Chapter 18
CD36: An Inflammatory Mediator in Acute Brain Injury

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Abstract Stroke is a major leading cause of death and disability in the human population. The pathology of stroke-induced brain injury involves multifactorial pro-death processes. Among them, inflammation is an important contributor to stroke pathology as indicated by the close association between excessive inflammation and exacerbation of the disease process. Considerable experimental evidence indicates that disease outcome is modulated by several factors including predisposing clinical conditions. Stroke compromises vascular permeability and leads to breakdown of the blood–brain barrier. While the pathology primarily occurs in the CNS, the presence of peripheral immune cells in the infarcted area suggests their potential role in post-ischemic inflammation. Given recent advances highlighting the heterogeneity of peripheral immune cells and diversity of their function, we review neuroimmune interaction in the setting of acute cerebral ischemia, post-ischemic inflammation, and the trafficking of peripheral immune cells to inflamed tissue, with specific focus on the involvement of the class B scavenger receptor, CD36. We discuss CD36 expression and functions, the contribution of the receptor to stroke pathology, its relevance to peripheral inflammatory conditions, and potential strategies to target the CD36-associated neuroinflammatory pathway.

List of Abbreviations

AGE	Advanced glycation end product
BBB	Blood–brain barrier

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CCR2	c–c chemokine receptor type 2
DAMP	Damage-associated molecular pattern
EAE	Experimental autoimmune encephalitis
fAβ	Fibrillar beta-amyloid
ICAM	Intercellular adhesion molecule
MCP-1	Monocyte chemotactic protein-1
mLDL	Modified low-density lipoprotein
oxLDL	Oxidized low-density lipoprotein
$_{ox}PC_{CD36}$	Oxidized choline glycerophospholipid species
PAMP	Pathogen-associated molecular pattern
PPAR-γ	Peroxisome proliferator-activated receptor-γ
PRR	Pattern recognition receptor
TLR	Toll-like receptors
TSPs	Thrombospondins
SAB	Salvianolic acid B

CD36, A Multifunctional Scavenger Receptor

Overview

CD36 is an 88 kDa heavily N-linked glycosylated membrane protein [1, 2]. It has to date defied crystallization, so we can only imagine its structure based on protein prediction and modeling. Short intracellular tails extend from the two transmembrane domains (the N-terminal tail results from an uncleaved signal peptide), anchoring the protein, and exposing a large extracellular loop. There is a hydrophobic region that is predicted to dip back towards or into the plasma membrane, and disulfide bonds of the 6 extracellular cysteines constrain the molecule [3, 4]. Two cysteine residues that are palmitoylated characterize both cytoplasmic domains, and both cytoplasmic tails are necessary for efficient plasma membrane CD36 expression [5, 6]. Posttranslational disulfide bond formation, glycosylation, and palmitoylation are all essential in targeting CD36 to the plasma membrane, and the latter is also required for positioning CD36 in caveolae, detergent-resistant membranes, or lipid rafts [4, 7, 8]. In some cell types, expression of caveolin-1 has been shown to be mandatory for plasma membrane targeting of CD36, and disruption of caveolae may affect some CD36-dependent functions [9–11]. The partitioning of CD36 to specific plasma membrane domains may facilitate interaction with signaling partners and interacting proteins that are a requirement for CD36-dependent responses.

The human CD36 gene (including all variants) extends about 77 kb on chromosome 7q11.2 and encodes a predicted protein of 471 amino acids with a predicted molecular weight of 53 kDa (http://www.ncbi.nlm.nih.gov/gene/948). Human CD36 has ten potential N-linked glycosylation sites, and thus the actual molecular weight varies from ~80–100 kDa [12]. The thick complex carbohydrate coat of

CD36 may protect it from proteolysis in harsh environments. Variant transcripts and a multitude of single nucleotide polymorphisms (SNP) mostly in noncoding regions have been identified [13, 14]. Mutations which result in absence of CD36 expression in platelets (Type II CD36 deficiency) or in monocytes and platelets (Type I CD36 deficiency) have been found at a frequency of 3–10 % in Asian and African populations and may persist as a result of selective pressure by the malaria parasite [15–18]. There is controversy as to whether absence of CD36 leads to or predisposes to human pathology, or is protective against malaria or other disease states. This may relate to whether CD36 is absent from all cells and tissues or some subset that differs depending upon the particular polymorphism, and the presence or absence of other interacting gene products.

Signaling

CD36 binding sites for oxidized low-density lipoprotein (oxLDL), growth hormone-releasing peptide and the family of thrombospondins (TSPs) are well defined, while the site for fatty acid binding is less precise and has not been tested definitively [19–22]. Other ligands have been assigned to the immunodominant domain (amino acids 155–183) by virtue of antibody blockade [23]. Alternatively, antibody binding to this domain may lead to a disruptive conformational change. There are two potential phosphorylation sites, both on the extracellular face of CD36, threonine 92 and serine 237. To date, phosphorylation at serine 237 has not been observed. However, there is data suggesting important biological consequences with regard to the phosphorylation of threonine 92. On platelets, phosphorylation reduces palmitate uptake and inhibits binding of TSP-1 and perhaps platelet activation [24–26]. Although it was long presumed that the "default" status in resting platelets was the phosphorylated state, recent evidence points towards a low basal level of CD36 phosphorylation in both platelets and microvascular endothelial cells [26]. Thus, why there is little platelet TSP binding and activation remains an open question. Threonine 92 is recognized by protein kinase C and to a lesser extent by protein kinase A [25, 27]. Recent work in transfected cell lines suggests that phosphorylation may also occur intracellularly as a posttranslational modification under certain conditions [26].

