies targeting VEGF.

Research to develop the anti-VEGF agents has also provided a secondary benefit to elucidate the pathogenesis of DR; chronic inflammation underlies much of the vascular complications in DR[4, 5]. Obviously, macroscopic signs of inflammation such as redness (*Rubor*), heat (*Calor*), swelling (*Tumor*) and pain (*Dolor*), are not representative pathological features in diabetic retina and therefore the classical definition of inflammation is inadequate to describe the characteristics of DR. However, at a microscopic level, inflammatory responses including vessel dilatation, hemodynamic alteration, exudation and leukocyte accumulation/migration are present in retinal and choroidal tissues during DR development. Indeed, levels of inflammatory cytokines and leukocyte adhesion molecules were reportedly elevated in the specimens of patients with DR[6], indicating the role of inflammatory process in microvascular complications in retinal tissues caused by diabetes.

However, despite recent advances, there is still a fundamental lack of understanding of the inflammation-associated mechanisms underlying the pathophysiology of DR. To enhance the understanding of DR as an inflammatory disease, it would be beneficial to organize and integrate the latest evidence on the molecules related to inflammatory response in DR. In this review, we focus on the leukocyte adhesion molecules and inflammatory cytokines participating in the pathophysiology of DR and highlight an intriguing molecule relevant to both inflammation and oxidative stress, namely, vascular adhesion protein (VAP)-1.

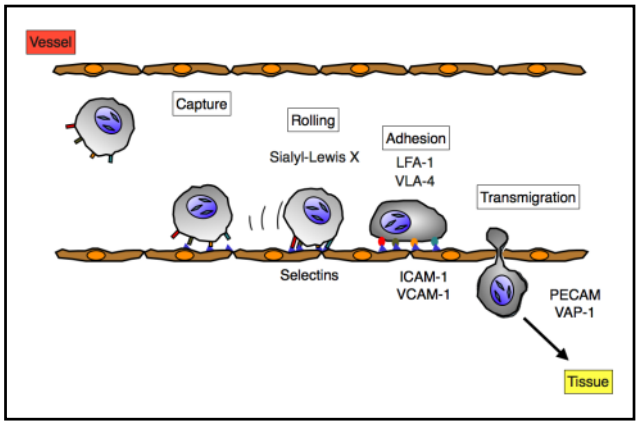

Fig.1 Leukocyte Recruitment Cascade

During inflammation, leukocytes are recruited in a cascade-like fashion, starting with capturing and rolling, followed by firm adhesion and transmigration to the extravascular space.

Leukocyte Adhesion Molecules in DR

Inflammation is a nonspecific, defensive response of the body to tissue injury in which leukocytes are recruited to inflamed tissues. The recruitment of leukocytes from circulating blood into tissues is crucial for the inflammatory response. During this process, a number of well-studied adhesion molecules on the endothelium sequentially interact with their ligands expressed on the cell surface of leukocytes. The interaction between adhesion molecules and ligands occurs in a cascade-like fashion, guiding the leukocytes from the circulation to the extravascular space, *i.e.*, through the steps of leukocyte rolling, firm adhesion and transmigration (Fig.1).

There is an accumulating body of evidence showing that leukocytes play a significant role in the pathogenesis of DR. Extensive accumulation of polymorphonuclear leukocytes has been observed in the lumen of microaneurysms, a cause of retinal vascular leakage, in human type I diabetic subjects[7, 8]. Correlations between elevated numbers of accumulated leukocytes and capillary damage have been shown in postmortem DR patients[7] and in spontaneous diabetic monkeys[9]. Previous studies using animal models of early DR have also revealed that leukocytes adhering to the endothelium damage the endothelial cells and increase the vascular permeability of retinal vessels[10, 11]. In addition, leukocytes are also located in human fibrovascular tissues, a characteristic feature of the pathologic changes associated with PDR[12]. It has been furthermore reported that T lymphocytes infiltrate the fibrovascular tissues[13] and this infiltration correlates well with the severity of retinopathy and poor visual

prognosis[14]. Therefore, these lines of evidence indicate that leukocytes disrupt the homeostasis of the vasculature and facilitate proliferative change in DR. The following sections describe, along with leukocyte recruitment cascade, the emerging findings regarding the leukocyte adhesion molecules that play significant roles in DR.

