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Commentary on Myers et al.: Growing role of the innate immunity receptor CD36 in central nervous system diseases

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Abstract

Activation of innate immunity by sterile inflammation has emerged as a key event in selected CNS diseases, with a defining impact on all stages of the pathological process. Due to its multiple functions and assembly with other pattern recognition receptors, the innate immunity receptor CD36 has been implicated in a wide variety of brain pathologies, ranging from acute brain injury to neurodegeneration. However, the role of CD36 is complex involving both tissue destruction, related mainly to oxidative stress and inflammation, and beneficial reparative effects due to the involvement of CD36 in tissue repair and reorganization. A recent paper of Meyer et al. provided novel evidence for a role of CD36 also in spinal cord trauma, a condition in which the effect of CD36 was found to be univocally deleterious. This commentary will provide a brief overview of the pathobiology of CD36 and its expanding role in diseases of the brain and spinal cord.

Recent evidence indicates an emerging role of innate immunity in CNS diseases (Amor and Woodroffe, 2014; Lampron et al., 2013). Although innate immunity receptors are essential for the detection and disposal of invading pathogens, recognition by these receptors of endogenous ligands generated during disease states, termed danger associated molecular patterns (DAMPs), can also trigger adaptive or maladaptive responses that have a profound impact on the outcome of the diseases process (Lampron et al., 2013; Ransohoff and Brown, 2012). The innate immunity receptor CD36 has recently been implicated in a wide variety of brain diseases, ranging from stroke to neurodegeneration. Recently, Myers et al. provided evidence that CD36 is also involved in spinal cord injury (SCI), extending the participation of this receptor to diseases of the spinal cord. In this commentary we will briefly review the role of CD36 in adaptive and maladaptive innate immunity responses in the CNS with the intent to place the findings of Meyer et al. in a more general context.

CD36: a multifunctional scavenger receptor of the innate immunity

CD36 is an 88-kDa membrane glycoprotein belonging to the class B scavenger receptors, a large family of pattern recognition receptors that recognize native and modified host-derived molecules and microbial pathogens (Prabhudas et al., 2014). CD36 has two transmembrane domains, two short cytoplasmic domains and a large, highly glycosylated extracellular domain. The extracellular domain comprises several ligand-binding sites. The 155–183

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amino acid region binds oxidized low-density lipoprotein (oxLDL), oxidized phospholipids, advanced glycated products, growth hormone-releasing peptide hexarelin, monoclonal antibodies, and apoptotic neutrophils (Collotteixeira et al., 2007). Another region, which spans amino acids 93 to 120, binds thrombospondin-1 (TSP-1) and other anti-angiogenic proteins containing TSP-1 homology repeat domain (TSR) (Silverstein and Febbraio, 2009). A third site (amino acids 146–164 or 145–171) binds the *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP-1), a protein specifically expressed by *P. falciparum* infected erythrocytes (Collotteixeira et al., 2007). CD36 can form macromolecular complexes with different co-receptors, a process that amplifies its functional repertoire (see Canton et al., 2013 for review). For example, CD36 can interact with toll-like receptors 2 (TLR2), TLR4 and TLR6, β 1 integrin, β 2 integrin, β 5 integrin and tetraspanins, such as CD9 and CD81 (Canton et al., 2013). Furthermore, the amyloid- β peptide (A β), another CD36 ligand, binds to a complex formed by CD36, CD47 and α ₆ β ₁ integrin receptors (Bamberger et al., 2003) (Fig. 1). A CD36–TLR2/4 complex seems to be involved in systemic inflammation (Hoebe et al., 2005), whereas in a model of cerebral ischemia CD36 has been suggested to form a complex with TLR2/1 heterodimers (Abe et al., 2010) (Fig. 1). On the other hand, A β or oxLDL has been reported to induce the assemblage of CD36 with TLR4/6 heterodimers (Stewart et al., 2009), suggesting that the association of CD36 with TLR occurs in multiple configurations.