CD36 facilitates fatty acid uptake, but not by a classical transporter mechanism. Fatty acids probably bind transiently in the hydrophobic domain, and this facilitates flip-flop across the membrane, followed by rapid esterification or sequestration by cytoplasmic fatty acid binding proteins [28, 29]. Alternatively, CD36 may provide a hydrophobic pore facilitating fatty acid entry into membranes, analogous to the hypothesized mechanism by which scavenger receptor B1 facilitates cholesterol exchange between high-density lipoprotein and cells [30]. In contrast, uptake of oxLDL is via a caveolin-independent endocytic pathway and depends upon CD36-mediated lyn activation of the vav family of guanine exchange factors for Rho

family GTPases, for subsequent vesicle maturation [31, 32]. There is recent evidence suggesting that CD36 is also expressed on mitochondrial membranes, but its function remains controversial [33–35]. While all groups consistently show that increased fatty acid oxidation is accompanied by increased CD36-mediated fatty acid uptake at the plasma membrane, there has been no definitive evidence that CD36 plays a direct role in fatty acid delivery into mitochondria.

Expression and Function in the CNS and Periphery

Initially characterized as a platelet receptor for thrombospondin-1 (TSP-1, designated glycoprotein IV), CD36 expression has subsequently been found on many types of cells and tissues [36]. CD36 is expressed on blood cells and cells of the vasculature, including platelets, reticulocytes, monocytes and macrophages, dendritic cells, endothelial cells, and smooth muscle cells [37–44]. It is found in specialized epithelium, including mammary epithelium, retinal pigment epithelium, apical enterocytes of the proximal small intestine, and the proximal tubule epithelium of the kidney [45–50]. CD36 is expressed in insulin-sensitive cells and tissues, including adipocytes, hepatocytes, cardiac and skeletal muscle, and pancreatic beta cell granules [28, 51]. CD36 is also found in taste receptors of the circumvallate papillae and steroidogenic cells of the adrenal, testes, and ovary [48, 52, 53].

The functions of CD36 are dictated by the cell type, circumstances, and ligand (Fig. 18.1). For example, CD36 plays a major role in fatty acid uptake required for production of energy or heat, especially in heart, skeletal muscle, and brown adipose tissue, and also in fat storage in white adipose tissue, and pathologically in liver and muscle [54–56]. CD36 also functions in recognition of malaria parasites and plays a role in fatty acid sensing by taste buds in the mouth and enterocytes in the gut [2, 48]. The uptake of oxLDLs by monocytes/macrophages leads to the formation of "foamy" macrophages and is a key step in atherosclerotic lesion development [57]. In binding the matricellular protein TSPs, CD36 may not only function as an adhesion receptor in platelets and between platelets, monocytes, tumor cells, sickled erythrocytes, and endothelium but can also modulate TGF-β activation, inhibit angiogenesis, and facilitate uptake of apoptotic cells [58]. CD36 is classified as a pattern recognition receptor (PRR) because it recognizes pathogen-associated molecular patterns or PAMPs, and danger or damage-associated molecular patterns also known as DAMPs [59]. These are repetitive motifs found on pathogens, modified phospholipids, or oxidatively denatured cytoplasmic or nuclear constituents that present as nonself [59, 60]. Some examples include oxidatively modified phospholipids in rod outer segments, apoptotic cells and low- and high-density lipoproteins, advanced glycation end products (AGEs), neurotoxic prion protein, amyloid-beta (Aβ), and diacylglycerides in the cell walls of Gram-positive bacteria. The diverse responses by interacting with specific CD36 ligands often converge into endothelial dysfunction and inflammation, common pathological features of cardio- and cerebrovascular diseases.

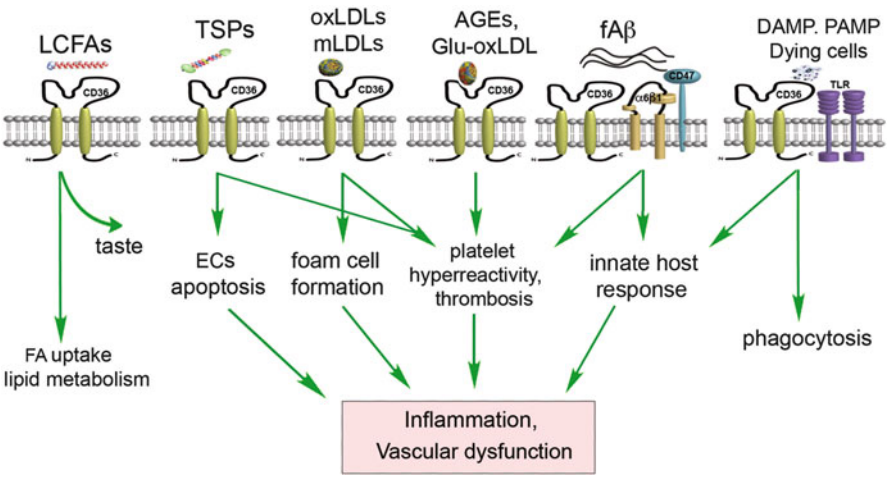

Fig. 18.1 CD36 as a multifunctional receptor. By recognizing a host of ligands, CD36 elicits myriad responses and the interaction between specific ligands and the receptor results in diverse physiological and pathological responses. CD36 forms a complex with α6β1 integrin and CD47 to elicit downstream function and also acts as a coreceptor for TLRs. Many CD36-associated pathways converge in inflammatory responses. *LCFAs* long chain fatty acids, *TSPs* thrombospondins, *EC* endothelial cells, *ox(m)LDLs* oxidized (modified) low-density lipoprotein, *AGEs* advanced glycation end products, *Glu-oxLDL* Glucose-oxLDL, *fAβ* fibrillar β amyloid, *TLR* toll-like receptor

