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CD36 as a therapeutic target for endothelial dysfunction in stroke

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Abstract

Stroke pathology involves multifactorial pro-death responses, including inflammation, oxidative stress, vascular dysfunction, and activation of necrotic and apoptotic pathways. The interruption of a single specific pathway in defined stroke model systems has not been sufficient to address the multifactorial nature of stroke-induced injuries in the human population. CD36 is a class B scavenger receptor that functions in regulating normal physiological and pathological functions. CD36 pathways are activated by several distinct ligands. Convergence of these pathways results in inflammatory responses and endothelial dysfunction, which may be an underlying cause of cardio- and cerebrovascular diseases. The current review describes receptor CD36-ligand interactions relevant to endothelial function and discusses how targeting CD36 may have therapeutic utility in stroke.

Keywords

CD36; Stroke; Angiogenesis; inflammation; endothelial dysfunction

CD36 overview

CD36, an 88 kDa glycoprotein, was originally described as a platelet receptor glycoprotein IV that recognizes thrombospondins and *plasmodium falciparum*-parasitized erythrocytes [1–3]. The receptor belongs to the class B scavenger receptor family that also includes Lysosomal Integral Membrane Protein II (LIMP-II) and the receptor for selective cholesterol ester uptake from HDL, CD36-LIMP-II Analogous-I (CLA-1; known as SR-BI in rodents). CD36 consists of two transmembrane domains, a large extracellular domain, and two short cytoplasmic tails. Features of the extracellular domain include a hydrophobic region that may be buried within the plasma membrane, a proline-cysteine rich domain and ten potential N-linked glycosylation sites. Both the N- and C-terminal intracellular domains have a pair of cysteines that are palmitoylated [4], a process that may target the protein to lipid rafts within the membrane [5].

CD36 is expressed in many types of mammalian cells, including microvascular endothelial cells, microglia, monocytes/macrophages, platelets, cardiac and skeletal muscle, adipocytes, and epithelia of a number of tissues including retina, breast, kidney, and tongue [6–12]. As a result of its expression in multiple cell types and its ability to recognize a host of structurally

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distinct lipid and non-lipid based ligands, the activation of CD36 results in highly diverse cellular responses.

Acting either singly or in concert with other proteins as a multi-protein complex, CD36 elicits signaling cascades in response to diverse ligands and regulates cellular responses (Fig. 1). Also known as fatty acid translocase (FAT), CD36 is also involved in lipid metabolism. Its localization in the circumvallate papillae in the tongue was reported to be important for distinguishing food that contains lipids, indicating that CD36 functions as a taste receptor for free fatty acids [6, 13, 14]. CD36 also recognizes membranes of cells undergoing apoptosis [15, 16]. Although the ligand on lipoproteins and apoptotic cells recognized by CD36 was thought to be a phosphatidylserine [17], several studies show that the recognized ligand is a phosphatidylcholine/serine species whose specific esterified sn-2 fatty acid has been modified by reactive oxygen or nitrogen species to yield a γ-hydroxy, oxo, or α,β-unsaturated carbonyl moiety [18–20]. As a pattern recognition receptor, CD36 is involved in innate immunity, in conjunction with toll like receptors (TLRs) [21, 22]. CD36 is also able to recognize thrombospondin type I repeats (TSR) in thrombospondin-1 and -2, functioning as an angiostatic factor [23]. Interaction of CD36 with fibrillar β-amyloid (fAβ)/integrins induces inflammatory responses by elevating the expression of pro-inflammatory cytokines and chemokines [24, 25]. Inflammation associated with foam cell formation by excess uptake of lipids by macrophage CD36 is an underlying cause of atherosclerotic lesion development [26–28]. The diverse functionality of CD36 in the regulation of angiogenesis, inflammation, atherosclerosis, oxidative stress and lipid metabolism, innate immunity, and taste preference has been described in detail elsewhere (refer to reviews [29, 30]).

The nature of multi-ligand recognition and the diverse expression of CD36 outside of the vasculature make difficult to render the receptor's contribution to vascular dysfunction. Nevertheless, CD36 pathways that result in the production of inflammatory factors in endothelial cells or in non-endothelial cells including astrocytes, microglia, and macrophages suggest that the receptor is either directly or indirectly involved in negatively regulating vascular tone and integrity. This review describes potential roles for CD36 in vascular dysfunction and angiogenesis in cerebrovascular diseases with a particular focus on ischemic stroke.

Vascular Dysfunction

The responses elicited by the interactions between CD36 and its respective ligands are predicted on the basis of the specific ligand and the type of cell expressing CD36, both of which may be coupled to multiple downstream effectors. Although CD36 responses occur in a ligand-specific manner, the pathways triggered by different ligands often converge, generating free radicals and inflammatory mediators within the cell, both inside and outside of the vasculature. The resultant inflammatory responses compromise endothelial function and the integrity of the blood brain barrier (BBB) (Fig. 1 outlined area).