Selectin family of adhesion molecules mediate the capture and rolling steps of leukocytes along the endothelial cells. The selectins consist of three members of C-type lectins: P-, E-, and L-selectin[15]. All of the selectins bind to sialyl-Lewis X carbohydrate ligands, such as P-selectin glycoprotein ligand-1 (PSGL-1)[16]. In patients with DR, P-selectin and E-selectin were localized on the vascular endothelium of fibrovascular tissues[17]. P-selectin is upregulated and accompanied with an increased number of polymorphonuclear leukocytes in the diabetic choroid[18]. Since the number of polymorphonuclear leukocytes is correlated with the area of capillary dropout[7], P-selectin is likely to participate in the vaso-occlusion in the choroidal tissue of patients with diabetes. In addition, the level of soluble E-selectin was considerably higher in the vitreous from subjects with PDR[19]. Furthermore, vitreous levels of soluble E-selectin in the eyes with PDR complicated by traction retinal detachment were significantly increased in comparison with the eyes with vitreous hemorrhage alone[17]. Interestingly, it has been shown that soluble E-selectin stimulates retinal capillary endothelial cell migration[20] and promotes angiogenesis through a sialyl Lewis-X-dependent mechanism[21]. These data indicate the role of P-selectin and E-selectin in the development of DR. However, L-selectin is reportedly decreased in on peripheral blood neutrophils[22] and lymphocytes[23] in patients with diabetic microangiopathy in comparison with healthy controls. Further studies are needed to elucidate the role of L-selectin in the pathogenesis of DR.

Along with selectins, a different set of adhesion molecules play a role to reduce the leukocyte-rolling velocity and allow the leukocytes to firmly adhere to the endothelial surface. This firm adhesion step is largely mediated by the molecules of the immunoglobulin superfamily, such as intercellular adhesion molecule (ICAM)-1, expressed on endothelial cells. Several studies suggest that ICAM-1 and its binding partners, LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18)[24], are operative in DR. In fact, ICAM-1 is found to be highly expressed in the blood vessels of the retina, choroid and fibrovascular tissues in patients with diabetes[18, 25], and its expression correlates with the number of migrated neutrophils in the retina and choroid of these patients[18], indicating that elevated ICAM-1 facilitates leukocyte recruitment and vascular complications in DR. In accordance with these clinical observations, ICAM-1 is increased in the retinal vessels in an animal model of DR, and blockade of ICAM-1 attenuated leukostasis, endothelial cell death and vascular leakage in the retinal vessels of the diabetic animals[11]. Not only ICAM-1, but also LFA-1 and Mac-1, ligands for ICAM-1, are upregulated in patients with diabetes. The β-integrin subunit CD18 is increased in patients with DR[26], and likewise significant increases in α-integrin subunits CD11a[27] and CD11b[22] are found in these patients. Consequently, these data indicate that ICAM-1 and its ligands are important and interruption of either component of the integrin — ICAM-1 interaction may be beneficial in preventing the deterioration in DR.

Similar to ICAM-1, a role for vascular cell adhesion molecule (VCAM)-1 in DR is also emerging, although there has not been as much research conducted on VCAM-1 as on ICAM-1. Before its potential role in DR was examined, it first came to light that VCAM-1 is involved in the macrovascular complications of diabetes[28]. However, it has recently been revealed that the interaction of VCAM-1 with its ligand, integrin very late antigen (VLA)-4, is important in the development of DR. For instance, it has been demonstrated in an animal model of DR that hyperglycemia upregulates VCAM-1 expression in the retinal vessels[29]. Also, in an animal model of early DR, it has been found that VLA-4-mediated leukocyte adhesion to the retinal vessels is significantly increased, and blockade of VLA-4 attenuates vascular leakage and production of inflammatory cytokines[30]. In addition, increased serum levels of soluble VCAM-1 have been found in type II diabetic patients with microvascular complications, similar to E-selectin[31], and levels of soluble VCAM-1 are elevated in the vitreous of DR patients as well[17, 19]. Notably, it has been shown that soluble VCAM-1 acts on endothelial cells as an angiogenic factor through a VLA-4 dependent mechanism, in common with E-selectin[20, 21], suggesting that blockade of both soluble adhesion molecules, soluble forms of E-selectin and VCAM-1, could be of value on treatment of DR.

Overall, leukocyte adhesion molecules are upregulated in the vasculatures of retina, choroid and fibrovascular tissues in DR and involved in the pathogenesis of DR. Leukocyte adhesion molecules may serve as potential targets for therapeutic interventions for DR.