CNS

CD36 is expressed in neurons, microglia, astrocytes, and the endothelium of the blood–brain barrier. CD36 is expressed in neurons found in regions involved in pheromone responses and reproductive behavior. Specifically, it is found in neurons of the pyramidal layer of the ventral hippocampus, CA1 field, amygdalopiriform transition area, the perirhinal cortex, and the ectorhinal cortex [61, 62]. Neurons of the ventromedial hypothalamic nucleus utilize both glucose and fatty acids as signaling molecules and regulate energy homeostasis through central modulation of feeding behavior, hepatic glucose production, and hormone secretion. About 50 % of oleic acid sensing by ventromedial neurons of the hypothalamus was shown to be CD36 dependent, and this sensing was independent of fatty acid metabolism [62]. The mechanism of CD36-dependent fatty acid sensing is presumed to be analogous to that which has been defined in taste buds; CD36 binding by fatty acids is postulated to cause neurotransmitter release by activation of a protein tyrosine kinase and liberation of inositol 1,4,5-triphosphate, leading to calcium-dependent membrane depolarization [62, 63]. Dysfunctional central fatty acid sensing by CD36 may play a role in insulin-resistant states and obesity.

Long chain fatty acid uptake by endothelial cells at the blood–brain barrier is at least partially receptor dependent, and the role of CD36 in this process has been

evaluated. The uptake of monounsaturated fatty acids is probably partially CD36 dependent; CD36 knockout mice have a significant decrease in this class of fatty acids, and in cultured blood–brain barrier-derived endothelium, knockdown of CD36 significantly decreased oleic acid uptake [64, 65]. Uptake of polyunsaturated fatty acids is most probably CD36 independent. The role of CD36 in fatty acid uptake within the brain remains to be elucidated.

CD36 expression was found in a subset of astrocytes in the post-ischemic brain [66]. The expression was temporally and spatially limited, only found 3 days following stroke and in the peri-infarct area, where the glial scar forms. Bao and colleagues subsequently showed a close relationship in the expression of CD36 and glial fibrillary acidic protein (GFAP). Inhibition of CD36 expression coincided with decreased GFAP expression and reduced glial scar, suggesting the involvement of CD36 in injury-induced scar formation [67].

CD36 has been found to play a role in microglial activation induced by amyloid-beta (Aβ) in Alzheimer's disease (AD) plaque and by the neurotoxic prion protein, leading to secretion of pro-inflammatory cytokines [68–70]. There are apparently multiple mechanisms of microglial activation and downstream signaling that are CD36 dependent. Studies demonstrated that fibrillar amyloid beta (fAβ) engaged microglia by a complex of receptors that included CD36, scavenger receptor A, α6β1 integrin, CD47, and toll-like receptors (TLRs) 2 and 4. These initiate a signaling cascade that includes p38, src kinase, vav proteins, rac, and reactive oxygen species, leading to cytokine release and phagocytosis [71, 72]. Stewart et al. suggested that TLR 4/6 and CD36 engaged Aβ and activated the inflammasome, leading to release of inflammatory cytokines. This group also found that CD36 was essential to a signaling cascade involving the src kinase fyn phosphorylating p130CAS, a focal adhesion scaffolding protein. This led to recruitment and phosphorylation of pyk2 and paxillin to the leading edge and membrane ruffles, resulting in an increase in microglia migration [73].

Periphery

CD36 is highly expressed in mononuclear phagocytes, including monocytes, macrophages, and dendritic cells [41, 74, 75]. Receptor-mediated uptake of oxidatively modified LDL (mLDL)/oxLDL by monocytes increases transcription of CD36 and several other genes via activation of the nuclear hormone receptor peroxisome proliferator-activated receptor-γ (PPAR-γ) [76]. The activating ligand(s) for PPAR-γ are oxidized phospholipids, such as 9- and 13-HODE, and these and/or their precursor lipids are delivered to the cell within the oxLDL particle. Similarly, in heart and liver, uptake of ligands for other members of the PPAR family is mediated by CD36 and may contribute to cardiac lipotoxicity and hepatic steatosis [77, 78].

On platelets, CD36 expression is variable in the population, and this is attributed to genetic polymorphisms but potentially may also relate to physiological status [79]. For example, both a high-fat diet and insulin resistance upregulate CD36 on monocytes/macrophages and could have similar effect on megakaryocytes.