Cellular localization and signaling pathways

First discovered in platelets (McGregor et al., 1989), CD36 has been localized to several cell types including monocytes/macrophages, dendritic cells, microglia, microvascular endothelium, astrocytes, erythroid precursors, hepatocytes, adipocytes, cardiac and skeletal myocytes and specialized epithelium (Cho et al., 2005; Silverstein and Febbraio, 2009). CD36 activates diverse intracellular signaling pathways depending on the ligand (Fig. 1). Because the intracellular amino terminus is short, the C-terminal tail is thought to be the main site of signal transduction (Collotteixeira et al., 2007; Silverstein and Febbraio, 2009). When CD36 binds to TSP-1, oxLDL or A β , the C-terminal region leads to activation of Src family tyrosine kinases, such as Fyn and/or Lyn, and mitogen-activated protein kinases (MAPKs) (Fig. 1). TSP-1 binding to CD36 induces the association of Fyn, activation of caspase 3-like proteases and stress-activated p38 and Jun-kinase (JNK) 1 mitogen-activated protein kinases (MAPKs) leading to suppression of angiogenesis (Jiménez et al., 2000, 2001). In macrophages, the interaction between CD36 and oxLDL induces Lyn phosphorylation and subsequent MAPK signaling, such as JNK1/2 activation that mediates the uptake of oxLDL (Rahaman et al., 2006). Additionally, the oxLDL uptake is also regulated by Vav. Vav is a scaffold protein for various signaling molecules including dynamin. The activation of Vav by Lyn induces the Vav–dynamin interaction, regulating oxLDL uptake (Y. M. Park, 2014; Rahaman et al., 2011). Furthermore, internalized oxLDL can bind to peroxisome proliferator-activated receptor- γ (PPAR- γ) and up-regulate the expression of CD36 (Nagy et al., 1998), facilitating further uptake of oxLDL (Y. M. Park, 2014). In microglia, CD36 engagement by A β initiates a signaling cascade involving Lyn, Fyn, p44/42 MAPKs (Moore et al., 2002) and Vav (Wilkinson et al., 2006). Vav also acts as a guanine nucleotide exchange factor for Rac1 and Rho GTPases. Upon interaction with

fibrillary A β , Vav activates Rac1, inducing its translocation to the membrane and interaction with other NADPH oxidase subunits to form the active oxidase complex and produce superoxide (Wilkinson et al., 2006). A new role of CD36 as a central regulator of inflammasome activation in sterile inflammation has been recently unveiled (Sheedy et al., 2013). CD36-TLR4/6 complex formation induced by the binding of either A β or oxLDL to CD36, leads to prime NLRP3 inflammasome, a complex involved in the proteolytic activation of caspase-1 and interleukin-1 β (IL-1 β) secretion (Lamkanfi and Dixit, 2012). CD36 facilitates the accumulation and intra-lysosomal conversion of oxLDL into insoluble crystals and soluble A β into amyloid oligomers and fibrils, triggering the activation of NLRP3 and IL-1 β secretion (Sheedy et al., 2013). CD36 signaling also leads to NF- κ B activation. Upon ligand binding, CD36 induces the recruitment of TLR heterodimers (TLR1/2, TLR2/4) activating myeloid differentiation factor-88 (MyD88)-dependent pathways. Assembly of MyD88, IL-1R-associated kinase and TNF receptor associated factor-6 ultimately leads to a nuclear translocation of NF- κ B, which, in turn, induces the synthesis of pro-inflammatory cytokines (Fig. 1). This process has been implicated in the inflammatory reaction contributing to atherosclerosis (Janabi et al., 2000) and cerebral ischemic injury (Abe et al., 2010; Kunz et al., 2008).

CD36 functions

Due to its expression in diverse cells and capacity to recognize a large number of ligands, CD36 is involved in a wide variety of functions in various cells and organs (Silverstein and Febbraio, 2009). CD36 inhibits angiogenesis through its binding of TSP-1 (Asch et al., 1987; Dawson et al., 1997) and modulates lipid metabolism by the translocation of long-chain fatty acids in adipocytes, heart and skeletal muscle (Abumrad et al., 1993; Febbraio et al., 2001). In macrophages, CD36 recognizes oxidatively modified lipids present in the membrane of apoptotic cells (Albert et al., 1998; Ren et al., 1995) and lipoprotein components of bacterial cell walls (Hoebe et al., 2005), triggering their cellular internalization and clearance. Thus, CD36 participates in the clearance of apoptotic cells produced during organ development, tissue homeostasis and infection (Prabhudas et al., 2014). On the other hand, recognition and uptake of oxLDL by CD36 in macrophages leads to the formation of foam cells which may play a role in the development and stability of atherosclerotic plaques (Febbraio et al., 2000; Y. M. Park, 2014). For example, an imbalance between CD36-mediated lipid uptake and ABCA1-mediated lipid efflux has been implicated in carotid plaque instability and ulceration, which underlies thromboembolic stroke (Isoviita et al., 2010).

