Vasoregression: A Shared Vascular Pathology Underlying Macrovascular And Microvascular Pathologies?

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Abstract

Vasoregression is a common phenomenon underlying physiological vessel development as well as pathological microvascular diseases leading to peripheral neuropathy, nephropathy, and vascular oculopathies. In this review, we describe the hallmarks and pathways of vasoregression. We argue here that there is a parallel between characteristic features of vasoregression in the ocular microvessels and atherosclerosis in the larger vessels. Shared molecular pathways and molecular effectors in the two conditions are outlined, thus highlighting the possible systemic causes of local vascular diseases. Our review gives us a system-wide insight into factors leading to multiple synchronous vascular diseases. Because shared molecular pathways might usefully address the diagnostic and therapeutic needs of multiple common complex diseases, the literature analysis presented here is of broad interest to readership in integrative biology, rational drug development and systems medicine.

Introduction

VASCULAR RESEARCH HAS BEEN AT THE EPICENTER of integrative biology scholarship (Black and Wang, 2015). The part of the cardiovascular system that transports oxygenated blood away from the heart through the aorta of the left ventricle, and delivers it to the body tissues is termed as systemic circulation. The oxygenated blood from the systemic circulation also removes carbon dioxide and toxic waste from the tissues, returning to the right atrium of the heart.

Systemic circulation can be of two types: macrocirculation and microcirculation. Macrocirculation comprises of arteries and veins to circulate blood to and from the organs. The arteries that enter an organ branch repeatedly to become arterioles, which release blood into the capillaries. The venules collect blood from the capillaries and gradually coalesce into larger veins. The microcirculation is composed of arterioles, capillaries, and venules that supply and drain the capillary blood. The thin-walled capillaries are responsible for the exchange of materials between the blood and the interstitial fluid (Guyton and Hall, 2011). The microvasculature constitutes an important interface for the delivery of nutrients, removal of toxic wastes, exchange across the vessel wall, and fluid economy. Adequate microvascular perfusion is necessary for the cell survival (Gates et al., 2009).

Vasoregression is the phenomenon of progressive obliteration of capillaries that represents the first and crucial step in the development of microvascular complications. It plays a prominent role in microvascular diseases of the central and peripheral nervous system (Moran and Ma, 2015). In spite of being regarded as an early event in various human vascular pathologies, the underlying mechanism of vasoregression is still not well-elucidated. A sufficient understanding into the vasoregression phenomena may enable pharmaceutical intervention and subsequent treatment of multiple vascular pathologies.

It has been remarked that the vessels in atherosclerosis, glomerular nephropathy, and diabetic retinopathy (DR) possess comparable features (Geraldes et al., 2009). Our systems biology study showed that vasoregression of the ocular vessels may also be induced in systemic vascular diseases such as atherosclerosis (Gupta et al., 2014). Macrovascular cardiovascular function is correlated with progression of certain eye diseases. Risk factors for the macrovascular disease arteriosclerosis include dyslipidemia, diabetes, or systemic hypertension. The same risk factors are important for retinal artery/vein occlusion, retinopathy, and macular degeneration. Local hypoxia, increased intraocular pressure, dysregulation of ocular blood flow, and barrier dysfunction in the eye can be linked to changes in systemic macrovascular function (Flammer et al., 2013). The eye is thus distinctly suited for the study of microvascular disease due to macrovascular changes.

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This review discusses the characteristics of vasoregression with special reference to retinal microvascular diseases, where it has been studied extensively. Further, we outline the factors modulating regression and the pathways involved in the development of vasoregression. Lastly, we note that characteristics, pathways, and molecular effectors similar to atherosclerosis are present in the development of vasoregression, thus indicating the effect of this macrovascular disease in peripheral microangiopathies. Because shared molecular pathways might address the diagnostic and therapeutic needs of multiple common complex diseases (Gomes et al., 2015; Keskin et al., 2015; Reddy et al., 2015), the analysis presented here is of broad interest to readership in integrative biology.

Macrovascular Disease

Macrovascular diseases affect the large blood vessels. Hyperlipidemia, sedentary lifestyle, and genetic predisposition are associated with macrovascular disease. Atherosclerosis, the main pathogenic mechanism of macrovascular disease, is characterized by the deposition of cholesterol and infiltrating macrophages under the endothelium of the large vessels. This results in atherosclerotic plaque deposition. Narrowing of the vessel to a critical point, local coagulation, or embolism causes distal ischemia due to vascular occlusion. Atherosclerosis can have several effects including ischemic heart disease, coronary artery disease, carotid artery disease, myocardial infarction, cerebrovascular disease, stroke, and peripheral artery disease (Guyton and Hall, 2011; Kim et al., 2011). Diabetes is associated with both macrovascular and microvascular disease affecting several organs.

The growth of atherosclerotic plaques occurs over many years and may remain silent for long periods. The clinical manifestations of atherosclerosis depend on the vascular bed affected. In the coronary artery, atherosclerosis causes myocardial infarction and angina pectoris. When atherosclerosis occurs in the vessels supplying the central nervous system, it frequently causes stroke and transient cerebral ischemia. In the peripheral circulation, atherosclerosis causes claudication, gangrene, and decreased limb viability. In the kidney, atherosclerosis can have a direct effect, leading to renal arterial stenosis. Alternatively, kidney can be a common site of atheroembolic disease. The clinical manifestations of atherosclerosis may be chronic (e.g., effort induced angina pectoris) or acute (myocardial infarction, stroke or sudden cardiac death) (Libby, 2012).

Microvascular Diseases of the Retina, Nerves, Brain, and Kidney

Microvascular disease affects the small blood vessels. Pathophysiological and biomolecular changes in the microvasculature are responsible for causing end organ damage associated with aging (Mitchell, 2008) and neurodegeneration (Brown and Thore, 2011). Microvascular disease is often associated with hypertension and hyperglycemia. Hypertension-induced changes in the microvasculature may also cause end-organ damage in the retina, kidney, heart, and brain, highly perfused organs with low vascular resistance such as retina, kidney, heart, and brain (Cheung et al., 2012; Feihl et al., 2009).

The clinical stages of diabetic microangiopathy affecting different tissues have been reviewed (Vojtková et al., 2012).

In diabetes, microvascular disease leads to complications such as diabetic retinopathy (DR), nephropathy, and neuropathy (Kim et al., 2011). Cerebral microvascular disease is associated with cognitive and motor impairment in the elderly (van Norden et al., 2011). Microvascular coronary disease patients show myocardial ischemia without evidence of obstructive coronary disease (Bairey Merz et al., 2006). Microvascular coronary disease affects midlife women (Khuddus et al., 2010), and is correlated with the occurrence of atherosclerosis and increased adverse cardiac events (von Mering et al., 2004; Pepine et al., 2010).

The characteristic features of DR are microaneurysms, endothelial damage, vascular occlusion and increase in vascular permeability of the retinal vessels. Severe DR may lead to aberrant neovascularization as observed in proliferative retinopathy. Progressive vasoregression accompanied by increased vascular permeability also causes increased retinal thickness and edema of the macular region of the retina. Changes to the retinal blood vessels may cause them to bleed or leak, thus distorting the vision. Cataract (clouding of the lens of the eye) and glaucoma (damage to the optic nerve) may also occur.

Symptoms of DR can go unnoticed for a long time. Floating spots appear in the vision due to leakage from abnormal blood vessels but may clear up on their own. However, recurrent bleeding can cause permanent vision loss, while macular edema (ME) can cause blurring of vision. Routine visual acuity testing can confirm eyesight. Tonometry is used to check the normalcy of the intraocular pressure. Examination of the dilated pupil can help to check the retina and optic nerve. Pathological changes in the eye may be reflected by blood vessel abnormalities, changes in the lens, swelling of the macula, and damage to the nervous tissue. Optical coherence tomography can capture detailed images of the eye tissues using light. Fluorescein angiograms are used to obtain pictures of the eye microvessels using fluorescent dye injected in the blood stream (NEI, 2015).

Neuropathy refers to the damage to peripheral nervous system accompanying diabetes. It may also be caused by uremia or alcoholism. Modifiable risk factors for neuropathy include obesity, hyperlipidemia, and hypertension. Patients typically experience pain, tingling, and numbness in the distal limbs. The sensation of numbness may induce loss of balance and falls. Severe neuropathies are associated with incidence of foot ulcer and amputation of the lower extremities (Callaghan et al., 2012). Distal neuropathy is common and can be confirmed by combining medical history with a foot exam. Loss of sensation in the feet and loss of the Achilles tendon reflex can further be confirmed by nerve conduction and biopsy studies. Autonomic neuropathies involve all the organ systems and cause increased mortality rates and can be screened using appropriate diagnostic tests (Boulton et al., 2005).

Cerebral small vessel disease is a group of diseases that affects the small arteries, arterioles, venules, and capillaries of the brain. It is typified by cognitive impairment and vascular dementia (Baker et al., 2012; van Norden et al., 2011). Diabetics face a higher risk of occurrence of cerebrovascular disease due to conditions that disrupt the blood supply to the brain (NHS, 2015). Additional contributing causes for cerebrovascular disease are stroke and hypertension. Interruption of the blood supply to the brain causes local ischemia and

death of the neural tissue. A transient ischemic attack is a temporary disruption of the blood supply to a part of the brain, subarachnoid hemorrhage, or vascular dementia (NHS, 2015). Clinical diagnostic techniques for cerebrovascular disease include neuropsychology testing, magnetic resonance imaging, computed tomography, single photon emission computed tomography, and positron emission tomography (Baker et al., 2012).