Humans and mice deficient in platelet CD36 do not have a significant phenotype. However, recent studies using pathophysiological ligands of CD36, specifically, oxidized phospholipids and AGEs, support the hypothesis that platelet CD36 can modulate platelet reactivity by transducing prothrombotic signals [80–82]. The pathway in platelets follows a recurring theme: src kinase activation (in platelets, fyn and lyn are associated with CD36 following oxLDL binding), phosphorylation of vav family proteins, and Map kinase (in this case, MKK4), resulting ultimately in jnk activation. AGEs also trigger platelet CD36-mediated jnk2 activation [83]. In addition to activation of signaling pathways, CD36 may foster exchange of phospholipids and fatty acids between platelets and lipoproteins. The type of fatty acid/phospholipid, and whether it is oxidized, may alter platelet membranes rendering them more susceptible to aggregation [84]. Platelet CD36 has been shown to interact with amyloids, and platelet aggregation was mediated by a p38 MAP kinase and thromboxane A2-dependent pathway [85]. Thus, increased platelet expression and sensitization by pathophysiological CD36 ligands may explain platelet hyperreactivity in inflammation and hyperlipidemic and insulin-resistant states, among others, and lead to appreciable thrombosis in response to subthreshold platelet stimulating agents. In contrast to CD36-expressing mice, CD36 KO mice do not show platelet hyperreactivity in response to high-fat diet feeding or insulin-resistant states and have normal thrombosis profiles in experimental in vivo models that enrich for CD36 ligands [80, 84].

Neuroinflammation

Post-ischemic Inflammation

Post-ischemic inflammation is a contributing negative factor in stroke, exacerbating injury, and influencing outcome [86, 87]. Stroke increases inflammatory mediator: free radical, cytokines/chemokines (IL-1β, TNF-α, IL-6, monocyte chemotactic protein (MCP)-1, macrophage inflammatory protein-1, C-C chemokine receptor type 2 (CCR2), and inflammatory proteins (inducible nitric oxide synthase, cyclooxygenase, and matrix metalloproteinases). These mediators increase endothelial expression of adhesion molecules, such as intercellular adhesion molecule (ICAM)-1 and p-selectin, leading to leukocyte arrest and transendothelial migration at the injured site. These mediators either act in concert or converge into an inflammatory response following activation of temporally and spatially separated cascades [88, 89]. A number of studies have shown that targeting specific neuroinflammatory mediators attenuates stroke-induced brain injury [90–92]. Mice deficient in ICAM-1 or p-selectin displayed smaller infarct size compared to wild type [93–95]. Deficiency in either MCP-1 or its cognate receptor, CCR2, also resulted in protection in murine stroke models [96, 97], while increased expression of MCP-1 exacerbated ischemic outcome with enhanced recruitment of inflammatory cells at the injury sites [98].

Despite apparent benefits of attenuating neuroinflammatory pathways in animal models, clinical trials in human stroke, using antibodies against adhesion molecules and neutrophils, were not effective [99, 100].

Recent studies recognized the complexity in targeting neuroinflammatory pathways. Stroke-induced inflammation is a double-edged sword in that it not only is necessary for containment and repair but can also lead to further damage. It has become increasingly clear that peripheral inflammatory status and comorbidities are important factors in neuroinflammation and outcome [101–103]. Understanding the temporal sequence of activation of inflammatory mediators, spatial localization of the cascade in the infarct (core vs. penumbra), and identification of cell types activated remain to be investigated to selectively reduce adverse while preserving beneficial aspects of the inflammatory response.

CD36: A Modulator of the Innate Immune System

In response to an encounter with microbes, the host elicits a rapid, specific, and self-constraining acute inflammatory response to avoid inflammatory-mediated damage to neighboring tissues [104]. This primordial defense response involves initial recognition of the triggers, so-called PAMPs, through pattern recognition receptors (PRRs), which include scavenger receptors. Subsequently, triggered adaptive immune responses lead to resolution to reinstate tissue homeostasis in a timely manner. Sterile inflammation occurs in post-ischemic tissues in the absence of microbes [105, 106]. The triggers of sterile inflammation are elements of damaged tissue, including oxidized lipids and cytoplasmic proteins, DNA, RNA, and proteolyzed or oxidized extracellular matrix components, which, as previously noted, are collectively termed DAMPs. Regardless of microbial or endogenous in nature, PRRs are believed to be involved in recognizing the triggers and eliciting inflammatory responses (Fig. 18.2).

In addition to playing a role in the endocytic uptake of modified lipoproteins leading to foam cell formation, an important role for monocyte/macrophage CD36 as a PRR in innate immune modulation has emerged [107–109]. This is both in association with and independent of TLRs. CD36 recognizes nonself, and this is one of the oldest and most conserved functions of these receptors, beginning with recognition of apoptotic cells during development as a result of normal homeostasis [110]. The recognition motif, altered fatty acid chains that become hydrophilic and more easily accessed by surface receptors, accounts for the crossover recognition to modified lipoproteins carrying these ligands as a result of oxidative stress [111, 112]. CD36 interaction with apoptotic cells invokes an anti-inflammatory response, consistent with the maintenance of organism status quo. This response involves p38 activation and transcriptional upregulation of the IL-10 promoter by Pbx-1 and Prep-1 [113, 114]. On dendritic cells, CD36 mediates uptake of apoptotic cells and is also involved in cross-presentation of antigens to cytotoxic T cells [41].