Loss of vascular tone and BBB integrity underlies the pathology of cardio- and cerebrovascular diseases such as stroke, Alzheimer's disease, and atherosclerosis. Examining functional characteristics of CD36 in other diseases associated with vascular dysfunction helped to predict the potential roles of the receptor in cerebral ischemia because of commonly shared pathological mechanisms among these vascular diseases (Fig. 2). Overwhelming evidence also indicates that the expression and function of CD36 are altered in prevalent risk factors, including hypertension, dyslipidemia, and diabetes. Understanding and managing the risk factors that modulate CD36 expression suggest the importance of CD36 as a common mediator for vascular diseases. Hypertension, whether isolated systolic, isolated diastolic, or in combination, is a major modifiable risk factor for the increased

incidence of stroke [31, 32]. Various clinical trials employing antihypertensive agents that reduce blood pressure have been effective in the management and prevention of stroke [33, 34]. A link between CD36 and hypertension is derived from the observation that changes in CD36 expression are related to the clustering of multiple cardiovascular risk factors. The Spontaneously Hypertensive Rat (SHR) is a widely used animal model for hypertension, and a defective c*d36* gene in chromosome 4 has been implicated as a risk factor. Transferring a segment of chromosome 4 from Brown Norway rat onto the SHR background reduces blood pressure and ameliorate glucose intolerance, hyperinsulinemia, and hyperlipidemia [35]. Although the study suggested that c*d36* deletion is not critical to the initial selection for hypertension in the SHR model, the linkage of c*d36* to other genes within the differential segment of the SHR was implicated in influencing multiple cardiovascular risk factors, including hypertension. A recent study showing that the stroke-prone SHR rats display increased CD36 expression in vessels and BBB impairment in the brain, supports a role for CD36 in cerebral vascular injury [36].

Endothelin-1, a vasoactive peptide, is synthesized and secreted by vascular endothelial cells and is a potent endogenous vasoconstrictor [37]. By stimulating the proliferation of vascular smooth muscle cells (VSMCs), the mitogenic property of VSMCs results in the formation of lesions within the intima and leads to hypertension and atherosclerosis. Both CD36 and endothelin-1 are considered atherosclerosis-related genes. Haug and colleagues [38] reported the involvement of CD36 in the endothelin-1 mediated atherogenic effect of oxLDL. The study showed that LDL and oxLDL up-regulate endothelin-1 expression in smooth muscle cells and monocytes, and pre-incubation of antibodies against CD36 reduced the expression. Similarly, angiotensin II, another vasoconstrictor oligopeptide, has been shown to enhance oxLDL uptake, and CD36 is involved in the process [39, 40]. Hypertensive subjects show significant increase in CD36 expression in macrophages with an enhanced adhesion of monocytes to endothelial cells and greater production of ROS [41]. In contrast, Kwok and colleagues reported a regulatory effect of endothelin-1 that inhibits CD36 protein expression in VSMCs through endothelin receptor A [42], although the functional significance of this finding *in vivo* remains to be addressed. Investigations on the effects of the vasoactive peptides on CD36 expression, or *vice versa*, following cerebral ischemia would provide a contributing role for CD36 in the pathology of cerebral ischemia in hypertensive subjects.

CD36 ligands to elicit inflammatory responses

CD36 is involved in free radical production and contributes to brain injury associated with post-ischemic inflammation [43]. Reduced free radical production and injury size in CD36 KO mice further substantiate the role of CD36 in stroke-induced brain injury. Several CD36 ligands including fibrillar β amyloid (fAβ), modified/oxidized low density lipoproteins (mLDL, oxLDL), TSPs, long chain fatty acids, and membrane components of apoptotic cells are elevated following stroke [44–48]. Depending on prevalent clinical co-morbid conditions, differential sets of CD36 ligands may prevail and affect vascular integrity following stroke. Because CD36 expression occurs in a feed forward manner [49], the presence of CD36 ligands in the infarct territory suggests excess activation of CD36 pathways. CD36 ligands that influence vascular dysfunction are amyloid-β, oxLDLs and lipid based ligands, and advanced glycation end products (AGE)-LDL, which are closely associated with AD, dyslipidemia, and diabetes.

a. Fibrillar β amyloid (fAβ)

Accumulation of amyloid β (Aβ) in the vicinity of plaques is one of the hallmarks of AD. The deposition of Aβ in the microvasculature contributes to oxidative stress and compromises BBB integrity [50, 51]. Due to the nature of the ligand, many of the studies on

CD36 relevant to fAβ were focused on innate host response and inflammation associated with AD. Aβ binds to a number of biomolecules such as proteins and membrane lipids. Binding of membrane lipids facilitates fibrillation of Aβ (fAβ) which, in turn, alters the structure and function of the membrane [52].