Opposing roles of CD36 in CNS diseases

Several lines of evidence suggest a contribution of CD36 to a number of CNS diseases (Table 1). However, the role of CD36 is double edged, and can be either protective or destructive depending on the nature of the disease process and its stage of development. In cerebral malaria, erythrocytes infected with *P. falciparum* adhere to microvascular endothelium through different molecules including CD36 (Oquendo et al., 1989). The cytoadhesion triggers the sequestration of the parasite in post-capillary brain endothelium, a hallmark of cerebral malaria (Pongponratn et al., 2003). However, CD36 may also have a

beneficial effect in this disease because the binding of PfEMP-1 to CD36 on macrophages may also facilitate the clearance of the parasite (Smith et al., 2003).

In cerebral ischemia, CD36 plays a key role in promoting inflammatory responses, although the ligands remain unknown. CD36 expression is up-regulated in microglia, astrocytes and/or infiltrating macrophages following ischemia (Cho et al., 2005). CD36 signaling in microglia/macrophage leads to the production of reactive oxygen species (ROS) (Cho et al., 2005) and NF- κ B activation (Kunz et al., 2008), contributing to ischemic injury (Cho et al., 2005; Kim et al., 2012; Kunz et al., 2008) (Fig. 1). On the other hand, differential expression of CD36 in specific subsets of cells following ischemia might be beneficial (Cho and Kim, 2009). For example, PPAR- γ induced upregulation of CD36 in microglia/macrophages has been recently shown to participate in the phagocytic disposal of neutrophils, contributing to the resolution of post-ischemic inflammation and promoting tissue repair (Ballesteros et al., 2014). Although PPAR- γ represses inflammation by inhibiting NF- κ B, this effect seems to be independent of CD36 signaling (Chawla et al., 2001). Additionally, CD36 may participate in the astroglial scar formation after ischemia (Bao et al., 2012). In contrast to adult stroke, the deletion of CD36 in a neonatal stroke model is detrimental, probably due to an impaired removal of apoptotic cells (Woo et al., 2012). Similarly, in models of cerebral hemorrhage, CD36 expression on macrophage/microglia is also associated with an augmented phagocytic activity promoted by PPAR- γ and hematoma resolution (Fang et al., 2014; Zhao et al., 2007). Interestingly, a slowing of cerebral hematoma re-absorption has also been reported in 11 patients with a null mutation of CD36 (Fang et al., 2014), supporting the involvement of this receptor in human hemorrhagic stroke.

CD36 has also been implicated in the mechanisms of Alzheimer's Disease (AD), the most common form of dementia in the elderly. A β , a key causative factor in AD, binds CD36 in microglial cells, triggering NADPH oxidase-mediated oxidative stress and pro-inflammatory responses (Coraci et al., 2002; El Khoury et al., 2003; Moore et al., 2002) (Table 1). Moreover, in a mouse model of AD, CD36 has been implicated in the mechanisms of the alterations in cerebrovascular function and in the cognitive deficits induced by A β (Table 1). Thus, the deletion of CD36 in mice overexpressing the amyloid precursor protein (Tg2576 mice) ameliorates the regulation of the cerebral circulation and counteracts the deterioration in cognitive function observed in these mice (Park et al., 2011, 2013). These beneficial effects are associated with reduction in the deposition of A β in cerebral blood vessels (amyloid angiopathy), but not in the brain parenchyma (amyloid plaques) (Park et al., 2013) implicating CD36 specifically in the mechanisms of vascular A β accumulation. On the other hand, CD36 has also been reported to have opposite effects on amyloid deposition, contributing to the clearance of amyloid plaques. PPAR- γ -stimulated microglial phagocytosis, mediated by CD36 upregulation, promotes A β clearance from the brain parenchyma and reduces amyloid plaques (Yamanaka et al., 2012). These conflicting effects of CD36 on A β trafficking and clearance cannot be easily reconciled at the present, but are likely to be related to differences in the animal models and experimental approaches used. Nevertheless, these findings provide proof-of-principle that CD36 can affect diverse aspects of the pathobiology of A β , which may be relevant to distinct phases of the disease process in AD. Thus, the deleterious vascular effects of CD36 may predominate in the early phase of

the disease, whereas the beneficial effects on microglial phagocytosis and amyloid clearance may be relevant at later times. However, this hypothesis requires experimental verification.