In recognition of lipids in cell walls of bacteria, CD36 may play a role not only in endocytosis/phagocytosis but also in TLR signaling responses [73, 115–121]

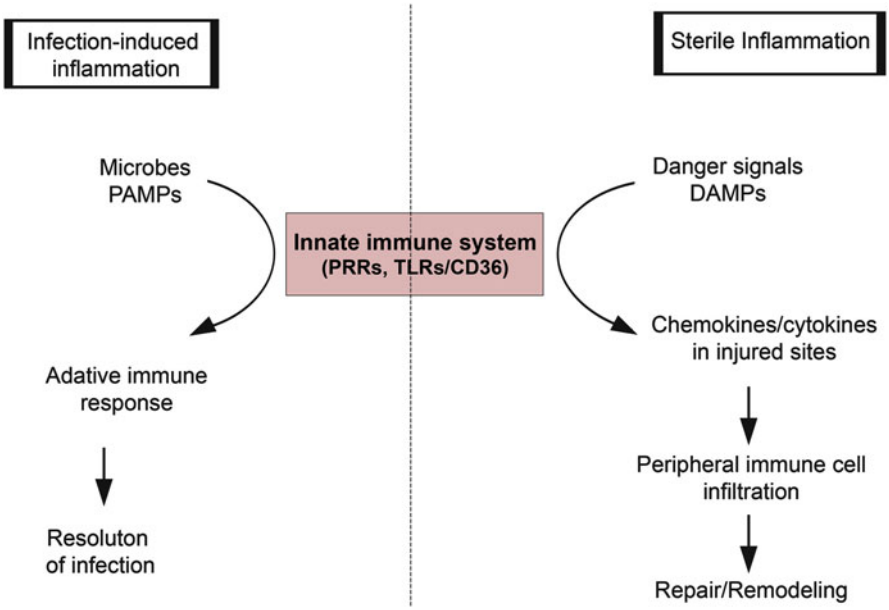

Fig. 18.2 Innate immune receptors resolve pathogen-induced and sterile inflammation. Convergence of innate immune system to resolve inflammation. PAMPs or DAMPs are recognized through pattern recognition receptors such as TLRs and/or CD36. The interactions elicit appropriate downstream responses to resolve infection and repair tissue damage. *TLRs* toll-like receptors, *PAMPs* pathogen-associated molecular patterns, *DAMPs* damage-associated molecular patterns

(Fig. 18.1). This is an emerging topic in CD36 biology, and the exact mechanism is still under investigation. One hypothesis is that CD36 acts an accessory protein for TLRs to deliver ligands, while alternative data suggest that CD36 enhances downstream signaling. This may prove to be important in many of the inflammatory responses mediated by CD36, as there is significant crossover between TLR and CD36 ligands, including fatty acids, amyloid-beta, modified LDL, and other PAMPs/DAMPs. Specifically, CD36 acts as a co-receptor for the recognition of bacteria-derived diacylglyceride through a TLR2/6 complex [115, 122]. OxLDL and Aβ trigger inflammatory signaling through TLR4/6 [73]. Abe and colleagues found that CD36 plays a key role in the inflammatory response and tissue damage mediated by TLR2/1, but not TLR2/6, as a result of cerebral ischemia [121]. This differed from the accessory role of CD36 in monocyte/macrophages in the periphery, where it was instead important for TLR 2/6 signaling. The explanation for this difference was not explored and may relate to differences in expression of other TLR accessory proteins. Nonetheless, these studies suggest that CD36 is involved in the pathogenesis of sterile inflammation through convergence with TLR signaling.

CD36: An Inflammatory Receptor

The pro-inflammatory nature of CD36 has been implicated in atherosclerosis, vascular dysfunction, and neurodegenerative diseases [57, 69, 123, 124]. The concept that CD36 is a prototypic inflammatory receptor and contributes to stroke pathology also has been recognized [66, 102, 125]. In addition to elevated CD36 expression, CD36 ligands such as fAβ, mLDL, oxLDL, and TSPs are elevated in the post-ischemic brain [126–130]. Several studies showed CD36 activation is associated with elevated levels of free radicals, IL-1β, TNF-α, IL-6, MCP-1, and CCR2 [66, 102, 131]. CD36 expression was found predominantly on CD11b+ cells within the infarct territory and the presence of the cells occurs throughout the course of infarct development. However, the identity of the CD11b+ cells as to resident microglia versus infiltrated peripheral mononuclear phagocytes has not been explored. Although CD36 expression was not detected in neurons in the injured tissue, the expression was shown in the subsets of GFAP-expressing astrocytes in the glial scar area [66]. As inflammation is essential in glial scar formation [132], the involvement of CD36 in injury-induced scar formation was addressed. The study by Bao and colleagues reported that CD36 expression covaries with GFAP, an intermediated filament in astrocytes [67]. This study identified CD36 as a novel mediator of GFAP expression and glial scar formation and suggested that targeting CD36 may decrease the barring effect of scar tissue to promote regeneration.

Comorbidities Influencing CD36 Expression/Function

Cardiovascular and cerebrovascular diseases share many prevalent risk factors. These comorbid conditions include hyperlipidemia, insulin resistance associated with metabolic syndrome, obesity and diabetes, impaired vascular function, and hypertension. CD36 expression has been shown to be modulated in comorbid conditions. Since comorbidities increase CD36 expression and a specific set of ligands in a feed-forward manner [76], excessive ligands/receptor interaction associated with risk factors presumably intensify CD36 pathways in disease conditions (Fig. 18.3).