Progressive kidney disease characterized by damage to the glomeruli in the kidney is associated with atherosclerosis, diabetes, metabolic disorder, hypertension, obesity, and dyslipidemia. Increased oxidative stress and inflammation may mediate the initial effect of these factors on the kidney. Progressive deterioration of renal function may further cause dyslipidemia and accumulation of toxins, proinflammatory as well as fibrogenic factors leading to endothelial cell (EC) dysfunction. Atherogenic factors play a direct role in the silent phase of overt ischemic disease, as well as overt ischemic nephropathy (NKF, 2014).

Diabetes is the leading cause of chronic kidney disease leading to kidney failure and death. The symptoms of diabetic kidney disease include hypertension, swelling in the lower extremities, increased urination, decline in glomerular filtration rate, nausea, vomiting, weakness, pallor, and anemia. Screening for diabetic neuropathy may be carried out by detection of albumin in spot or 24 hour urine collections, elevated serum creatinine, and hypertension (NKF, 2014).

Vasoregression

Blood vessels constitute the fundamental unit of the vasoregression phenomenon. The vessel wall consists of two interacting cell types, EC and the surrounding mural cells (MCs). ECs form the inner lining of the vessel wall, while MCs coat the outer surface. The MCs or pericytes are present intermittently on the surface in capillaries. In larger vessels, the MCs are represented by vascular smooth muscle cells (VSMCs) that share the same lineage as pericytes and completely cover the outer surface, often in multiple layers (Gaengel et al., 2009).

Vascular development involves processes such as formation, maturation, remodeling, and regression of the vessels. The structure of the newly formed vessels is immature and requires further stabilization by specific cells, extracellular components, and signaling pathways. Sufficient and normal interactions between the ECs and MCs are critical for various aspects of vessel formation, stability, remodeling, and function (Armulik et al., 2005; Carmeliet, 2003). The ECs of immature cells secrete signals required for migration and proliferation of MCs. They also secrete a thin layer of matrix known as the basement membrane (BM), leading to the formation of stable blood vessels (Brey, 2011).

Disruption of pericyte–endothelial interaction and perivascular extracellular matrix (ECM) components such as neural cell adhesion molecule may lead to destabilization or regression of mature blood vessels (Benjamin et al., 1998; Brey, 2011; Gerhardt and Semb, 2008; Hammes et al., 2002). Regression of blood vessels may also occur once the initial network of vessels has been formed, and needs to be remodeled into its final differentiated form. This process requires apoptosis of ECs for removal of excessive blood vessels by regression (Darland and D'Amore, 1999). Thus,

prevention of EC apoptosis by providing sufficient growth factors may also prevent vasoregression (Dimmeler and Zeiher, 2000).

The integrity, tightness, and mechanical strength of the endothelium is maintained by junctional structures that also provide a barrier to molecular transport (Carmeliet, 2003). During vessel sprouting, the junctions are partially compromised to accommodate increased vessel permeability, but are re-established during vessel stabilization (Dejana, 2004). Molecules in endothelial junctions can form multiprotein complexes with growth factors, and help to regulate vessel stabilization through control of EC responses (Lampugnani, 2012). Junctional complexes can also be envisaged as therapeutic targets for reversing the regression of blood vessels.

Therefore, vessel regression may be caused by: a) insufficient stimulus during vessel formation leading to failure of stabilization of the vascular structure; b) EC apoptosis or loss of essential growth factors during the process of remodeling of vessels leading to their tissue-specific maturation (Brey, 2011); c) factors such as inflammation leading to pericyte loss either by apoptosis or migration (Armulik et al., 2011); and d) pathological disruption of junctional structures in the endothelium.

In the retinal vasculature, vasoregression is the result of capillary occlusion and degeneration of a large number of capillaries that ultimately causes decrease in retinal perfusion (Aiello et al., 1998; Robinson et al., 2012). In turn, retinal capillary occlusion may either be an outcome of a) blockage of vascular lumen by white blood cells or platelets, b) death of capillary cells induced by biochemical abnormalities within the vascular cells or; c) death of capillary cells due to products generated by nearby cells like neurons or glia (Kern, 2007). In the eye, retinal capillaries have the highest density of pericytes.

Recent studies have established that loss of pericytes either by migration or apoptosis marks the initiation of the process of vasoregression (Porta, 2005). The lack of pericyte protection makes the endothelium more susceptible and prone to damage (Armulik et al., 2011; Hammes et al., 2004; Pfister et al., 2008; Porta, 2005; Romeo et al., 2002). It has been suggested that death of photoreceptor cells due to apoptosis of cells of inner nuclear layer precedes vasoregression. This is accompanied by upregulation of certain neurotrophins like nerve growth factor (NGF) and ciliary neurotrophic factor (CNTF) (Feng et al., 2009). Upregulation of inflammatory cytokines and growth factors are also associated with retinal vessel regression.

Junctional disruption leading to breakdown of blood–retinal barrier (BRB) is also accompanied with early retinal vessel regression. In the eye, endothelial damage causes BRB breakdown with subsequent retinal edema and extravasation of lipids, proteins, and fluid, causing ocular defects such as ME and DR (Pfister, 2011). Diabetic vasculopathy is the most devastating complication of diabetes and is typified by rapid development of atherosclerosis at multiple distal sites. Vasoregression due to depletion of endothelial progenitor cells (EPCs) during diabetes may also lead to poor collateralization, a late event leading to clinical manifestations such as limb ischemia and other peripheral arterial diseases (Waltenberger, 2001).

Similarly, tumor formation requires vasoregression and neoangiogenesis of the newly formed cell mass. Proteins

mediating destabilization of blood vessels are potential targets for antiangiogenic tumor treatment (Gerald et al., 2013). Thus, vasoregression is an important step leading to numerous pathologies within the vascular subunit.

Hallmarks of Vasoregression

The phenotype of vasoregression is characterized morphologically by the formation of acellular capillaries in retina of humans and experimental diabetic rats (Hammes et al., 2011). Formation of acellular capillaries in skeletal muscles of the neck, calf or foot in diabetic subjects has been observed in diabetic subjects and is often accompanied by pericyte loss and BM thickening. The occurrence of these characteristic features in skeletal muscle may be due to the underlying peripheral neuropathy in diabetes and suggest a common pathophysiological mechanism with the retinal microvessels (Tilton et al., 1985). Additional characteristic features of vasoregression, namely loss of mural cells (MC) and endothelial damage due to macrovascular disease (atherosclerosis), and ocular microangiopathies are detailed below.

Loss of MCs

During atherosclerosis, proliferation, migration, and apoptosis of VSMCs are vital for lesion formation, vascular remodeling, plaque formation, and rupture (Lim and Park, 2014; Rudijanto, 2007). In normal blood vessels, VSMC occur in quiescent or differentiated or contractile phenotype regulating the blood flow and vessel diameter (Owens, 1995; Schaper and Ito, 1996; Wolf et al., 1998), whereas in the atherosclerotic condition, a reverse phenotypic shift takes place, resulting in the synthetic or noncontractile or de-differentiated VSMCs that can migrate from the media to the intima and proliferate in the intimal region (Stegemann et al., 2005). This VSMC migration forms an indispensable part of the pathological condition and is regulated by various growth promoters and inhibitors such as matrix metalloproteinases and platelet-derived growth factor (PDGF) (Schachter, 1997; Schwartz, 1997).

Recent studies on atherosclerosis have highlighted the role of VSMCs in propagating inflammation. Once the plaque has been formed, VSMCs also stabilize the atherosclerotic plaque by synthesis of ECM molecules. However, in case of inflammation or injury, the activated inflammatory and immune cells in the plaque lead to VSMC apoptosis (Geng and Libby, 2002). Predominance of VSMC apoptosis over proliferation in the atherosclerotic state is instrumental in causing plaque rupture (Bennett, 2002; Newby et al., 1999). Thus, VSMCs not only participate in atherosclerotic lesion growth, but are also responsible for plaque rupture (Rudijanto, 2007).

In the microvessels, perivascular pericytes possess contractile fibers that wrap around the ECs of capillaries and venules throughout the body. Pericytes consist of a cell body with a nucleus and cytoplasm embracing the endothelial wall. The function of pericytes is not fully understood, but they have been found to regulate the microvascular diameter and blood flow (Kutcher and Herman, 2009; Peppiatt et al., 2006). Pericytes, besides being key components of the neurovascular unit, also serve a variety of important functions such as providing vascular stability, maturation of the developing vasculature, control of EC proliferation, and regulation of capillary blood flow. Pericytes are also involved in maintenance, clearance, and phagocytosis of

cellular debris, maintenance of blood–brain barrier permeability, and mediating physiological and pathological repair processes.