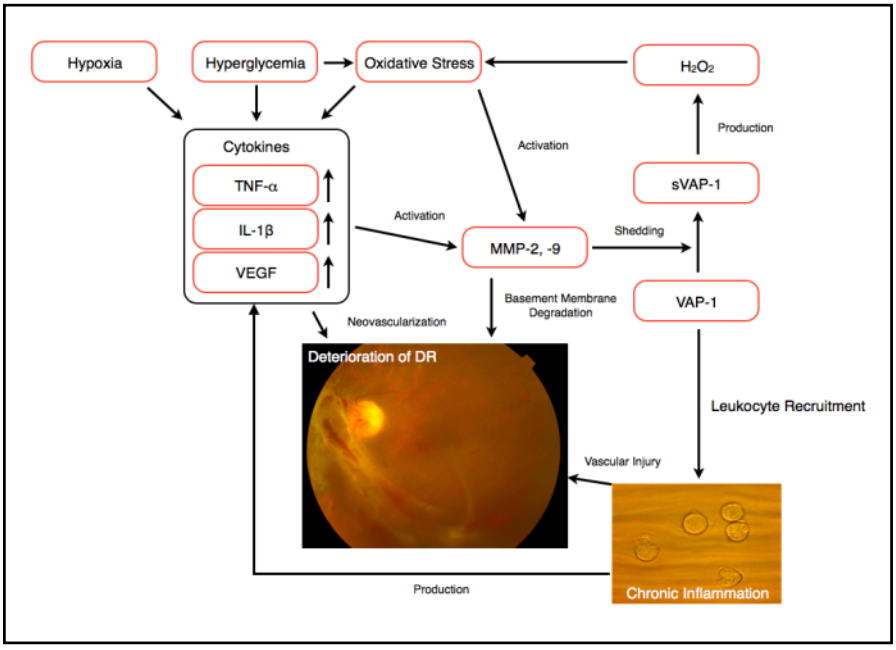

Fig.2 Schematic of the Role of Inflammation-associated Molecules in DR

Inflammation-associated molecules such as cytokines, proteases and adhesion molecules play a role in the development of DR.

Inflammatory Cytokines in DR

It has been reported that serum levels of inflammatory cytokines are elevated in patients with diabetes[32]. Since BRB is disrupted in the eye with DR, the cytokines may be released from leaky vessels to tissues and intraocular fluid. In addition, leukocytes adherent to endothelial cells and transmigrated leukocytes in fibrovascular tissues produce inflammatory cytokines. As mentioned, VEGF is a key regulator of DR and increases in the vitreous samples from patients with PDR[33] and DME[34]. However, in addition to VEGF, the vitreous levels of inflammatory cytokines Tumor necrosis factor (TNF)-α and Interleukin (IL)-1β are also reported to be elevated in patients with PDR[35-37].

TNF-α is an important mediator of inflammation in tissues under pathological condition. Previously, it was demonstrated that TNF-α is localized in cellular components of fibrovascular tissues[38] and elevated in the vitreous fluid[36]. Experimental studies have shown that expression of TNF-α is upregulated in diabetic animals and its inhibition prevents the pathologic events of DR including BRB breakdown[39]. Importantly, systemic administration of the TNF-α inhibitor infliximab led to visual improvement and decrease in central macular thickness in patients with DME[40], indicating the role of TNF-α in the pathogenesis of DR. However, further follow-up studies are needed to assess its ultimate efficacy.

IL-1β is also a pro-inflammatory cytokine. Serum and vitreous levels of IL-1β are increased in patients with PDR[36]. Several observations showed that IL-1β plays a role in the pathogenesis of DR. *In vitro* experiments have demonstrated that high glucose stimulation increases IL-1β production in cultured endothelial cells[41, 42]. IL-1β was found to stimulate its own synthesis in endothelial cells and macroglial cells in DR[43] and to induce apoptosis of endothelial cells[41]. E-selectin and P-selectin are increased by stimulation of TNF-α and IL-1β [44-46]. Since selectins are important molecules that initiate leukocyte recruitment cascade, IL-1β and TNF-α potentially promotes inflammatory cascade in DR by direct insults to the endothelial cells and increase of leukocyte trafficking to the retinal tissues and/or fibrovascular tissues in DR. Taken together, in addition to VEGF, inflammatory cytokines TNF-α and IL-1β are also participants in the pathogenesis of DR and further studies are required to elucidate the role of the cytokines in DR.