Dyslipidemia

Podrez and colleagues reported increased lipid-based CD36 ligands in ApoE KO mice fed a high-fat diet [80]. They demonstrated a profound upregulation of structurally defined, oxidized choline glycerophospholipid species ($_{ox}PC_{CD36}$), that serve as high-affinity ligands for CD36 in lipoproteins in the plasma of hyperlipidemic mice and also in humans with low HDL levels [133]. The abundance of $_{ox}PC_{CD36}$ in hyperlipidemia led to vascular foam cell formation, a key event in atherosclerotic lesion development [57]. Compared to controls, hyperlipidemic mice subjected to

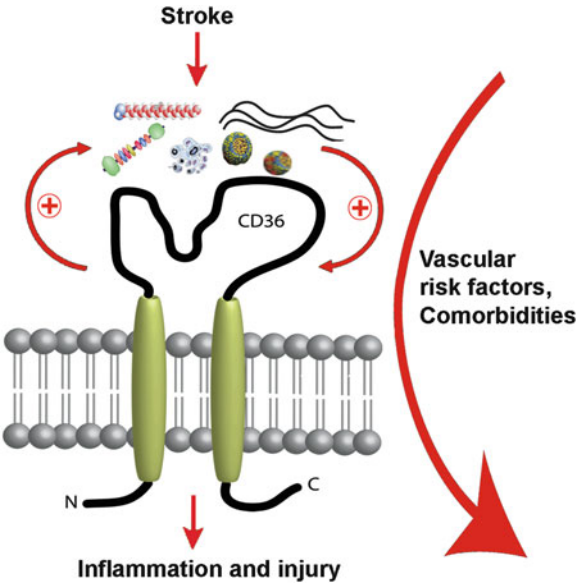

Fig. 18.3 CD36 exacerbates stroke-induced injury as a result of disease modifying risk factors. Following stroke, interaction of CD36 with its ligand occurs in a feed-forward manner. Vascular risk factors and cormodities such as hyperlipidemia, insulin resistance, vascular dysfunction, and hypertension enhance the generation of CD36 ligands and intensify CD36 pathways

cerebral ischemia displayed larger infarcts and heightened post-ischemic inflammation [131]. An underlying hypothesis is that "priming" of peripheral mononuclear phagocytes by CD36/ligands prior to stroke might account for the exacerbation. This study also showed higher expression of CD36 in peripheral monocytes/macrophages in hyperlipidemic mice prior to ischemia. Following stroke, the mice displayed elevated CD36 expression, foam cell area, and pro-inflammatory cytokines/chemokines (MCP-1, CCR2, IL-1β, TNFα, and IL-6) in the post-ischemic brain. The absence of CD36 reversed the hyperlipidemia-associated phenotype [131]. Clear indication from the study is CD36's involvement in hyperlipidemia-induced exacerbation of ischemic inflammation and injury and notably, its peripheral influence on CNS injury development. The possibility that CD36-dependent stroke outcomes could be influenced by the presence of other comorbidities at the time of stroke and also involvement of other factors such as developmental stage (neonatal vs. adult) remain to be investigated.

Insulin Resistance

Insulin resistance associated with diabetes is a predisposing risk factor for stroke as indicated by the fact that 70 % of new stroke victims were previously diagnosed with diabetes, occult diabetes, or were prediabetic with impaired insulin sensitivity [134, 135]. Diabetic conditions promote a chronic pro-inflammatory state that increases the burden of CD36 ligands via modifications of LDL and AGEs, and

augments CD36 expression and function. Increased expression of CD36 in monocytes/macrophages not only influences the peripheral inflammatory state but also impacts at the localized site of cerebral ischemic injury.

A potential link between CD36 and impaired insulin sensitivity has been found experimentally in mice. However, in humans, studies are less equivocal, and this may depend upon which cells/tissues are affected by the specific CD36 mutation/SNP, whether the mutation/SNP leads to reduced or increased CD36 expression, and expression of other gene products [136–138]. CD36 KO mice not only have overall increased insulin sensitivity, as a result of increased glucose uptake in muscle, but also show liver-specific insulin resistance as a result of reduced capacity to utilize fatty acids in heart [139, 140]. Further studies showed that CD36 is linked to inflammation in insulin resistance and defective insulin signaling [55, 141]. The increased burden of CD36 ligands in the diabetic state was shown to promote a pro-inflammatory state and a CD36-dependent paracrine loop between adipocytes and macrophages that facilitated chronic inflammation and contributed to insulin resistance common in obesity and dyslipidemia [142].

Moreover, there is abundant evidence that glucose/diabetes modulates CD36 expression and thus impacts CD36 downstream effects. For example, glucose administration upregulates CD36 expression on macrophages [143] and in proximal renal tubular epithelia in humans [144]. Other studies have shown that CD36 expression is increased in monocytes from type 2 diabetic patients [145] and in diabetic mouse hearts [146]. In diabetes associated with atherosclerosis, increased plasma MCP-1 levels were associated with increased monocyte CCR2, CD68, and CD36 and increased vessel wall monocyte number [147]. Liang and colleagues reported increased CD36 protein in macrophages as a response to defective insulin signaling [148]. Glucose was also shown to promote LDL oxidation, and the resulting glucose-oxLDLs stimulated macrophage proliferation in a manner that was dependent on CD36 [149]. Human THP-1 macrophages that were exposed to glucoxidized LDLs increased both CD36 gene expression and accumulation of cholesterol ester (an indicator of foam cell formation) to extents greater than those produced by glycated LDLs or oxLDLs [150].

CD36 has been shown to be localized on insulin-containing granules in human pancreatic beta cells and mediates fatty acid effects on insulin secretion [151]. Handberg and colleagues identified CD36 in plasma (later shown to be contained within microparticles) as a novel marker of insulin resistance [152, 153]. Thus, multiple lines of evidence show that CD36 is modulated by insulin and glucose pathways, and that CD36 has effects on these pathways.