Receptors that interact with fAβ include scavenger receptor (SR-A) [53], SR-B1[54], the receptor for advanced glycation end products (RAGE) [55], and CD36 [25, 56]. In response to fAβ, CD36 activates signaling cascades to trigger innate host responses [24, 25, 56]. A key role of CD36 in innate pro-inflammatory events was demonstrated. CD36 deficiency attenuated fAβ-induced secretion of cytokines, chemokines, and reactive oxygen species in microglia. Intraperitoneal and intracerebral injection of fAβ in CD36 KO mice attenuated macrophage and microglia recruitment into peritoneum and brain [24]. Bamberger and colleagues further identified a multi-receptor complex comprising the B-class scavenger receptor CD36, $\alpha_6\beta_1$-integrin, and the integrin-associated protein/CD47 [57]. This cell surface receptor complex stimulates intracellular Tyr kinase-based signaling cascades and cellular activation, which leads to the secretion of pro-inflammatory molecules. A mechanistic study revealed that intracellular signaling by the receptor complex and fAβ involves Vav guanine nucleotide exchanging factor phosphorylation and Rac1, an essential component of NADPH oxidase, demonstrating a direct link of Vav phosphorylation to free radical production through the fAβ-receptor complex [58]. In the animal model of AD, interaction of Aβ with CD36 causes cerebrovascular oxidative stress and neurovascular dysfunction. The dysfunction was abrogated in the absence of CD36, suggesting that a strategy of CD36 inhibition to normalize cerebrovascular dysfunction might be effective [59]. Although literature regarding Aβ-induced vascular dysfunction following stroke is limited, cerebral amyloid angiopathy, in which amyloid is deposited in the vessel walls of the brain, is a risk factor for hemorrhagic stroke [60, 61]. Lee and colleagues showed an increased level of circulating Aβ in patients with acute ischemic stroke and suggested that the ligand is derived from brain as a consequence of ischemic insult [62].

b. Oxidized/modified LDLs

High cholesterol in conjunction with elevated inflammatory mediators in plasma is positively correlated with increased incidence of stroke in humans [63]. The episode occurs either singly or in association with other risk factors including obesity, hypertension, and insulin/glucose intolerance [63, 64]. These clinical conditions may influence the progression and outcomes of stroke-induced injury. Podrez and colleagues reported that an excess amount of lipid-based CD36 ligands are generated in hyperlipidemia [65]. This study demonstrated a profound up-regulation of structurally defined oxidized choline glycerophospholipid species ($_{ox}PC_{CD36}$) that serve as high affinity ligands for CD36 in the plasma of hypercholesterolemic mice and also in humans with low HDL levels [20]. Although the study did not investigate the potential up-regulation in non-lipid based ligands such as TSPs, the abundance of $_{ox}PC_{CD36}$ (oxidized or modified lipid moiety on lipoproteins) in hyperlipidemic plasma suggests the relevance of the lipid-based ligands in intensifying CD36-mediated function. Uptake of excess lipid ligands by monocyte/macrophage CD36 leads to foam cell formation, a key event for atherosclerotic lesion development in vessels [27].

High fat diet fed ApoE KO mice that were subjected to ischemic stroke exhibited increased infarct size as well as increased CCR2 and MCP-1 levels [66]. The hyperlipidemic ApoE KO mice showed increased IL-1β, TNF-α, and IL-6 mRNA levels, increased lipid content in the infarct, and displayed an increased number of lipid laden foam cells in the peri-infarct area. The involvement of CD36 in hyperlipidemia-induced exacerbation in ischemic outcome was further supported by the reversal of the hyperlipidemic phenotype in mice that lack CD36. CD36/ApoE double KO mice that were subjected to ischemic stroke exhibited

smaller infarct size, reduced expression of the pro-inflammatory cytokines MCP-1 and CCR2, and fewer foam cells in the ischemic brain [66]. Whereas these findings suggest the importance of CD36 in stroke pathology in hyperlipidemic conditions, several other studies showed the effect of hyperlipidemia on endothelial dysfunction. In carotid arteries of ApoE-deficient mice, hypercholesterolemia causes loss of endothelial-dependent relaxation in response to acetylcholine. The deficit occurs via impairment of activation of endothelial nitric oxide synthase (eNOS) via superoxide anion [67, 68].

Specialized micro domains in the plasma membrane, caveolae, are enriched with cholesterol, sphingomyelin, caveolin and eNOS, and they are involved in signal transduction [5, 69]. Hypercholesterolemia was shown to deplete eNOS in the caveolae [70, 71]. CD36 is enriched in this cholesterol-rich lipid raft. A role of CD36 on eNOS-mediated vascular dysfunction in hyperlipidemic conditions was reported. Using ApoE KO and ApoE/CD36 double KO mice, the study showed reduced agonist-stimulated NO generation and vasodilation in ApoE KO. The eNOS-mediated vascular dysfunction was reversed in the absence of CD36 in the hyperlipidemic condition, thereby providing a direct link between CD36 function and eNOS activation in the presence of excess CD36 ligands [72]. Additionally, exposure of oxLDL, a major CD36 ligand in the development of atherosclerosis, to endothelial cells increases endothelial cell stiffness, supporting the influence of the CD36 lipid ligands in vascular diseases [73].

c. Advanced glycation end-product (AGE)-LDL

Evidence suggests an involvement of CD36 in insulin resistance [74, 75]. The receptor was identified as a novel marker of insulin resistance, and soluble CD36 level in plasma was positively correlated with type 2 diabetes risks [76, 77]. There is a strong association between diabetes and CD36 expression. The expression of CD36 occurs in the types of cells where diabetic complications prevail, including microvascular endothelium, retinal pigment epithelium, and proximal renal tubular epithelial cells, respectively resulting in vascular neuropathy, retinopathy, and nephropathy. It has been shown that diabetic conditions upregulate CD36 expression in several types of cells and tissue [78, 79].