In the ocular vessels, pericytes stabilize the vessels and protect against vasoregression (Jyothi, 2013). The role of pericytes in vasoregression is highlighted by their loss much prior to the development of acellular capillaries (Hammes, 2011). Pericytes also manifest the crosstalk between systemic inflammation and several vascular disorders. Yet, contradictory reports show abundance of pericytes in the retinal capillaries does not guarantee vascular stability in the retinal microvasculature and the vessels may still regress (Brey et al., 2004). Thus, the role of pericytes and its associated factors in the formation of a mature, stable microcirculation requires further elucidation.

Several mechanisms have been proposed to explain pericyte loss accompanying vasoregression: a) pericyte apoptosis occurs early just after a few days of the induction of diabetes in animal models. It is considered as one of the initiators of vasoregression leading to complications in the eye (Hammes et al., 2011; Li et al., 1997). This loss of pericytes is attributed to endothelial hyperplasia, increased capillary diameter, abnormal shape/structure of EC, modified/irregular shaped proteins, and alterations in junctional protein distribution leading to activation of pro-apoptotic pathways (Curtis et al., 2009; Hammes et al., 2004; Hammes, 2011; Stirban et al., 2014); b) pericyte migration is the translocation of pericytes from one allocated position in the capillary to another. Recent studies show that the number of pericytes lost largely exceeds the number of pericytes lost by apoptosis, indicating the participation of additional mechanisms like pericyte migration (Hammes et al., 2011; Pfister et al., 2008). However, quantitative contribution of pericyte migration to pericyte loss and the destiny of the translocated pericytes remains to be elucidated. Thus, migration and alterations in the resting, quiescent phase is a shared feature of atherosclerosis and DR. However, the tissue-specific response of MCs in the large vessels is proliferation while that of DR is marked by apoptosis/migration.

Endothelial damage

Endothelial cells (EC) line the inner surface of blood vessels. Systemic endothelial damage results in a cluster of diseases such as atherosclerosis and coronary heart diseases. Endothelial damage disrupts the balance between vasoconstriction and vasodilation and initiates the plethora of events of endothelial permeability, platelet aggregation, and leukocyte adhesion, resulting in atherosclerosis (Davignon and Ganz, 2004). Endothelial damage induces a state accompanied by reduced nitric oxide bioavailability, pro-vasoconstriction, pro-oxidative stress, and proinflammation, resulting in atherosclerotic plaque formation and its sequelae (Mudau et al., 2012). Thus, it constitutes an initial and reversible step in atherosclerotic development. Early clinical identification of the damaged endothelium may become an important tool in the prognosis of atherosclerosis (Mudau et al., 2012).

In the microvessels of the eye, several studies on animal models have demonstrated clearly that pericytes disappear much before EC start to vanish (Hammes et al., 2004; 2011). This pericyte dropout is conceived as the primary step in endothelium reactivation and reducing endothelial protection. A

recent study on transgenic rats has suggested that neuronal dysfunction and glial changes occur prior to vasoregression during development of DR. The endothelium, along with the junctional proteins occludins, claudins, and zona occludens proteins, comprise the functional part of BRB. Endothelial damage may cause BRB breakdown, leading to increased permeability and seepage of lipids, proteins, and fluid into extracellular spaces (Jyothi, 2013), ultimately leading to various ocular complications such as blurring of vision and macula swelling. This BRB breakdown occurs secondary to the alterations in tight junctions, pericyte loss, EC loss, increased vesicular transport, and membrane permeability. Thus, pericyte migration and apoptosis are the initiators of vasoregression, followed by subsequent degeneration of EC making the remaining vasculature vulnerable to destructive signaling (Fig. 1).

Factors Modulating Vasoregression

Inflammation

Inflammation is an immunovascular response to harmful stimuli such as infection, stress, or injury, via the triggering of the corresponding inflammatory cascade. This may involve several immune cells, blood vessels, and molecular mediators. It has become clear in recent years that acute and chronic inflammatory events are associated with and critical for

vascular remodeling and atherosclerosis (Aihara et al., 2012). Inflammation has been known to participate in endothelial desquamation, a hallmark of atherosclerosis by local production of inflammatory mediators and oxidized lipoproteins (Libby, 2002).

These inflammatory mediators in turn activate matrix metalloproteinases that degrade the subendothelial BM (Rajavashisth et al., 1999). Inflammatory stimulation may also promote EC to produce enzymes that degrade the ECM constituents to which they adhere under normal circumstances (Libby, 2002). Inflammation also plays a vital role in plaque disruption and rupture (Libby, 2002). An *in vivo* study in patients with inflammatory arthritis showed that inflammation leads to immature and unstable vessels with no pericyte recruitment and thus disrupted pericyte–EC cross-talk (Kennedy et al., 2010).

The link between inflammation and retinal vasoregression is both crucial and multifaceted (Hammes et al., 2011). Inflammation of the eye vasculature induces high levels of certain inflammatory cytokines and mediators that may result in several microvascular pathologies (Calonge et al., 2010; McCluskey and Powell, 2004; Wakefield and Lloyd, 1992). Additionally, systemic inflammation can lead to ocular manifestations in many diseases (McCluskey and Powell, 2004; Mohsenin and Huang, 2012). Pro-inflammatory proteins that

FIG. 1. Cartoon schematic illustrating the mechanism of vessel regression associated with atherosclerosis (macrovascular pathology) and ocular vasculopathies (microvascular disease). During inflammatory and/or stress conditions, a blood vessel may lose its mural cell (MC) coverage either due to migration or apoptosis. Under normal conditions, homeostatic repair occurs due to the presence of various growth factors and survival factors. On the contrary, in sustained inflammatory microenvironment, MC loss serves as a precedent for disruption of EC–MC interaction resulting in degradation and stripping of the EC from their basal membrane. Here, due to the participation of various signaling pathways, vascular permeability gets altered, resulting in the exudation of proteins, lipids, and fluid to the ECM, causing vasculopathies in both macro- and microvasculature.

activate NF- κ B also lead to cell damage and death of retinal tissues (Kern, 2007; Rathnasamy et al., 2014; Yoshida et al., 1998). BRB breakdown, a critical event in the occurrence of vessel regression, is also a consequence of inflammation (Occhiutto et al., 2012; Viores et al., 2001).

Lipids

Low density lipoproteins (LDL) gets oxidized into oxidized LDL (oxLDL) resulting in an alteration of its properties. This makes the oxLDL appear as 'foreign' to the immune system. OxLDL is pro-atherogenic and marks the initiation of development of atherosclerotic plaque. This is followed by leukocyte attraction into the intima, ingestion of lipids by leukocytes, and their differentiation into foam cells, as well as proliferation of leukocytes, SMCs, and EC (Dokken, 2008). Recent studies confirm the role of oxLDL in increasing the reactive oxygen species (ROS) generation, EC activation and dysfunction, macrophage foam cell formation, SMCs migration and proliferation, leading to vascular complications like atherosclerosis (Pirillo et al., 2013).

Vasoregression in the diabetic retina may also result from hyperglycemia-induced modifications of levels and/or the chemical makeup of lipids and fatty acid-based hormones in blood. Two main types of modifications are reported, namely; 1) post-translational modification of lipoproteins, and 2) changes in the biosynthesis of eicosanoids (Chew et al., 1996; Keech et al., 2007; Lyons et al., 2004). Elevated serum lipid levels are associated with an increased risk of ocular problems like DR and loss of vision (Idiculla et al., 2012). The oxLDL also mediates capillary injury in DR (Zhang et al., 2008).

Previous studies on bovine retinal capillary EC have very well established the impact of modified or oxLDL on retinal pericytes contributing to early DR (Li et al., 2012; Lyons et al., 1994; Zhang et al., 2008). Increase in proinflammatory eicosanoids derived from eicoanoids combined with a decrease in anti-inflammatory ω 3 unsaturated fatty acids in the diabetic retina has been implicated in the development of vasoregression and neovascularization (Tikhonenko et al., 2010). The role of the hyperlipidemic state in atherosclerosis (Kanter et al., 2007) and its frequent occurrence in diabetes, taken together with its role in pathogenesis of DR, also establishes a clear link for the development of ocular microangiopathies in cardiovascular diseases (CVD). Hyperlipidemia-induced premature vessel atherosclerosis can also lead to hyperlipidemic vascular lesions and lipid infiltration into the retina in disorders such as lipemia retinalis (Rymarz et al., 2012).

Leukostasis

Leukostasis is the attraction and adhesion of leukocytes to the vascular wall. It is a fatal complication characterized by the abnormal aggregation of leukocytes in vascular tissues, which can be seen as white cell plugs in the microvasculature. This acute condition causes occluded circulation leading to the complications of headache, chronic ischemia, cerebrovascular incidents, ocular accidents, and even death.

During atherogenesis, cholesterol-laden molecules in the blood stream infiltrate the arterial walls and prompt the expression of leukocyte adhesion molecules in the endothelium that results in aggravation of atherosclerosis (Mestas and Ley, 2008; Vanderlaan and Reardon, 2005). An atherogenic diet

triggers the expression of vascular cell adhesion molecules that lead to the attachment of circulating monocytes and other leukocytes (Cybulsky and Gimbrone, 1991; Li et al., 1993).