Vascular Dysfunction

The deposition of Aβ in the microvasculature, a hallmark of AD, contributes to oxidative stress and compromises blood–brain barrier (BBB) integrity [154, 155]. Due to the nature of the ligand, many studies on CD36 relevant to fAβ were focused

on innate host response and inflammation associated with AD [69, 71, 156]. A key role for CD36 was reported, as CD36 deficiency attenuated fAβ-induced secretion of cytokines, chemokines, and reactive oxygen species in microglia. Macrophage or microglia recruitment into the peritoneum or brain, respectively, in response to injection of fAβ was attenuated in CD36 KO mice [69]. A multi-receptor complex comprised of CD36/$\alpha_6\beta_1$-integrin/CD47 stimulates intracellular tyrosine kinase-based signaling cascades and cellular activation, as detailed previously, which leads to the secretion of pro-inflammatory molecules [72]. In animal models 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 [123, 157]. 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 [158].

Hypertension

Hypertension is a major risk factor for stroke [159, 160]. Clinical trials employing antihypertensive agents that aim at reducing blood pressure have been effective in management and prevention [161, 162]. CD36 has been implicated in blood pressure control and modulated by hypertension. Pravenec and colleagues showed that CD36 mutation in the kidney can increase blood pressure and identified renal CD36 as a genetical determinant of blood pressure and risk factor for hypertension [163]. In the stroke prone spontaneous hypertensive rat, BBB impairment was associated with increased CD36 expression in the vessel [164]. Similar to what occurs in diabetics, macrophages from hypertensive subjects show significant increase in CD36 expression, and this was associated with enhanced adhesion to endothelial cells and greater production of ROS [165]. Circulating human endothelial cells also show increased CD36 expression in pulmonary hypertensive states [166]. In hypoxia-induced pulmonary hypertension, CD36 expression increases on intrapulmonary arteries [167]. Human gene association studies have been equivocal with respect to CD36, probably for similar reasons described above in the case of insulin resistance/diabetes.

Neuroimmune Interaction

The presence of granulocytes (neutrophils), subsets of T cells, and monocytes/macrophages in the post-stroke brain suggests mobilization of peripheral immune cells to the injured tissue [88, 168]. There has been controversy regarding the order and timing among the types of immune cells for trafficking. An early study reported that neutrophil infiltration occurs prior to macrophages/activated microglia following

stroke [169], while others showed that the accumulation of microglia and/or macrophages in the infarct territory precedes neutrophils [170]. Despite disagreement regarding the order of infiltrating cell types, it is believed that the accumulation of peripheral immune cells contributes to injury development during the acute phase of stroke.

MCP-1/CCR2 Axis for Monocyte Trafficking

Experimental autoimmune encephalitis (EAE) in mice is an example of how inflammatory cells impact disease in the CNS and demonstrates the importance of the MCP-1/CCR2 axis in monocyte recruitment. Among the types of infiltrating cells, monocytes was most tightly coupled to neurobehavioral severity in EAE [171]. Specific inhibition of monocyte recruitment reduced EAE lesion progression, while the presence of T cells was independent of disease severity, strongly implicating infiltrating monocytes in EAE pathogenesis, and confirming an earlier finding [172]. Through serial experimental manipulation using parabiosis (suturing a pair of mice to share circulation) and irradiation/bone marrow transplant of stem cells from genetically engineered mice, CCR2, a G-protein-linked membrane receptor, was found to be the essential mediator of monocyte trafficking, as the study showed the absence of monocyte CCR2 profoundly attenuated paralytic progression of the disease [171].

Monocytes exhibit distinct subsets that are reminiscent of macrophage phenotypes [173–175]. The subset that expresses a high level of the hematopoietic cell differentiation antigen Ly-6C (Ly-6C^{hi}) also expresses CCR2. Ly-6C^{hi} (CCR2+) monocytes are specifically recruited to an injury site and become classically activated M1 macrophages. This CCR2+ subset is chemotactic to MCP-1, which is produced in the inflamed tissue. Recruitment of this subset to inflammatory sites is believed to be CCR2 dependent since monocytes from CCR2-deficient mice do not traffic as efficiently into areas of inflammation [176, 177]. The Ly-6C^{low} monocyte subset expresses CX3CR1, a receptor for CX3CL1 (fractalkine), but is devoid of CCR2 expression. This anti-inflammatory Ly-6C^{low} (CCR2-/CX3CR1+) subset is recruited to normal tissues and develops into resident M2 macrophages that function in host defense and repair after injury [174].

Secreted by microvascular endothelial cells, monocytes/macrophages, and astrocytes upon injury [98, 178–180], MCP-1 is a member of the CC chemokine family and functions in the trafficking of CCR2-expressing monocytes into an injury site. Previous work has established the importance of the MCP-1/CCR2 axis in monocyte/macrophage trafficking in cerebral ischemia. Stroke increases MCP-1 expression in the affected hemisphere. The overexpression of MCP-1 increases infarct volume and enhances the recruitment of monocytes to the injury site [98]. The absence of CCR2 or MCP-1 reduces infarct size [96, 97]. In the absence of CD36, CD36 ligands and injury-induced CC and CXC chemokine production were attenuated [102, 131]. In other disease models that involve recruitment of

classically activated M1 macrophages, such as obesity and atherosclerosis, the absence of CD36 is associated with decreased monocyte/macrophage migration/infiltration and reduced overall numbers of macrophages [141, 181–183], suggesting MCP-1/CCR2 as a major chemokine/ receptor axis for immune cell trafficking.