Hyperglycemia increases the formation and accumulation of AGEs, which are recognized by CD36 [80]. In elevated levels of plasma AGE, CD36 protein expression is increased in VSMCs [81]. The advanced glycation end product-modified LDL (AGE-LDL) also has high affinity toward CD36. The study by Sima and colleagues showed that exposure of AGE-LDL induced a pro-oxidant and pro-inflammatory state in human smooth muscle cells, increasing lipid accumulation [82]. These studies indicate that increasing the burden of CD36 ligands in diabetic conditions promotes a pro-inflammatory state and compromises endothelial functions. Because post-ischemic inflammation is a contributing component of ischemic brain injury, inhibition of CD36 pathways by reducing the burden of diabetes-relevant CD36 ligands may be a potential strategy to attenuate vascular inflammation and dysfunction following stroke.

Angiogenesis in stroke

The survival of ischemic tissue heavily depends on the level of oxygen and substrate from collateral blood flow. Injury-induced angiogenesis plays a critical role in stroke outcome and recovery [83, 84]. Unlike vasculogenesis during development, angiogenesis in ischemic tissue involves a sprouting of new vessels from pre-existing vessels. The process requires endothelial cell replication, degradation of surroundings, and migration of endothelial cells to form lumen vessels to revascularize the injured area [85]. Enhanced angiogenesis in the peri-infarct area was correlated with longer survival in stroke patients [84]. Thus, the

promotion of ischemia-induced angiogenesis, especially within the ischemic boundary, has been suggested as a therapeutic strategy to improve stroke outcome [83, 86].

The infarct typically begins to develop only hours after ischemic insult. However, studies indicate that endothelial cell proliferation occurs over several days post-ischemia [45, 87, 88]. Although a time point for the cessation of angiogenesis is not known, it was reported that new vessels are formed up to 92 days after stroke in human [89] and up to 21 days in an animal model of stroke [45]. In line with a potential benefit of promoting angiogenesis in the post-ischemic brain, several pro- and anti-angiogenic factors relevant to CD36 activation have been identified.

CD36, an angiostatic receptor

The relevance of CD36 function in vasculature is its anti-angiogenic nature, which offsets compensatory angiogenesis-promoting cascades in response to tissue ischemia. Binding of thrombospondin repeat (TSR) type 1 in TSP-1 to CD36 activates a signaling cascade that leads to endothelial cell apoptosis [23, 90, 91]. The ligand/receptor-mediated angiostatic effect requires the C-terminal cytoplasmic tail of CD36, since a point mutation in the region blocks CD36-mediated intracellular signaling [92].

Stroke up-regulates CD36 expression in the ipsilateral side of the brain. CD36-deficient mice exhibited smaller injuries and the neuroprotection was associated with reduced free radical generation in these mice [43]. Our lab investigated whether an underlying mechanism for this neuroprotection was partly mediated by enhanced angiogenesis in the absence of this negative regulator. To exclude the possible effect of infarct size between the genotypes on the degree of angiogenesis, infarct size between wild type and CD36 KO was normalized by increasing the ischemic duration to 45 min in CD36 KO mice in contrast to 30 min for WT mice. In spite of similar infarct size, CD36 KO mice showed profoundly increased vessel densities in the post-ischemic brain (Fig. 3). The observation supports the necessary role of CD36 in antagonizing injury-induced vessel formation. Additionally, reported down-regulation of VEGFR-2 phosphorylation by CD36 suggests a mechanism by which CD36 negatively modulates the classical mitogen signaling pathway [92]. Whether the increased vessel density in the absence of CD36 is due to the absence of the negative regulator alone, an increased pro-angiogenic cue, or a shifted balance toward a pro-angiogenic state still remains unknown.

TSPs, inhibitors of angiogenesis

TSPs are extracellular matrix proteins that mediate cell-cell interaction via several membrane receptors including integrins, MMPs, fibronectin, CD36, other extracellular matrix proteins, and cytokines [93]. Among the five known TSPs, each coded by a separate gene, TSP-1 and-2 are involved in platelet aggregation, inflammation and angiogenesis [94]. TSPs are synthesized and secreted by several different cell types in response to injury and injury-induced growth factors. The importance of TSP-1 in inhibiting angiogenesis was demonstrated by antagonizing NO-stimulated angiogenic pathways. NO-stimulated angiogenesis is significantly increased in the absence of TSP-1, and exogenous TSP blocks NO-stimulated increase in endothelial cell proliferation, adhesion and migration [95]. Produced in vascular cells, TSP-1 also modulates cellular functions through a number of cell surface receptor complexes. CD36 was shown to be involved in the anti-angiogenic action of TSP-1 and 2 [96–99]. Additionally, the necessity of CD47, an integrin associated protein that forms a surface receptor complex with CD36, was reported in the inhibition of NO-stimulated vascular cell responses by TSP-1 [100].