Leukostasis in retinal capillaries is also a cause of non-perfusion and death of retinal EC (Kern, 2007). Adherence of leukocytes to diabetic endothelium in retinal vasculature can obstruct capillaries due to the large cell volume and high rigidity of leukocytes. Leukostasis also leads to EC apoptosis via FasL in the retinal vasculature (Joussen et al., 2003). Inhibition of NF- κ B blocks the hyperglycemia-induced production of inflammatory molecules in ocular tissues and attenuates leukostasis (Miyamoto et al., 1999; Zhang et al., 2011).

Leukostasis can be prevented by blocking or genetic elimination of intracellular adhesion molecule-1 (ICAM-1) or CD-18 (Adamis, 2002; Joussen et al., 2004). High dose anti-inflammatory agents reduced leukostasis, EC death, and suppressed BRB breakdown in diabetic rats (Joussen et al., 2004). Events leading to formation of acellular capillaries in the eye due to leukostasis have been proposed (Lutty, 2013) as: a) increased levels of leukocyte ICAM-1 in EC; b) ICAM-1 binding to neutrophils and causing expression of CD11/18; c) oxidative burst from bound polymorphonuclear lymphocytes (PMNs) injures ECs and causes their loss; d) bound PMNs occlude the capillary leading to local ischemia and reperfusion; e) loss of ECs exposes the BM and causes formation of a platelet/fibrin thrombus; and f) loss of pericytes and formation of acellular capillaries. Thus, leukostasis is an inherent characteristic of inflammation driven changes of the macro- and microvasculature.

Endothelial progenitor cells (EPCs)

EPCs are the circulating cells in bone marrow that enter the bloodstream and travel to the injured blood vessel to repair the damage, thus strengthening the integrity of the vascular endothelium. They are inherently required for vessel homeostasis, formation, stabilization, and maturation. EPCs have the ability to differentiate into EC. They are also involved in endothelial homeostasis and formation of new vasculature. The endothelium plays a role in protection against inflammation, thrombosis, and CVD (Yang et al., 2008). During atherosclerosis, reduced number and dysfunction of EPCs have been observed.

EPC-based therapies have been proposed for improving vascular structure and functioning for treatment of atherosclerosis (Du et al., 2012). Cytometric studies demonstrate that depletion of EPCs may lead to endothelial dysfunction, which is marked as an initial event in the pathogenesis of atherosclerosis (Fadini et al., 2005). EPCs are also involved in repair of damaged lining of the blood vessels and angiogenesis after injury (Shantsila et al., 2007). Dysfunction or exhaustion of EPCs from the bloodstream may additionally cause vascular diseases such as aging, coronary artery disease, and hypercholesterolemia, while levels of circulating EPCs can also be used as a surrogate index or marker for the occurrence of atherosclerosis and other CVD (Fadini et al., 2005). At present, the factors responsible for modulation of the number and characteristics of circulating EPCs are under investigation.

In DR, there is an altered number and functioning of EPCs. Interpretation of the level and type of EPCs reported in the clinical condition remains inconclusive. However, specific

EPC subtypes may be important for disease prognosis, stratification, and therapeutic treatment of diabetic ME and proliferative DR (Lois et al., 2014). EC dysfunction and poor collateralization as an effect of EPC depletion is also prominent in early stages of DR. The impaired function of EPCs may be restored by improving their mobilization, for example, by statins, vascular endothelial growth factor (VEGF), estrogen, or by drugs that improve function leading to the self-repair of damaged capillaries in the diabetic retina (Cabrero et al., 2007).

Increased production of Advanced Glycation Endproducts (AGE)

AGE compounds are formed by a non-enzymatic reaction between reducing sugars and proteins/lipids/nucleic acids. AGE compounds diffuse out of the cell and cause modification of ECM molecules, leading to cellular dysfunction (Charonis et al., 1990; Farooqui, 2015). Highly reactive AGE compounds also modify intracellular proteins, change their structure, cross-linking, enzymatic activity, receptor recognition, and impair their clearance.

AGE also interact with specific RAGE receptors that are present on all the cells involved in atherosclerosis. The AGE-RAGE axis is associated with triggering of oxidative stress, inflammation and apoptosis (Stirban et al., 2014). Elevated levels of AGE lead to heightened adverse atherosclerotic effects and thus have also been proposed to be a biomarker of atherosclerotic lesions in diabetic subjects (Chang et al., 2011). Hyperlipidemic stress was also found to cause upregulation of the receptor for AGE accompanied by increased phosphorylation of AKT and could be attenuated by treatment with Fluvastatin, a drug used to treat cardiovascular disease (Georgescu and Popov, 2000).

Increased levels of AGE have been reported in retinal vessels in DR (Stitt et al., 1997). AGE modify the circulatory proteins by binding to RAGE and leading to the activation of downstream pathways like NF- κ B pathway. However, isolated studies have demonstrated the age-dependent accumulation of AGE in vascular beds and lens in an animal model (Georgescu and Popov, 2000). AGE induce apoptosis in retinal pericytes by activation of transcription factors like FOXO1, mediated by p38 and JNK MAP kinases (Alikhani et al., 2010; Curtis et al., 2009; Farooqui, 2015; Stirban et al., 2014). Moreover, inhibition of formation of AGE has also been found to reduce the progression of DR (Bhatwadekar et al., 2008; Kern and Engerman, 2001; Stitt et al., 2002; Thallas-Bonke et al., 2008). Apart from its proinflammatory role, eicosanoids can increase the angiopoietin Ang-2 expression either directly or through VEGF expression, further leading to vasoregression (Guo et al., 2009). Thus, it may be postulated that increased levels of AGE and their receptors constitute a key factor in atherosclerosis, as well as vascular diseases of the eye, through the process of vasoregression.

Increased vascular permeability

Vascular permeability, or the capacity of a blood vessel wall to allow the passage of molecules through the vessel, is altered during the inflammatory state. Atherosclerosis has been regarded as an inflammatory disorder during which the pervading endothelial dysfunction causes an increased permeability to plasma constituents and lipoproteins (Ross,

1999). Increase in a number of vascular permeabilizing factors (e.g., VEGF-A, histamine) causes the influx of protein-enriched plasma into the surrounding tissues. Chronic vascular hyperpermeability is associated with pathological angiogenesis found in various chronic inflammatory diseases (Nagy et al., 2008). The angiogenesis is assisted by remodeling of the ECM by proteases. Specific inflammatory responses also activate unique subtypes of specialized EC to invade the tissues for perfusion and repair (Arroyo and Iruela-Arispe, 2010).

In the microvasculature of the eye, the prolonged stimuli of permeability-inducing agents such as VEGF can affect the barrier integrity, making the vessels fragile. This is compounded by the unstable endothelial junctions and pericyte insufficiency (Jyothi, 2013). During DR, increase in leukostasis, cytokines, growth factors, and acute inflammation leads to increase in capillary hydrostatic pressure and may finally result in the breakdown of the BRB (Pfister, 2011). The increased permeability associated with the disruption of junctional integrity of BRB forms the developmental basis of ocular complications such as DR and ME (Romero-Aroca, 2011). Accordingly, treatment of DR with aldose reductase inhibitors, protein kinase C (PKC) inhibitors, tyrosine kinase inhibitors, cyclooxygenase (COX)-2 inhibitor, steroids, VEGF antagonist, TNF- α receptor antagonists, and PPAR γ ligands (Kern, 2007) aid the normalization of vascular permeability.

Glial activation

In the peripheral nervous system, glial Schwann cells provide myelination to the large axons and clear the cellular debris around the neurons. Non-myelinating Schwann cells associated with small axons are critical for neuronal survival (Bunge, 1994). Satellite cells control the response to the external chemical environment around the neurons (Hanani, 2005). Schwann cell damage is thought to be an important component of diabetes-induced neuropathy. The LDL receptor related protein (LRP1) is a regulator of inflammation and neuronal injury, conditions found to co-occur in atherosclerosis. Schwann cells show greatly increased expression of LRP1 as a pro-survival tactic in response to nerve injury (Gonias and Campana, 2014). LRP1 also shows anti-atherogenic activity in VSMCs by limiting PDGF- β receptor signaling (Boucher et al., 2003). Other mechanisms of anti-atherogenic activities of LRP1 include lowering of inflammatory mediators and modulation of ECM remodeling (Gaultier et al., 2008; Overton et al., 2007; Yancey et al., 2011). LRP1 also controls vascular remodeling by its effects on the TGF- β signaling pathway (Muratoglu et al., 2011).

There exists a tight functional association between glial cells and retinal vasculature. The principal glial cells induce production of growth factors such as neurotrophin and inflammatory factors such as CNTF, fibroblast growth factor (FGF), NGF, and cytokines affecting retinal vasculature. Under retinal cell stress, glial cell activation occurs as an early event in vasoregression. When glial cells, including astrocytes and Müller cells, become activated, pericytes and EC fail to maintain vascular integrity, which results in vasoregression. Glial cells, on one hand, protect the retina by producing heat shock proteins and neurotrophins and aid in elimination of harmful molecules, but on the other hand, may

also release inflammatory cytokines that aggravate blood vessel damage (Wang, 2009). Glial cells express Ang2 that induces vascular cell depletion and progressive capillary occlusion (Hammes et al., 2011). Several retinal pathologies such as photoreceptor degeneration and DR involve microglial activation. However, the exact mechanism of microglial activation leading to vasoregression is still unclear (Pfister, 2011).