CD36 in Monocyte/Macrophage Trafficking

Studies indicate the involvement of CD36 in cell mortality and mobility, an important function in cell trafficking. CD36 has been shown to signal through the P130Cas complex to the actin cytoskeleton and regulate microglial migration [184]. Harb and colleagues addressed the role of CD36 in regulating mononuclear phagocyte trafficking to pro-inflammatory atherosclerotic lesions. This study showed that inhibition of CD36 attenuated macrophage accumulation in atherosclerotic lesions, and this was associated with reduced expression of MCP-1 [182]. Cell polarization is essential for migration and mobility of leukocytes. Thus, studies by Park et al. showing that oxLDL/CD36 interaction induced loss of cell polarity and reduced macrophage migration through a vav-Rac-myosin II pathway provide a mechanistic framework to consider CD36 actions [185]. This work explains why macrophages become trapped in areas rich in CD36 ligands and promote further inflammation.

CD36 ligands are elevated in hyperlipidemic conditions and in injured tissues where oxidative or damaged products from cells are released [80, 107]. Through the uptake of lipid-based ligands and foam cell formation in hyperlipidemic conditions, monocyte/macrophage CD36 has been shown to play a role in atherosclerosis and stroke pathology [102, 131, 182, 186]. In a recent study, Kim and colleagues showed that infiltrating immune cells from the periphery are the major source of CD36 in the post-ischemic brain and contribute to stroke-induced brain injury in a hyperlipidemic condition. Mice receiving CD36-deficient bone marrow showed attenuated infarct volume and MCP-1 and CCR2 expression in the brain. The reverse transplantation study (transplantation of CD36-expressing bone marrow-derived cells to CD36 KO mice) showed no increase in infarct volume. The study suggested that CD36 in both host and periphery is required for peripheral CD36 to exert its effect on the hyperlipidemia-induced exacerbation in stroke injury. The underlying mechanism of the exacerbation presumably is that CD36 regulates immune cell trafficking via modulation of the expression of MCP-1 and CCR2 [102].

Targeting CD36 to Attenuate Inflammation

In light of the receptor's pro-inflammatory properties, downregulation of CD36 has been suggested as a strategy to reduce inflammation-associated cerebro- and cardiovascular diseases including altherosclerosis and stroke. Several pharmacological

agents were identified to attenuate CD36 expression and function. The antioxidant, α-tocopherol, reduces expression of CD36 and the uptake of oxLDL into macrophages [187–190]. Statins downregulate CD36 expression and suppress oxLDL uptake [187, 191, 192] and subsequently prevent oxLDL-induced macrophage foam cell formation [193]. Hexarelin is a member of the hexapeptide growth hormone-releasing peptide family and binds to CD36 and inhibits its expression [20]. Treatment of mice with hexarelin or a structurally related analogue, EP80317, resulted in a marked decrease in atherosclerotic lesions [194]. Using a high-throughput screening approach for CD36 antagonists based on competition in an oxLDL-binding assay, salvianolic acid B (SAB) was identified as a CD36 inhibitor [195]. SAB is a water-soluble polyphenolic antioxidant isolated from *Danshen*, a Chinese herb that has been used for the prevention and treatment of atherosclerosis and stroke in Asian countries. The specificity and efficacy of SAB in the inhibition of CD36-mediated lipid uptake were confirmed by binding studies for the physical interaction of SAB with CD36. SAB reduces oxLDL-induced CD36 gene expression in cultured cell lines and primary macrophages. Moreover, SAB reduces CD36 gene expression and lipid uptake into macrophages in hyperlipidemic ApoE KO mice [196].

Due to the issues regarding developmental compensatory changes with germ line deletions, investigation on the efficacy of CD36 inhibitors has been complemented by genetic approaches. Besides finding from CD36 KO mice that displayed attenuated stroke-induced inflammation and brain injury [66, 125], effects of a new class of antioxidants peptide, SS31, has been tested against cerebral ischemia [197]. Mice treated with SS31 peptides had attenuated ischemia-induced glutathione (GSH) depletion in the cortex and showed smaller infarct size. The absence of stroke-induced glutathione depletion and no effect on infarct volume in CD36 KO mice treated with the peptide suggested that the protection occurred through the downregulation of CD36 pathways. Because CD36 is a multi-ligand and multifunctional receptor and its expression occurs in a positive feed-forward manner that promotes its functions, targeting at the level of the receptor by interrupting the feed-forward loop to downregulate the CD36 pathway (a multimodal approach) has been suggested [125].

Conclusion

CD36 is an inflammatory receptor that is at the junction of cardio and cerebral vascular disease. Defining the role of CD36 in the CNS and periphery through neuroimmune interactions has been an important emerging area in understanding the pathophysiology of brain injury as a result of cerebral ischemia. CD36 expression is altered in peripheral inflammatory conditions, including obesity, insulin resistance, hyperlipidemia, and hypertension, which also increase stroke incidence either singly or through clustering of these risk factors. Accumulating evidence suggests that CD36 regulates injury-induced mobilization of peripheral immune cells and influences the outcome of stroke. Thus, stroke-induced injury is viewed as the summation

of intrinsic ischemic insult and peripheral influences through the neuroimmune interaction. As less favorable outcomes are predicted in patients with various risk factors, targeting CD36-associated pathways may modulate the neuroinflammatory responses in comorbid conditions and serve as a potential approach to limit secondary expansion of primary injury in the setting of acute ischemia.

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