Although ischemia increases the expression of TSP-1 and TSP-2 in the post-ischemic brain [45, 94], their expression profiles show distinct temporal and spatial expressions with an early rise of TSP-1 and delayed TSP-2 expression after stroke [94]. My lab determined the temporal expression of TSP-1 and TSP-2 following stroke. Temporal CD36 expression overlaps with that of TSP-1, but not TSP-2, during acute cerebral ischemia (Fig. 4). The observation suggests that the early CD36/TSP-1 interactions contribute to the angiogenic deficit associated with acute stroke pathology. Complete profiles of TSP and CD36 expression during a long-term stroke recovery phase will identify whether there is a secondary rise of CD36 and TSP expression and how their expression may regulate functions that are relevant to late angiogenesis.

BDNF, a pro-angiogenic factor

Vascular endothelial growth factors (VEGF), basic fibroblast growth factor (FGF), and hepatocyte growth factor, among others, promote stroke-induced angiogenesis [101–104]. Besides these mitogens, brain derived neurotrophic factor (BDNF) was also shown to be essential in maintaining vessel stability through direct angiogenic actions on endothelial cells [105]. Numerous reports have uncovered critical roles for BDNF and receptors in non-neuronal cells, such as endothelial cells, smooth muscle cells, immune cells, and epithelial cells in different organs [106–108]. Unlike VEGF-A that activates receptors that are expressed mostly in endothelial cell populations and are critical for early stages of vascular development, BDNF is expressed in an organ-specific manner in perinatal and adult vasculature [105]. BDNF deficiency causes reduced endothelial cell-cell contacts and endothelial cell apoptosis leading to hypo-contractility of the heart and perinatal lethality. Conversely, BDNF overexpression in the mid-gestational mouse heart results in an increase in capillary density, establishing an essential role for BDNF in modulating cardiac microvascular endothelial cells during development [105].

BDNF has been described as a newly identified angiogenic mediator in ischemic tissue that acts through TrkB receptor tyrosine kinase [109, 110]. Given the critical role of BDNF in perinatal vessel stabilization and continued expression of TrkB in the adult vasculature, Kermani and colleagues studied direct angiogenic actions of exogenous delivery of BDNF in normal and ischemic conditions in the adult mouse [110]. In a femoral artery ligation model, BDNF protein is significantly induced in ischemic tissue in comparison to non-ischemic tissue. Local overexpression of BDNF promotes blood flow recovery and capillary density comparable to that elicited by VEGF. Importantly, these effects appear to be mediated by TrkB, as the effects of exogenous BDNF are attenuated in haplodeficient animals (TrkB+/−), as assessed by blood flow and capillary density.

In the normal brain, BDNF is localized in neurons with the highest expression in the hippocampus and lower expression in the cortex [111, 112]. Transient focal ischemia induces BDNF mRNA and increase the number of BDNF immunoreactive neurons in the ipsilateral cingulate and frontal cortices outside the infarct, but less within the infarct core, suggesting a role for BDNF in survival and plasticity of cortical neurons after focal ischemia [113, 114]. The role of BDNF in stroke outcome and recovery is controversial. While some studies indicate that enhanced BDNF availability and signaling protect against ischemic brain injury and promote functional recovery [115–118], others argue against the beneficial effect of BDNF [119, 120]. The reason for the discrepancy needs further investigation.

Effect of BDNF SNP on CD36/TSP expression and angiogenesis

A single nucleotide polymorphism (SNP) of the *bdnf* gene occurs only in humans with high frequency. The BDNF SNP results in a substitution of a valine (Val) with a methionine (Met) in the prodomain of the BDNF protein at codon 66 and represents the first genetic

alteration in the neurotrophin system that has been linked to human disease [121–125]. This alteration of the BDNF protein has been implicated in conferring susceptibility to depression, bipolar disorder, as well as altered episodic memory in patients with psychiatric disease [122, 126, 127]. Using mice with humanized BDNF variant in both allele ($BDNF^{Met/Met}$) and wild type ($BDNF^{+/+}$), Chen and others reported that the BDNF SNP is associated with the impairment of activity-regulated, but not constitutive, BDNF secretion [128].

From the observation that BDNF is critical for post-stroke outcome and recovery in rodents, we and others have investigated the effect of this BDNF SNP on stroke outcome. Although limited, clinical studies showed that the $BDNF^{Met}$ allele is correlated to poor ischemic outcome and low memory performance among survivors of subarachnoid hemorrhage [129, 130]. In contrast, the $BDNF^{Met}$ allele, not $BDNF^{Val}$ allele, is responsible for the promotion of executive function recovery in individuals with traumatic brain injury [131], suggesting a controversy in the effect of the BDNF SNP in post-injury outcome. Our lab investigated the effect of the BDNF SNP on infarct size and post-stroke angiogenesis. The study showed that $BDNF^{Met/Met}$ mice exhibited reduced BDNF levels in the post-ischemic brain compared to $BDNF^{+/+}$ mice. In spite of the reduced BDNF levels in the post-ischemic brain of $BDNF^{Met/Met}$, infarct size did not differ between the genotypes, indicating that stroke-induced BDNF secretion is not critical for acute infarct development [132]. However, $BDNF^{Met/Met}$ mice displayed reduced angiogenesis in the peri-infarct. The angiogenic deficit was associated with elevated expression of CD36 and TSP-1, suggesting the functional role of CD36 in antagonizing angiogenic response in Met homozygosity at the BDNF locus (Fig. 5). The observation in $BDNF^{Met/Met}$ mice - a shift toward angiostatic state with reduced BDNF and increased TSP-1/CD36 - suggests that CD36 inhibition may be a viable strategy to enhance angiogenesis and possible recovery in human stroke victims who have the BDNF SNP.