Pathways Leading to Development of Vasoregression

Formation of a stable vasculature and prevention of vessel regression are tightly regulated by numerous signaling pathways. A stable, properly functioning vasculature can be achieved from the balance between signals favoring vessel stabilization and factors favoring vessel regression (Busso-lino et al., 1997). Signaling pathways affect vessel stabilization by regulating the proliferation and apoptosis of EC and MCs. Some of the signaling pathways affecting vascular stability and causing regression are discussed below.

Immune response pathways and complement cascade

The complement pathway has a central but dual role in atherosclerosis. The classical complement pathway may be atheroprotective by removing cell debris and apoptotic cells from the atherosclerotic plaque. However activation of the alternative pathway may activate proatherogenic stimuli and promote plaque rupture (Speidl et al., 2011). There is evidence for the upregulation of innate immunity and complement cascade members like CD74 in systemic diseases like atherosclerosis. Their enhanced expression has been detected in inflammatory VSMCs (Martin-Ventura et al., 2009).

Several components of immune response pathway and complement cascade such as CD74, beta-2-microglobulin, alpha-2-microglobulin, interleukin-1 (IL-1), tumor necrosis factor receptor superfamily, member 1a, Serpin1, and C1qa play critical roles in the development of vasoregression in rat models. The complement cascade components are also expressed in microglial cells during vasoregression (Feng et al., 2011). The molecular components of immune response and complement cascade also mediate endothelial proliferation and regulation of apoptosis, as well as control of prostaglandin metabolism. Thus, the complement cascade presents an important link between inflammatory stimuli and vasoregression (Shi et al., 2006).

PDGF pathway

PDGF is a family of four ligands (A–D) secreted by EC that plays a critical role in MC neural development as recruitment, proliferation, and stabilization during vascular maturation. All PDGF family members can exist as disulfide-linked homodimers, while the A and B isoforms can also form heterodimers (Betsholtz, 2004; Hoch and Soriano, 2003; Lindahl et al., 1997). It has been observed that MCs are first induced in the absence of PDGF pathway but fail to proliferate in the growing blood vessels in the absence of PDGF pathway induction (Hellstrom et al., 1999). During atherosclerosis, PDGF-B and PDGFR β receptor induce proliferation and migration of VSMCs (Ross, 1993), and conversely can be retarded by inhibition of PDGF signaling (Sano et al., 2001).

In vivo studies conducted on mice models also illustrate that PDGFR β -deficient mice possess very few pericytes, resulting in hyperdilated blood vessels (Lindahl et al., 1997). Interrupting EC–MC interactions by targeting the PDGF-B pathway also cause vascular destabilization and abnormal blood vessel remodeling (Benjamin et al., 1998; Hellstrom et al., 1999). Studies based on a disease model of retinitis pigmentosa revealed that PDGF-CC (a PDGF-C homodimer) renders a vasoprotective effect by playing a pivotal role in blood vessel maintenance and survival. Moreover, it has been mechanistically illustrated that the PDGF receptors PDGFR- α and PDGFR- β are essential for the vasoprotective effect of PDGF-CC in the retina (He et al., 2014). Thus, the PDGF pathway regulates the pericyte coverage and vascular remodeling in the human vasculature.

Neurotrophin pathway

Neurotrophins are a family of closely-related proteins that act as survival signals for neurons of the central and peripheral nervous system. They play a critical role in cardiovascular development and maintenance. Neurotrophins are also responsible for survival of EC, VSMCs, and regulation of vasculogenesis. Acting through different receptors, neurotrophins have been implicated in both neovascularization and impaired angiogenesis (Caporali and Emanuelli, 2009). The brain-derived neurotrophic factor (BDNF) has also been reported to be critical in EC survival and vessel stabilization in the myocardium (Donovan et al., 2000). During late embryonic development, recruitment of pericytes and SMCs, and the extension of the pericyte processes for coverage of the myocardial vessels, are dependent on activation by BDNF (Anastasia et al., 2014). Neurotrophin pathway has been implicated in the development of cardiac ischemia and atherosclerosis (Chaldakov et al., 2004).

Neurotrophins are essential for growth, differentiation, and survival in the developing and mature retina. Deregulated growth factor expression of neurotrophin signaling pathway like CNTF, FGF, NGF leads to early pericyte loss, resulting in the initiation and development of vasoregression process (Pfister, 2011). Neurotrophic factors like glia derived neurotrophic factor secreted by glial cells also regulate tight junctions, thus modulating BRB vascular permeability in DR (Nishikiori et al., 2007). Upregulated expression of FGF2 and CNTF prior to vasoregression is likely to reflect a response to photoreceptor damage, while NGF upregulation after the onset of vasoregression may have an association to microvascular degeneration (Pfister, 2011).

An imbalance of the NGF–ProNGF ratio is caused by the oxidative milieu in the diabetic retina. Elevated levels of ProNGF in ocular fluids from proliferative DR patients, raises a possibility that proNGF can contribute to development of proliferative stages of the disease. ProNGF also induces a potent angiogenic response in retinal EC that gets blocked by TrkA inhibition, suggesting the contribution of proNGF to proliferative DR, via activation of TrkA (Elshaer et al., 2013).

NGF–ProNGF balance has also been reported to alter VEGF expression but the mechanism of this mutual regulation in modulating retinal vasculature is yet to be deciphered. Taken together, these studies point to the potential contribution of proNGF and NGF in the development of DR

(Mysona et al., 2014). Thus, neurotrophin signaling is likely to play a significant role in the human vasculature, and its involvement in vessel regression needs further elucidation.

Angiopoietin (Ang)-2/Tie-2 pathway

The receptor tyrosine kinase Tie-2 is expressed on EC that binds to its vasoprotective, angiogenic ligand, Ang-1. Ang-2, its naturally occurring homologous ligand, antagonizes Ang-1 activity on Tie-2 and disrupts blood vessel formation. The balance between Ang-1 and Ang-2 determines Tie-2-mediated functioning of endothelial barrier, angiogenesis and response to inflammation (Cogan et al., 1961; Hanahan, 1997; Thurston et al., 2000). In the absence of VEGF, Ang-2 destabilizes the vessels by inducing ECs apoptosis. However, in the presence of VEGF, it causes vessel sprouting (Jain, 2003).

The role of Ang-2 in atherosclerosis has not been elucidated. However, novel athero-protective activity of Ang-2 in stressed EC through the activation of endothelial nitric oxide synthase prevents LDL oxidation (Ahmed et al., 2009). Angiopoietins are likely to have both pro-atherogenic and athero-protective effects in atherosclerosis (Trollope and Golledge, 2011).

Several studies have reported the upregulation of Ang-2 with the progression of vasoregression. Ang-2 plays an important role in coverage of vessels by pericytes, and its modulation is responsible for pericyte loss in early retinopathy (Pfister et al., 2008; Pfister, 2011). The Ang-2/Tie-2 system plays a critical role in detachment and migration of pericytes from microvasculature leading to pericyte loss (Hammes et al., 2011; Pfister et al., 2008). Under pathological conditions, Ang-2 modulates intra- and preretinal vessel formation in eye and is therefore critical for retinal neovascularisation initiation (Pfister, 2011). Ang-2-deficient mice manifested decelerated age-dependent vascular changes in the retina (Feng et al., 2008). These data suggest that Ang-2 pathway plays a critical role in the regression of blood vessels.

Peroxisome-proliferator activated receptor (PPAR)

PPARs are a group of nuclear receptor proteins available in three isoforms: PPAR- α , - β , and - γ . PPAR- α has beneficial effects in vasculature by protecting against hypertension, inflammation, and oxidative stress (Cervantes-Perez et al., 2012; Ding et al., 2014; Hu et al., 2013; Moran and Ma, 2015). Studies on hypertensive and diabetic models have illustrated that PPAR- γ regulation of PI3K and MAPK contribute to vascular remodeling (Benkirane et al., 2006). PPAR- α and γ activation has been found to reduce atherosclerosis progression by inhibiting the formation of macrophage foam cells and ROS formation (Duval et al., 2002; Neve et al., 2000; Zandbergen and Plutzky, 2007). PPAR- α increases plaque stability in atherosclerosis and prevents thrombogenicity. PPAR- γ activation affects the recruitment of monocytes in atherosclerotic lesions (Neve et al., 2000).

PPAR- γ has also been reported to play a vital role in the pathogenesis of various ocular diseases such as macular degeneration (AMD), DR, keratitis, and optic neuropathy. Several PPAR- γ agonists have been proved to prevent the eye diseases of corneal scar formation, dry eye disease, and DR (Zhang et al., 2015). Thus, PPAR- γ may emerge as a potential

drug target for the treatment of atherosclerosis, as well as ocular diseases.