VAP-1, Dual Function Molecule Relevant to Inflammation and Oxidative Stress

The preceding discussion provides information on the link between well-studied leukocyte adhesion molecules and inflammatory cytokines. Our group has also focused on the role of VAP-1, relatively novel leukocyte adhesion molecule, in DR. VAP-1 was originally discovered in inflamed synovial vessels[47], and thereafter it has been elucidated that VAP-1 is expressed on the endothelium of human tissues such as skin, brain, lung, liver and heart under both normal and in-

flamed conditions[48]. In the ocular tissues of humans[49] and rodents[50, 51], VAP-1 is localized on the endothelial cells of retinal and choroidal vessels. Upon inflammation, VAP-1 is known to facilitate the accumulation of leukocytes into the inflamed tissues via mediating the rolling and extravasation step during leukocyte recruitment[52]. Previous studies have elucidated that VAP-1 is crucial in the pathology of systemic inflammatory diseases, including rheumatoid arthritis, inflammatory bowel diseases, atherosclerosis, and diabetes[48, 53, 54]. As for ocular diseases, we recently reported, using animal models, that VAP-1 is involved in the molecular mechanisms of acute ocular inflammation[50] and inflammation-associated ocular angiogenesis[50]. These findings have indicated that, as a leukocyte adhesion molecule, VAP-1 plays a critical role not only in the systemic disorders, but also in ocular diseases associated with inflammation. Indeed, in DR animal model VAP-1 blockade significantly reduces the transmigration and capillary entrapment of leukocytes in the retina[51]. Leukocytes, under pathological conditions, are reported to play an important role in neovascularization, for instance, through secretion of VEGF[55, 56]. Furthermore, leukocytes firmly adhere to capillary endothelial cells and induce apoptotic changes in the endothelial cells[57]. Therefore, VAP-1 seems to be locally involved in the pathogenesis of DR by mediating leukocyte recruitment as a leukocyte adhesion molecule.

In addition, VAP-1 has a large homology with semicarbazide-sensitive amine oxidase (SSAO), which oxidizes aliphatic and aromatic primary monoamines and converts them to the corresponding aldehydes with the release of hydrogen peroxide and ammonia[58]. Metabolites generated by VAP-1/SSAO, *e.g.* hydrogen peroxide and methylglyoxal from aminoacetone, are known to be involved in cellular oxidative stress and advanced glycation end product formation, both of which are crucial in the pathogenesis of DR[59, 60]. As VAP-1 also exists as a soluble form (sVAP-1) in plasma, much attention has been paid to the serum concentration of sVAP-1 in patients with diabetes. It was reported that plasma VAP-1/SSAO activity is increased in patients with type I diabetes[61] and type II diabetes[62, 63]. Our group also reported that serum levels of sVAP-1 are elevated in type II diabetic patients[64]. Interestingly, the serum concentration of sVAP-1 correlates well with serum concentration of VEGF only in patients with type II diabetes, but not in non-diabetic patients. Whereas the mechanism(s) remains unclear, the data suggest the presence of certain mechanism(s) specific for diabetes, in which VEGF increases serum sVAP-1.

We also reported that level of sVAP-1 is increased and correlated with oxidative stress in the vitreous fluid of patients with PDR[42]. In addition, it was elucidated that retinal capillary endothelial cells release sVAP-1 via proteolytic cleavage of membrane form of VAP-1 by matrix metalloproteinases (MMPs) when stimulated with inflammatory cytokines such as TNF-α and IL-1β [42]. TNF-α and IL-1β, both of which are elevated in PDR[36, 38], are known to up-regulate MMP-2 and MMP-9. Accumulating data indicate that VAP-1 is regulated by inflammatory cytokines such as VEGF, TNF-α and IL-1β, and plays a crucial role in the pathogenesis of DR (Fig.2).

Conclusion

The pathogenesis of DR, particularly the early stage of DR, is not entirely known. However, a considerable amount of research over several decades has revealed the role of inflammation-associated molecules such as cytokines and leukocyte adhesion molecules in DR and provided insight that chronic inflammation is one of the main forces driving the development of DR. Further studies are required to elucidate the underlying link between the inflammation-associated molecules in DR.

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Conflicts of interest

No conflicts of interest to be disclosed.

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