Targeting CD36 to promote endothelial function

It has been suggested that down-regulation of CD36 pathways attenuates post-ischemic inflammation and injury [133, 134]. Genetic ablation of CD36 is associated with a less inflammatory state and delays in vascular disease progression. In light of the receptor's anti-angiogenic property, our lab observed enhanced stroke-induced angiogenesis in the absence of CD36 in C57BL/6 (Fig. 3) and in $BDNF^{Met/Met}$ genetic background [132].

Apart from genetic approaches, several pharmacological agents have been identified to reduce CD36 expression and functions. Synthetically engineered nanoblockers were targeted against scavenger receptors CD36 and SR-A. These nanoparticles block the uptake of oxLDLs and the subsequent formation of foam cells, thereby effectively attenuating the atherogenicity of inflammatory cells [135]. Other promising CD36 antagonists that block oxLDL uptake include hexarelin and its analogues. Hexarelin is a member of the hexapeptide growth hormone-releasing peptides (GHRPs) family that possesses growth hormone releasing activity and acts though G-protein-coupled ghrelin receptors in the hypothalamic-pituitary region [136]. In addition to binding to ghrelin receptors, it also binds to CD36 receptors [137]. Mice treated with hexarelin or a structurally related analogue, EP80317, demonstrated a marked decrease in atherosclerotic lesions [138]. The protective effect of hexarelin was mediated partly by negative modulation of CD36 expression [139]. A photo-affinity cross linking study showed that the binding domain of hexarelin overlaps with that of oxLDLs in CD36 [137], suggesting that the effect of hexarelin occurs through competition of the oxLDL binding site. Using a high-throughput screening assay, Wang and others reported several compounds that inhibit oxLDL uptake, including sodium danshensu, rosmaric acid, and salvianolic acid B [140]. While its efficacy *in vivo* remains to be

investigated, treatment with salvianolic acid B in rat was associated with improved motor function following stroke [141].

Other approaches have been used to modulate CD36 expression or its downstream effects. Statins have been used to reduce cardiovascular events, not only by lowering cholesterol but also through other beneficial effects. The beneficial effects of statins may be related to the reduction of CD36 expression and function because they down-regulate CD36 expression and also suppress oxLDL uptake [142–144]. For antagonism that is specific to amyloid β, a recent study identified ursolic acid as a novel inhibitor that blocks Aβ-CD36 interaction [145].

Increased expression of CD36 has been associated with pro-oxidative conditions. Antioxidants, such as α-tocopherol, can reduce expression of CD36 and the uptake of oxLDLs by macrophages [146–148]. In addition, a pro-inflammatory response triggered by oxidative stress is abrogated in macrophages from CD36-deficient patients [149], indicating a direct association between manifestations of oxidative stress and CD36 expression. Another new class of antioxidants, SS peptides, have been shown to protect against myocardial ischemia-reperfusion injury in isolated hearts and to significantly reduce reperfusion arrhythmia, myocardial stunning, and infarct size *in vivo* [150, 151]. The potency of the SS peptide antioxidants is due to their ability to penetrate cell membranes and concentrate in the inner mitochondrial membrane, the primary site of intracellular ROS generation [150]. In addition to their scavenging action, the SS peptides inhibit the mitochondrial permeability transition, mitochondrial swelling, cytochrome *c* release, and apoptosis induced by lipid peroxides [152]. The efficacy of SS31 as an antioxidant in stroke was investigated in our laboratory. Treating mice with SS31 peptide attenuated ischemia-induced glutathione (GSH) depletion in the cortex and reduced infarct size [153]. The protective effect of SS31 was absent in CD36 KO mice, suggesting that SS31-induced neuroprotection occurs through antagonizing CD36-mediated activity and indicates that anti-oxidative approaches that target CD36 may be a useful strategy to treat ischemic stroke.

Conclusions

Cardiovascular and cerebrovascular diseases share common pathological features. CD36, a multi-ligand and multi-functional inflammatory receptor, has been implicated in the pathogenesis of cerebro/cardiovascular diseases, including stroke. Because the expression of the receptor in the post-ischemic brain occurs in cells within vessels as well as in cells outside of the vasculature, including microglia, monocytes/macrophages infiltrating into injury sites, and astrocytes [43], summarizing a role for CD36 in vascular dysfunction is a complicated issue. While stroke-induced TSP expression suggests a direct inhibition of angiogenesis in the endothelial cells, heightened inflammation by CD36 in other types of cells also alters vascular tone and integrity. Several promising pharmacological agents that counteract CD36 expression and function are available. Some have shown efficacy in reducing atherosclerotic lesion size and infarct size in stroke. Rigorous characterization of a new class of CD36 antagonists and testing their efficacy in experimental animal models of stroke are essential to develop a potential stroke therapy that aims at restoring vascular dysfunction.