Protein kinase C (PKC) pathway

The PKC pathway and its constituent proteins play a crucial role in initiating pericyte apoptosis and impairment of vascular integrity. The PKC pathway, besides regulating the expression of numerous vasoactive proteins, also mediates EC permeability and extracellular remodeling. Activation of PKC pathway accelerates pro-atherosclerotic mechanisms, including endothelial dysfunction, nitric oxide synthase (NOS) expression, VSMC growth, migration, and apoptosis (Rask-Madsen and King, 2005).

Perturbations in vascular cell homeostasis caused by different PKC isoforms (PKC- α , - β 1/2, and - δ) are associated with both large vessel (atherosclerosis, cardiomyopathy) and small vessel (retinopathy, nephropathy and neuropathy) complications (Geraldes and King, 2010). Various PKC isoforms are involved in the pathogenesis of atherosclerosis. PKC- β increases the uptake of Ox-LDL, thus triggering a cascade of pro-atherosclerotic mechanisms (Osto et al., 2008). PKC- β depletion has been found to decrease atherosclerosis (Harja et al., 2009). PKC- δ participates in SMC apoptosis and deletion of this isoform leads to arteriosclerosis (Leitges et al., 2001).

However, additional isoforms may be involved in other steps of atherosclerosis. Activation of PKC isoforms may also trigger the impairment of vascular integrity, which is a major hallmark of initiation of vasoregression (Geraldes and King, 2010; Pfister, 2011). Therefore, whether it will be beneficial to inhibit multiple PKC isoforms to halt or prevent complex mechanisms related to atherosclerosis remains to be resolved.

The PKC pathway plays a crucial role in formation of acellular capillaries and cell apoptosis in retina (Geraldes et al., 2009). PKC isoforms (PKC- α , - β 1/2, and - δ) also regulate leukocyte adhesion, apoptosis, and cytokine activity in the diabetic retina (Geraldes and King, 2010). A PKC- β isoform inhibitor has been regarded as an important regulator of hyperglycemia-induced endothelial dysfunction and has yielded positive results in clinical trials (Beckman et al., 2002). Inhibition of PKC in earlier stages of retinopathy may increase the occurrence of pericyte apoptosis in retinal capillaries (Pomero et al., 2003).

Hexosamine pathway

The hexosamine biosynthetic pathway helps in the synthesis of amino sugars and building blocks for protein/lipid glycosylation. This pathway has been proposed to act as a nutrient sensor that aids in the development of insulin resistance and the vascular effects of diabetic hyperglycemia (Buse, 2006). Plasminogen activator inhibitor-1 (PAI-1) gets upregulated via hexosamine and PKC pathway and this PAI-1 overexpression promotes VSMC mitosis, which plays a key role in atherosclerosis development (Edwards et al., 2008; Sayeski and Kudlow, 1996). The participation of hexosamine pathway in vessel regression is still in its nascent stages and needs to be further explored.

Hyperglycemia enhances expression of certain growth factors like TGF β , thus stimulating ECM synthesis via the hexosamine pathway. High glucose levels also increase ROS

production, leading to formation of AGE compounds, which accumulate in microvascular cells and activate the hexosamine pathway (Giacco and Brownlee, 2010; Hammes, 2011). The consequent modification of the critical intra- and extracellular proteins causes a disturbance in energy metabolism leading to retinal damage (Pfister, 2011).

MAPK signaling pathway

Activation of the MAPK pathway is directly attributed to Ox-LDL. MAPK pathway plays an important role in regulating foam cell formation and pathogenesis of macrovascular pathologies like atherosclerosis (Muslin, 2008; Zhao et al., 2002). All three MAPK pathways get activated by LDL and perform the function of apoptosis in the occurrence of vascular regression. The MAPK pathway plays a pivotal role in the pathogenesis of many vascular diseases. It gets activated during systemic inflammation or environmental stress (Xia et al., 1995).

An activated MAPK pathway regulates various transcription factors or kinases by phosphorylation leading to pericyte apoptosis and vasoregression through the downstream activation of NF- κ B pathway (Gerald et al., 2009). This also results in several ocular complications such as DR and uveitis (Rohilla et al., 2012).

NF- κ B activation

NF- κ B is a widely expressed endothelial transcription factor regulating the key genes participating in inflammation, immune response, apoptosis, and proliferation (Gupta et al., 2014). There is significant participation of transcriptional factors like NF- κ B in vessel remodeling (Grosjean et al., 2006). The role of NF- κ B pathway in the pathogenesis of atherosclerosis is complex and depends largely on the mode of its inactivation. While NF- κ B inactivation by macrophage selective deletion of I κ B kinase 2 (IKK2) aggravates atherosclerosis (Kanters et al., 2003), NF- κ B inactivation by inhibiting subunit p50 results in attenuation of atherosclerosis (Kanters et al., 2004). A study on LDL receptor-deficient mice confirmed that inhibition of NF- κ B pathway may affect pro- and anti-inflammatory balance in macrophages leading to atherosclerosis (Kanters et al., 2003). It has been suggested that NF- κ B participation in atherosclerosis may not be due to its role in macrophages but more due to its role for ERK signaling in STAT1 activation (Sikorski et al., 2012). Especially in diabetes, high glucose levels trigger cytokine mediated proinflammatory state that causes increased NF- κ B activation and leads to vascular dysfunction (Patel and Santani, 2009).

Retinal NF- κ B is activated early in diabetes and remains activated for up to 14 months (Kowluru et al., 2003). Some studies on ocular complications have also indicated the effect of NF- κ B on the early onset of the disease. Inhibition of NF- κ B regulated proteins like iNOS inhibit retinal capillary degeneration and pericyte apoptosis. NF- κ B inhibitors such as salicylates reduce the expression of inflammatory mediators, thus inhibiting capillary degeneration and pericyte loss and slowing the development of retinopathy (Zheng et al., 2007). NF- κ B gets activated by oxidative stress and can lead to retinal cell death (Kowluru and Koppolu, 2002; Kowluru et al., 2003). Being a regulator of antioxidant enzymes, NF- κ B is also a key mediator for retinal cell apoptosis. NF- κ B

signaling pathway has been found to be activated in EC and pericytes under hyperglycemic condition and its activation may play a role in the early development of DR (Kowluru et al., 2003).

VEGF signaling pathway: A therapeutic approach

VEGF signaling plays a significant role in the proliferation, differentiation, and permeability of the endothelium. Members of the VEGF family include VEGF A, B, C, D and placenta growth factor. VEGF has a critical role in the development of normal vasculature and maintenance of viability of immature blood vessels by facilitating pericyte recruitment (Reinmuth et al., 2001). The various isoforms of VEGF differ in their ability to bind to heparin sulfate, possess differential bioavailability, and may play distinct roles in vessel development.

VEGF protects the EC from apoptotic cell death (Carmeliet et al., 1996; Dimmeler and Zeiher, 2000; Ferrara et al., 1996; Gerber et al., 1998) and performs junctional stabilization (Murakami, 2012). VEGF is also a vascular protective factor due to its remarkable ability to increase nitric oxide production. Nitric oxide prevents endothelial dysfunction, inhibits SMC proliferation, and acts as an anti-atherogenic factor preventing the development of atherosclerosis (Libby, 2012; Murakami, 2012). Blockage of VEGF signaling disrupts the pericyte coverage of EC and causes EC apoptosis (Gerber et al., 1998; Gupta et al., 2002) leading to regression of blood vessels.

Several studies have confirmed that the absence of VEGF results in capillary nonperfusion and abnormal vasculature (Carmeliet et al., 1996; Dimmeler and Zeiher, 2000; Ferrara et al., 1996; Gerber et al., 1998). VEGF promotes restoration of damaged endothelium under physiological conditions and stimulates microvessel formation inside the atherosclerotic plaque, leading to intraplaque hemorrhage (Tunon et al., 2009). Anti-VEGF therapy, when administered systemically, can compromise the patient's safety by causing cardiovascular complications such as hypertension, thrombosis, and hemorrhage (Tunon et al., 2009). Thus, the safety of new anti-VEGF therapies must be carefully assessed.

Retinal hypoxia results in the formation and release of VEGF. As VEGF leads to neovascularization, it is an optimal therapeutic target for the treatment of ocular diseases including macular degeneration, DR, vascular occlusion, and neovascular glaucoma (Sinha et al., 2009). VEGF-A is a potent angiogenic agent and its prolonged signaling disrupts endothelial junctions, thus compromising the vascular integrity. Therefore, anti-VEGF therapy is now used for treatment of microvascular diseases such as age-related macular degeneration and DR. The use of anti-VEGF agents in treatment of DR is still under investigation, as it has been found to encompass various side effects (Murakami, 2012).

Shared Characteristics and Unique Features of Microvascular Disease in Different Organs

The commonalities and differences between macrovascular disease and microvascular diseases have been noted in previous works (Cade, 2008; Forbes and Cooper, 2013). Similarities and unique features of microvascular disease in different tissues have also been highlighted (Cade, 2008; Forbes and Cooper, 2013; Kanbay et al., 2011). Microvascular disease is

characterized by VSMC proliferation and matrix deposition in the small arterioles leading to narrowing of the lumen. It may occur either due to distal ischemia or due to impaired autoregulation of the blood flow to the vascular bed. A number of proscloerosing factors cause endothelial dysfunction and VSMC proliferation. Proinflammatory effects induce a phenotypic switch in the VSMCs, marked by increased collagen deposition and diminished contractile response (Kanbay et al., 2011).