CD36 contributes to spinal cord injury

The recent paper of Myers et al. also implicates CD36 in the spinal cord injury (SCI) (Myers et al., 2014). Using a model of spinal cord contusion, the authors showed that CD36 deficient mice exhibit a modest but sustained improvement of motor function. These effects were associated with a relative sparing of white matter, an effect most evident in the caudal portions of the lesion. Then, the authors set out to elucidate the mechanisms of the protective effect exerted by CD36 deletion. CD36 absence resulted in an increase in the number of perfused microvessels associated with a reduction in vascular oxidative stress and suppression of markers of endoplasmic reticulum (ER) stress. Furthermore, the number of infiltrating inflammatory cells was reduced, consistent with the suppression of the inflammatory response associated with the injury. To follow up on the reduction in vascular ER stress observed in CD36-deficient mice, the authors established an in vitro system to examine the effect of oxidative stress on endothelial cells. They found that CD36^{-/-} endothelial cells are less susceptible to oxidative damage produced by the pro-oxidant 4-hydroxynonenal. The effect was coupled with a reduction in markers of ER stress, implicating CD36 in the ER stress initiated by oxidative injury. These observations are consistent with the multifunctional nature of the biological actions of CD36 (Fig. 1). Thus, the lack of CD36 may prevent microvascular loss, by suppressing endothelial cell oxidative damage, ER stress and TSP-dependent anti-angiogenic effects, while attenuating the associated inflammatory reaction. Interestingly, dampening the innate immunity response by CD36 deletion did not compromise long-term repair processes after spinal cord injury, since the functional improvement persisted up to 42 days after lesion. These findings of Myers et al. provide the first demonstration that CD36 is also involved in the mechanisms of white matter damage injury after SCI, and raise the prospect that this receptor may also play a role in the white matter disease underlying vascular cognitive impairment (Iadecola, 2013). Furthermore, their data highlight the role of CD36 in the development of ER stress, particularly in endothelial cells exposed to oxidative injury, which is also relevant to a host of acute and chronic brain diseases associated with endothelial dysfunction and damage (Faraci, 2011).

Conclusions

The harmful maladaptive consequences of sterile inflammation and innate immunity are becoming better appreciated in several CNS diseases. Due to its participation in a wide variety of CNS pathologies, approaches to modulate the signaling activity of CD36 may offer the opportunity to develop new therapeutic interventions for diseases ranging from neurodegeneration to spinal cord injury. However, due to its double-edged role in many pathological processes, approaches to enhance or suppress CD36 signaling would require targeting specific phases of the disease process. Therefore, a better understanding of the stage-dependent role of CD36 in tissue injury and repair would be required to harness the full therapeutic potential of this multifaceted receptor. Furthermore, reliable disease

biomarkers would be needed to apply the therapeutic intervention at specific stages of the disease process, when interfering with CD36 signaling would be most beneficial.

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Fig. 1.

CD36 signaling pathways: CD36 activates different intracellular signaling pathways depending on the ligand, co-receptor, and cell type. In endothelial cells, CD36, Fyn Src-kinase, caspase-3-like protein and p38 and JNK1 MAP kinases are essential for the induction of apoptosis and angiogenesis inhibition by TSP-1 (Jiménez et al, 2000, 2001). The interaction of oxLDL with CD36 activates a signaling complex, consisting of Lyn, other Src kinase, and Mek-2, which phosphorylates JNK and leads to foam cell formation (Rahaman et al, 2006). Vav activation via Lyn also regulates foam cell formation by controlling internalization of oxLDL (Rahaman et al, 2011). The association of CD36 with CD47 and $\alpha_6\beta_1$ integrin forms a multireceptor complex for A β on microglia, which activates specific Src family kinases (Lyn, Fyn or Syk) (Moore et al, 2002), and phosphorylates Vav (Wilkinson et al., 2006). Vav acts as a guanine nucleotide exchange factor for Rac-1, an essential component NADPH oxidase, leading to NADPH oxidase-mediated generation of reactive oxygen species and promoting phagocytosis (Wilkinson et al., 2006). In addition, the assembly of CD36 to TLR4/6 heterodimer, in response to oxLDL and amyloid- β , induces an inflammatory response through the activation of NLRP3 inflammasome (Sheedy et al, 2013). CD36 may also form a signaling complex with TLR heterodimers that activate NF- κ B in response to bacterial wall components (TLR2/6) or damaged cells (TLR2/1), which leads to the expression of inflammatory molecules (i.e. iNOS and Nox-2) (Abe et al, 2010; Hoebe et al, 2005). In addition, PPAR γ activation can upregulate the expression of CD36 on microglia/macrophage promoting the clearance of bacteria or apoptotic cells and contributing to resolve the inflammation (Ballesteros et al., 2014). Solid and dashed lines indicate direct and indirect activation of signaling pathways, respectively. f β A, β -amyloid

fibrils; IKK, inhibitor of κ B kinase iNOS, inducible nitric oxidase synthase; JNK, Jun N-terminal kinase; MAP kinases, mitogen activated protein kinases; Mekk-2, mitogen-activated protein kinase 2; MyD88, myeloid differentiation factor-88; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NF- κ B, nuclear factor Kappa B; oxLDL, oxidized low-density lipoprotein; PPAR γ , peroxisome proliferator-activated receptor gamma; TLR, toll like receptor; TRAF6, TNF receptor associated factor-6; TSP-1, thrombospondin 1.