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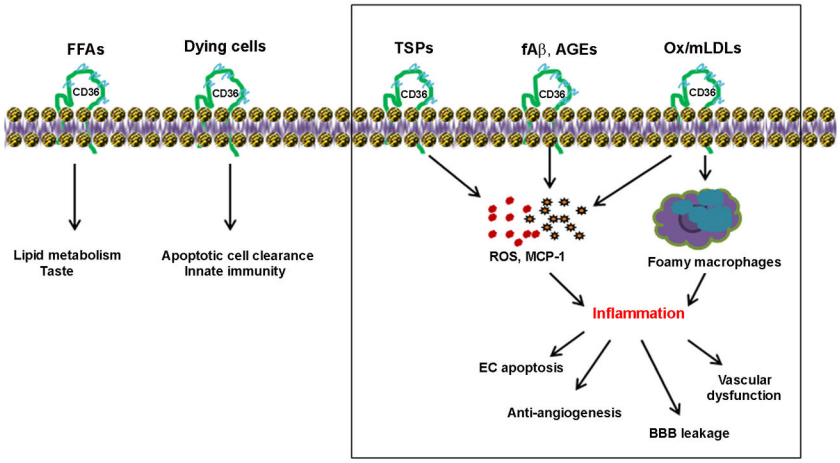

Figure 1. CD36 is a multi-functional receptor

CD36 elicits diverse cellular responses by interacting with specific ligands. CD36 is involved in lipid metabolism, taste preference, and innate immunity. Several CD36 pathways activated by distinct ligands elicit inflammatory responses. The binding of thrombospondins produces pro-inflammatory factors and causes endothelial apoptosis. β-Amyloid fibrils bind CD36/integrin complex, producing ROS and pro-inflammatory mediators. The uptake of oxidatively modified LDL by macrophage CD36 contributes to the pro-inflammatory atherosclerotic milieu. Outline area indicates CD36 contribution to endothelial dysfunction. FFA, free fatty acid; TSPs, thrombospondins; EC, endothelial cells; fAβ, fibrillar Aβ; ROS, reactive oxygen species; MCP-1, monocyte chemoattractant protein-1;ox/mLDL, oxidized/modified low density lipoprotein.

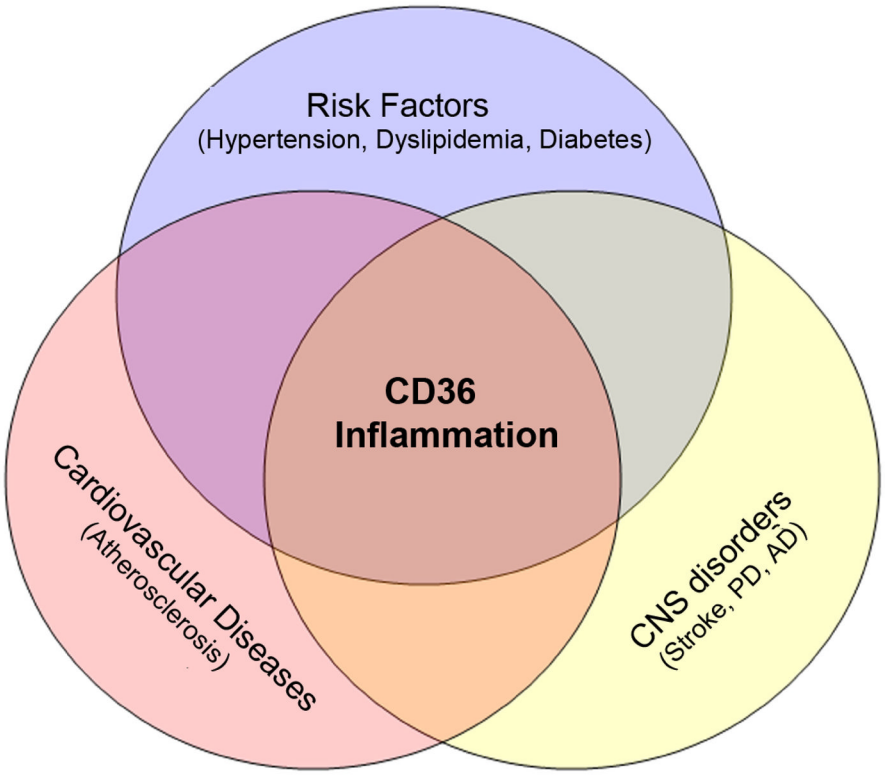

Figure 2. CD36 is a common mediator for neurological and vascular diseases

Cardiovascular and cerebrovascular diseases share common pathological features. Inflammation is one of the frequently observed pathologies in atherosclerosis, neurological, and neurodegenerative diseases. CD36 mediates inflammatory responses by generating free radicals, producing cytokines and chemokines. Risk factors such as hypertension, hyperlipidemia, and diabetes are associated with elevated expression of CD36 and higher incidence of vascular diseases.