Inflammation-related changes may be the early and perhaps primary cause for target end organ damage, and may also induce hypertension (Intengan and Schiffrin, 2001; Suematsu et al., 2002). Diabetic microangiopathy shares common etiopathogenesis. Persistent hyperglycemia leads to overactivation of multiple pathways, oxidative stress, and decreased vasodilation. Increased ECM production, BM thickening, and enhanced vascular permeability damage the cellular structure and function (Vojtková et al., 2012). The thickening of the BM remains one of the most common structural modification in diabetes. This thickening leads to altered vessel function, hypertension, reduced wound healing, and tissue hypoxia (Cade, 2008; Orasanu and Plutzky, 2009).

Additional mechanisms for vascular disease in diabetes include increased endothelial growth factor production, persistent inflammation, hemodynamic dysregulation, increase in platelet activation, and enhanced fibrinolytic capability (Cade, 2008). The ensuing endothelial damage and loss of microvessels leads to microangiopathic disorders in many organs (Fig. 1). Genetic, epigenetic, and immunologic factors can modify the clinical presentation, and are thus considered important factors for pathogenesis (Villeneuve and Natarajan, 2010).

Hypertension is another major modifiable risk factor for stroke and small vessel disease. Prevention of hypertension can diminish the occurrence of microvascular cerebral complications such as atherothrombotic stroke and vascular dementia (Sierra, 2012). Microvascular ocular complications and nephropathy share pathophysiological mechanisms leading to oxidative stress due to superoxide production. These mechanisms are also involved in the pathology of the in the macrovascular endothelium. Accordingly, overexpression of the enzyme superoxide dismutase in mice model prevented retinopathy, nephropathy, as well as cardiac myopathy (Giaccio and Brownlee, 2010).

Association of retinal microvascular abnormalities with renal dysfunction suggests that similar systemic mechanisms may underlie their damage (Wong et al., 2004). In diabetic neuropathy, microvascular damage to the vasa vasorum takes place due to increased oxidative stress (Thornalley, 2002) and inflammatory vasculopathy (Said et al., 2003). Clinical correlations have also been shown between chronic kidney disease, CVD, and neurological disorders. These similarities were attributed to the hemodynamic similarities between the vascular beds in the brain and kidney (Mogi and Horiuchi, 2011; O'Rourke and Safar, 2005).

The tissue-specific response to the microangiopathy may vary. In the eye, dysfunction of the pericytes, destabilization of the eye structure, leukocyte adhesion, capillary leakage, and microthrombosis occurs. Progressive retinopathy is likely to lead to complete loss of vision if unchecked. In the kidney, glomerular, tubular, and mesangial cell expansion is

seen with hyalinization of the connective tissue between the glomerular capillaries. Chronic kidney disease may finally lead to end stage renal disease and loss of life (Vojtková et al., 2012).

Imbalance between the sodium and potassium channels as well as deranged production of prostaglandins/thromboxanes lead to cellular dysfunction (Cameron et al., 1998). Activation of the immune response (Kelkar et al., 2000) and low nerve growth factor (Pittenger and Vinik, 2003) response may also contribute to the neuropathy. Thus, a common set of causes and mechanisms for microangiopathies exists even while the tissue-specific responses may vary.

Methods for Study of Microvascular Function

The patient's history and physical examination remain the mainstay of diagnostics in microvascular disease, neuropathies being the most difficult to recognize due to their subclinical nature or the variability of symptoms. Either sensory-motor disturbances or disturbances of the autonomic nervous system can manifest clinically. Autonomic neuropathy may cause symptoms in various organ systems. Both generalized and organ-specific exams are available for better diagnostics (Vojtková et al., 2012). To detect microvascular damage to the autonomic nervous system, heart rate variability is studied by spectral and frequency analysis using the Ewing's battery of cardiovascular tests.

Cough reflex sensitivity (Ciljakova et al., 2009) and electrodermal activity (Papanas et al., 2007) are used to examine the cardiovascular system and the presence of microangiopathic complications. Electromyography may be used to determine the subclinical forms of neuropathy (Shabo et al., 2007) and quantitative examination of sensitive function is used to determine the functioning of the peripheral nervous system. A battery of organ-specific exams can also be used for diagnosing autonomic neuropathy (Kincaid et al., 2007).

The serum level of AGE, reflected as glycosylated hemoglobin, is used in clinical practice for recognition of diabetic microangiopathy and correlates well with glycemic control. The plasma markers of endothelial function ICAM-1, VCAM-1, von Willebrandt factor, thrombomodulin, and P-selectin may help to recognize endothelial dysfunction (Adeghe, 2006). Apart from microalbuminuria, urine/blood creatinine, blood urea and nitrogen measurements, urine N-acetyl-beta-D-glucosaminidase, and blood metalloproteinase-9 can serve as early indicators of kidney damage. A number of gene-specific polymorphisms represent a patient-specific approach to diagnosis of diabetic microangiopathy (Vojtková et al., 2012).

A range of techniques have been developed for evaluation of microcirculatory function in vascular disease. Transcutaneous oxygen tension, skin pulp blood flow, iontophoresis, and capillaroscopy have been used for evaluation of microcirculatory function in health and disease (Abularrage et al., 2005; Aykut et al., 2015). Isolated small arteries of the organs and tissues can be studied by mounting them using a steel wire micromyograph. Vessel diameter, perfusion pressure and flow can be measured using this technique. Single microvessels and small microvascular networks of the internal organs can be studied by intravital microscopy and capillaroscopy. The parameters studied are vessel diameter, flow velocity, vessel density, permeability, leukocyte function and appearance time of the tracer.

Plethysmography is used to evaluate the regional blood flow in the organs and tissues regions, whereas the laser Doppler flux technique measures the red cell flux in small volume tissue regions of the skin and internal organ surfaces. Positron emission tomography, magnetic resonance imaging, and contrast echocardiography can be used to investigate the local blood flow and metabolic state of the organs (Struijker-Boudier et al., 2007). Direct videomicroscopic techniques are the best way to study the architecture and transport function of the microvessels (Romagnoli, 2013). In recent years, near infrared spectroscopy has emerged as a promising technology for microcirculatory evaluation (Romagnoli, 2013). The availability of these techniques at the bedside would be useful for directing interventional therapies for optimization of the microcirculation.

Evaluation of microcirculatory function and determination of clinical end points is vital as complications such as neuropathy remain asymptomatic in a majority of the patients. Minimally invasive laser Doppler Imager studies have been useful in diagnosing patients with diabetic neuropathy (Greenstein et al., 2007; Vas and Rayman, 2013). Corneal confocal microscopy is a noninvasive technique that correlates with the severity of somatic neuropathy and can be utilized as a measure of early nerve fiber regeneration due to therapy (Shtein and Callaghan, 2013). Noninvasive laser Doppler-based methods have also been used to study microcirculation in the skin in the presence of peripheral or autonomic diabetic neuropathy (Stirban, 2014).

While serum creatinine and microalbuminuria remain accepted end points for diagnosis of nephropathy, assessment of endothelial dysfunction using various laser Doppler flow cytometry techniques can help in the early diagnosis and prevention of chronic kidney disease (Babos et al., 2013). Laser speckle contrast imaging for monitoring skin microvascular functions can be used as a diagnostic tool to facilitate clinical microvascular studies (Mahé et al., 2012). Functional tests and imaging of the microcirculation using the techniques as discussed above will aid in detection of subclinical neuropathy and early stages of nephropathy.

For DR, standardized classification systems are used to categorize, classify, and stage the disease from stereoscopic color fundus photographs for establishment of adequate therapy (Wu et al., 2013). The retinal vasculature allows direct and non-invasive visualization of the microvasculature. As retina, brain, and kidney share several anatomical features and physiological properties, retinal vasculature changes can be correlated with the microcirculation in these organs. Retinal vascular changes can be used as a model to study the manifestations of hypertension, including stroke, coronary artery disease, heart failure, and renal disease. Global geometrical parameters and branching patterns of the retinal vasculature have been correlated with increased mortality in CVD and development of end organ damage (Cheung et al., 2012; Liew et al., 2008).

Biomarkers for Early Detection of Macrovascular and Microvascular Disease

The macrovascular and the microvascular diseases affect two distinct beds of the human vasculature. Vasoregression is proposed to be the underlying phenomenon in the etiology of these pathologies, thus unifying them. In view of the shared

risk factors, causes, pathways, and processes, it is likely that common diagnostic biomarkers may exist. We carried out literature mining to identify the potential protein biomarkers contributing to the process of vasoregression and helping in the early diagnosis of the condition. The lipids and lipoproteins present in the chylomicrons and LDL constitute established predictive measures of plasma atherogenicity/CVD risk as well as DR (Brown and Bittner, 2008; Kampoli et al., 2009; Sasongko et al., 2011; Upadhyay, 2015).