Table 1
Diverse roles of CD36 in central nervous system pathologies

CNS disease	CD36 ligand	Cell type expressing CD36	CD36 role	Suggested mechanism	Reference
Cerebral malaria	<i>nd</i>	EC	Detrimental	Adhesion of infected erythrocytes to brain microvessels	Barnwell et al. (1989)
	PFEMP-1	Platelets	Detrimental	Adhesion of infected erythrocytes to platelets and accumulation in brain microvessels	Ockenhouse et al. (1989)
Cerebral ischemia	PFEMP-1	Monocyte/macrophage	Beneficial	Clearance of erythrocytes infected with <i>Gammatocytes</i> of <i>Plasmodium falciparum</i>	Smith et al. (2003) McGilvray et al. (2000)
	<i>nd</i>	Macrophage/Microglia and astrocytes	Detrimental	Brain injury by increased ROS production	Cho et al. (2005)
	<i>nd</i>	<i>nd</i>	Detrimental	Inflammation through nuclear factor- κ B activation	Kunz et al. (2008)
	<i>nd</i>	<i>nd</i>	Detrimental	<i>nd</i>	Kim et al. (2008)
	<i>nd</i>	<i>nd</i>	Detrimental	Inflammation through association with TLR2/1	Abe et al. (2010)
	<i>nd</i>	Brain cells and infiltrating leukocytes	Detrimental	Worsening of ischemic injury through regulation of the MCP-1/CCR2 chemokine axis in hyperlipidemic conditions	Kim et al. (2012)
	<i>nd</i>	Microglia	Beneficial	Lack of CD36 affects removal of apoptotic cells and enhances brain injury after neonatal stroke	Woo et al. (2012)
Cerebral hemorrhage	<i>nd</i>	Microglia/macrophage	Beneficial	Increased CD36 expression by PPAR γ activation promotes resolution of inflammation by phagocytosis	Ballesteros et al. (2014)
	<i>nd</i>	Astrocytes	?	<i>nd</i>	Bao et al. (2012)
	<i>nd</i>	Microglia/macrophage	Beneficial	PPAR γ promotes hematoma resolution via phagocytosis in a CD36-dependent manner	Zhao et al. (2007)
Amyloid- β -related pathologies	<i>nd</i>	Microglia	Detrimental	Blood-brain barrier disruption	Ueno et al. (2011)
	<i>nd</i>	Microglia	Beneficial	Hematoma absorption by promoting RBC phagocytosis	Fang et al. (2014)
	A β	Macrophage/microglia	Detrimental	Pro-inflammatory response through Fyn and Lyn-MAPK pathway	Moore et al. (2002)
	A β	EC and microglia	Detrimental	Oxidative stress	Coraci et al. (2002)
	A β	Macrophage/microglia	Detrimental	Initiation of inflammatory response	Khoury et al. (2003)
Parkinson's disease	A β	EC	Detrimental	Oxidative stress and cerebrovascular dysfunction	Park et al. (2011)
	A β (?)	EC and perivascular macrophage	Detrimental	<i>nd</i>	Bin Wu et al. (2012)
	A β	Microglia	Beneficial	PPAR γ induced phagocytosis of amyloid- β	Yamanaka et al. (2012)
	A β	Pericyte	Detrimental	Promotes vascular amyloid deposition and neurovascular dysfunction	Park et al. (2013)
	α -Synuclein (?)	<i>nd</i>	Detrimental	Microglial activation by α -synuclein	Su et al. (2008)
Prion disease	<i>nd</i>	Microglia	Detrimental	CD36 is involved in microglia activation by prion protein	Kouadir et al. (2012)

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CNS disease	CD36 ligand	Cell type expressing CD36	CD36 role	Suggested mechanism	Reference
Spinal cord injury	<i>nd</i>	EC and macrophage	Detrimental	CD36 signaling contributes to inflammation and microvascular dysfunction	Myers et al. (2014)

Abbreviations: CCR2, chemokine (C–C motif) receptor 2; EC, endothelial cells; A β , amyloid- β ; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein 1; *nd*, non-determined; PIEMP-1, *P. falciparum* erythrocyte membrane protein 1; PPAR γ , peroxisome proliferator activated receptor-gamma; ROS, reactive oxygen species.