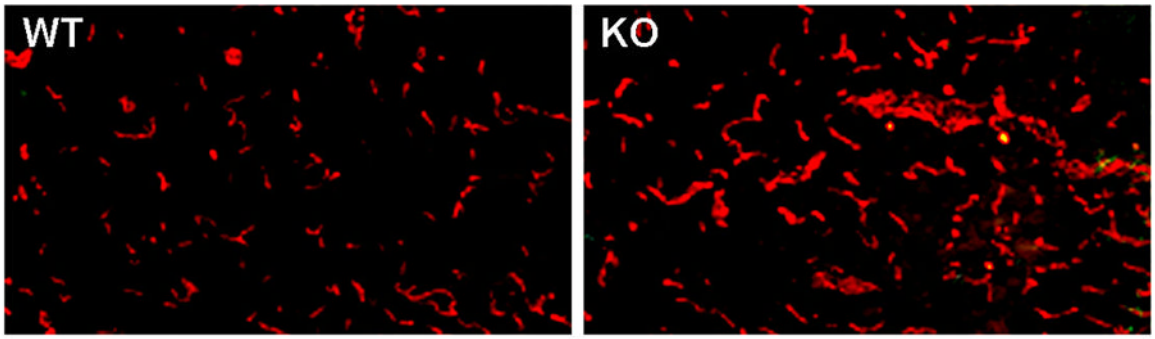

Figure 3. Absence of CD36 increases stroke-induced vessel density

Fluorescence Immunohistochemistry of CD31, an endothelial marker, in CD36 WT and CD36 KO mice 3 days after ischemia. Note the profound increase in vessel density in CD36 KO mice in the infarct territory.

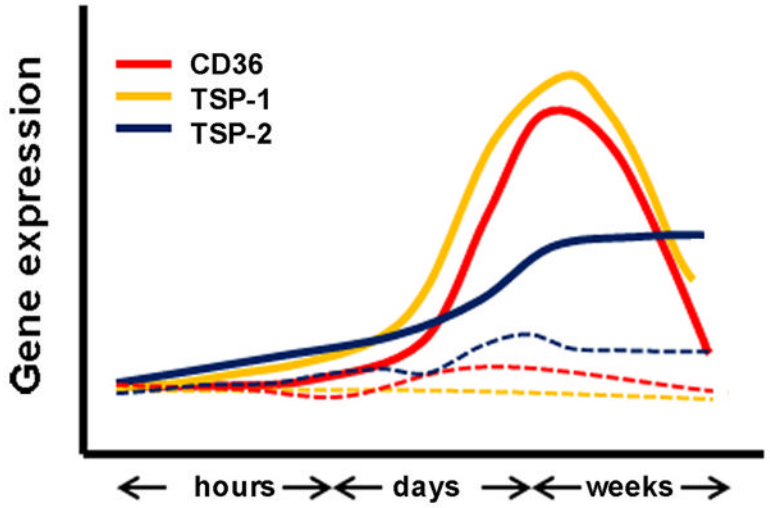

Figure 4. Expression of angiostatic factors, CD36 and TSP-1, overlaps following stroke

Relative CD36, TSP-1, and TSP-2 mRNA levels in the ipsilateral side (solid lines) of the brain hours, days, and weeks after ischemia. Expression of these factors in the contralateral side (dotted lines) was relatively unchanged.

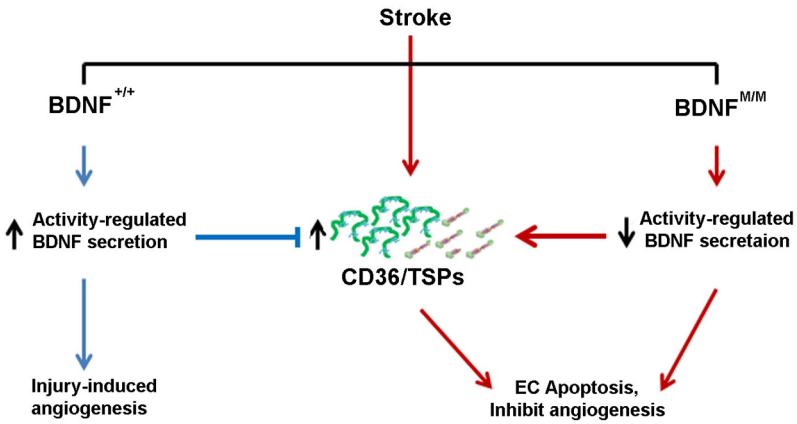

Figure 5. BDNF SNP increases CD36/TSP expression and reduces angiogenesis

The diagram depicts the effect of BDNF SNP on the expression of CD36 and TSP-1 in the post-ischemic brain. Compared to wild type ($BDNF^{+/+}$), BDNF SNP ($BDNF^{M/M}$) impairs activity-regulated BDNF secretions, elevates angiostatic factors CD36 and TSP-1, and attenuates stroke-induced angiogenesis. Arrows indicate pathways that promote (blue) or inhibit (red) angiogenesis.