The inflammatory cascade protein myeloperoxidase is released with neutrophil activation and implicated in endothelial dysfunction. Myeloperoxidase is enriched in atherosclerotic lesions, and its high systemic levels may serve as a promising prognostic marker for cardiovascular events (Body, 2012; Brown and Bittner, 2008; Koenig and Khuseyinova, 2007). The elevated levels of myeloperoxidase in vitreous of patients suffering from proliferative DR has also been observed (Augustin et al., 1993). The inflammatory C-reactive protein (CRP) produced primarily by liver is an established strong predictive biomarker for myocardial infarction, ischemic stroke, cardiovascular death, incident diabetes, incident hypertension, and peripheral arterial disease (Ridker, 2007). CRP is also involved in the initiation and progression of atherosclerotic lesion by activation and chemoattraction of circulating monocytes, mediation of endothelial dysfunction, induction of a prothrombotic state, increase of cytokine release, activation of the complement system, facilitation of ECM remodeling, as well as lipid-related effects (Kampoli et al., 2009; Verma et al., 2006).

In comparison with healthy individuals, where it is found in only trace quantities, the concentration of CRP rises exponentially during the early hours of acute inflammatory conditions. CRP is a robust clinical marker due to its analytical stability and reproducible results (Koenig and Khuseyinova, 2007). Higher CRP concentrations have been strongly correlated with increased numbers of thin cap fibroatheromas (Koenig and Khuseyinova, 2007). Some, but not all, studies have reported the association of CRP with diabetic nephropathy and DR (Seddon et al., 2005). A single nucleotide polymorphism of CRP was shown to be associated with diabetes (Peng et al., 2015). The production of CRP is under the transcriptional control of certain cytokines like IL-1, IL-6, and TNF- α (Virani et al., 2008).

Cytokine and chemokine biomarkers also have established potential in the assessment of clinical resolution of ocular inflammation. Various clinical studies have investigated the predictive value of IL-6 plasma concentrations for future cardiovascular events (Kampoli et al., 2009; Koenig and Khuseyinova, 2007), which possesses important proatherogenic properties and induces a prothrombotic state. Increased expression of IL-18 has also been reported in atherosclerotic lesion prone to rupture (Gerdes et al., 2002; Mallat et al., 2001). The use of IL-18 has been suggested as a marker for future CV events only in men and requires future investigations (Koenig and Khuseyinova, 2007).

A significantly high concentration of pro-inflammatory cytokine IL-12 has also been associated with rheumatoid arthritis, multiple sclerosis, diabetes, and ocular diseases such as DR (Gverovic et al., 2012; Kang and Kim, 2006; Rothe et al., 1996). Besides these, the credibility of cytokines like IL-5, IL-6, IL-12, and TNF- α as potential ocular inflammatory biomarkers have also been established. TNF- α

FIG. 2. Cause-Effect sketch illustrating the probable factors underlying vessel regression and their resultant effects. The figure depicts the probable causes underlying vessel regression that might invoke the signaling of the downstream pathways. The pathways denoted in *red* (Box 1) have been found to cause the effects enlisted in the *red box* (Box 4), while the pathways in *green* (Box 3) prevent vasculopathies by inserting vasoprotective effects enlisted in the *green box* (Box 5). Apart from these, there are pathways denoted in *blue* (Box 2) that have been reported to exert both disease-causing and vasoprotective effects.

participates in the loss of the tight junctions between the ECs of the retina and also between the cells of the retinal pigment epithelium, thus interrupting the integrity of the BRB (Zorena et al., 2013). Increased levels of TNF- α has also been associated with various disease pathologies such as diabetes and atherosclerosis (Boesten et al., 2005; Gustavsson et al., 2008; Kleinbongard et al., 2010).

The participation of complement factors as potential biomarkers have also been signified in CVD and other diseases (Ross et al., 2007; Speidl et al., 2011). Prospective studies based on animal systems have established the relationship between AGE compounds and ocular disease pathologies like DR (Ross et al., 2007; Stitt et al., 1997). The utility of RAGE as a novel biomarker has also been demonstrated in the prediction and treatment of coronary atherosclerosis (Lindsey et al., 2009).

Fibrinogen is also regarded as a promising independent biomarker for inflammation and early CVD events (Danesh et al., 2005; Kampoli et al., 2009). It has also been implicated in the prediction of certain ocular diseases like DR, but its use requires further validation (Azad et al., 2014; Kuzhupilly, 2010). Increased levels of cell adhesion molecules such as ICAM-1 have also been consistently associated with atherosclerosis and ocular diseases like dry eye disease (Ballantyne and Entman, 2002; Muni et al., 2013). Elevated serum levels of growth factors such as FGF-21 have been well demonstrated to be associated with atherosclerosis and DR, and their expression patterns can serve as a early biomarkers (Chow et al., 2013; Lin et al., 2014; Zorena et al., 2013).

Conclusion

Atherosclerosis is a macrovascular disease characterized by the thickening and hardening of arteries. Besides being a life-threatening disease and a major cause of mortalities world-wide, it may also involve microvascular complications. It is a systemic disease accompanied by regional disturbances in circulation leading to significant sequelae in brain, kidney, and limbs. Several retinal constituents such as pericytes, glial cells, and neurons are also affected by systemic vascular complications leading to disturbed cross-talk in retinal vasculature.

Vasoregression is the progressive demise of the blood vessels that underlies many diseases. It is a response to inflammation characterized by the disruption of the MC and EC crosstalk, ultimately causing the obliteration of blood vessels. While vasoregression is involved in a number of physiological (e.g., vessel formation, maturation, and stabilization) and pathological processes (e.g., peripheral neuropathy, diabetic nephropathy, tumor angiogenesis, and microangiopathies), many of its aspects have still not been well elucidated. The phenomenon of vasoregression has been studied extensively in the eye, as it is the initiating step in the development of vascular oculopathies. In the retina, vasoregression may lead to BRB breakdown resulting in subsequent ocular diseases such as DR and ME.

In this review, we have briefly listed the characteristic features of macrovascular and microvascular disease. Further, we have drawn a parallel between features of atherosclerosis in the

large vessels and vasoregression in the ocular microvasculature. The hall marks of vasoregression, namely, MC loss and endothelial damage are shared by atherosclerosis and ocular microangiopathies (Fig. 1). Both the pathologies are associated with common risk factors such as increased level of AGE, oxidative stress, and increase/modification of circulating lipids. Common response to inflammation in macrovascular and microvascular disease includes interleukin pathway, leukostasis, increase in the number and type of EPCs, increased vascular permeability, and glial activation.

We also provide a brief perspective on vasoregression at the molecular scale and show that it shares common molecular pathways and effectors with atherosclerosis and ocular diseases such as DR (Fig. 2). The common pathways shared by the two diseases are Immune response and complement pathway, Neurotrophin pathway, PDGF pathway, Ang2/Tie2 pathway, PPAR pathway, PKC pathway, hexosamine pathway, MAPK signaling, NF- κ B, and VEGF signaling. The shared pathways may provide biomarkers and therapeutic targets for diagnosis and treatment of microvascular and macrovascular disease. Shared features of different microvascular diseases indicate a common pathophysiology for their development. However, the various microvascular diseases manifest with different clinical symptoms due to unique tissue responses. Newer techniques and biomarkers for assessment of vascular function have potential utility in early detection of microvascular disease.

The commonalities between atherosclerosis and vasoregression shift the current view of DR as a local condition of the retina to a systemic, inflammation-induced vasculopathy. In DR, these may be attributed to the vascular changes accompanying the diabetic condition. However, many aspects of vasoregression need further elucidation (e.g., the functional role of neurons in vessel survival and photoreceptor damage in the retina is yet to be determined). The characterization of different types of EPCs involved in vasoregression is required. The role of vasoregression in vascular pathologies occurring at sites other than the eye is still not well elucidated. The expression, bioavailability, and role of various pleiotropic forms and isoforms of various signaling molecules such as PKC, NF- κ B, and VEGF in differential cellular effects requires elucidation. Future studies for unveiling these issues will prove to be beneficial in understanding the onset of human vascular pathologies.

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Abbreviations Used

AGE	=	advanced glycation endproducts
Ang	=	Angiopoietin
BDNF	=	brain derived neurotrophin Factor
BM	=	basement membrane
BRB	=	blood retinal barrier
CNTF	=	ciliary neurotrophic factor
COX	=	cyclooxygenase
CRP	=	C-reactive protein
DR	=	diabetic retinopathy
EC	=	endothelial cells
FGF	=	fibroblast growth factor
ECM	=	extracellular matrix
EPC	=	endothelial progenitor cells
ICAM	=	intracellular adhesion molecule
LDL	=	low density lipoproteins
LRP	=	LDL receptor related protein
MC	=	mural cells
ME	=	macular edema
NGF	=	nerve growth factor
NCAM	=	neural cell adhesion molecule
NOS	=	nitric oxide synthase
oxLDL	=	oxidized low density lipoprotein
PAI-1	=	plasminogen activator inhibitor-1
PDGF	=	platelet-derived growth factor
PKC	=	protein kinase C
PMN	=	polymorphonuclear lymphocytes
PPAR	=	peroxisome-proliferator activated receptor
ROS	=	reactive oxygen species
VEGF	=	vascular endothelial growth factor
VSMC	=	vascular smooth muscle cells