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REVIEW ARTICLE

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CD36 – A novel molecular target in the neurovascular unit

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Abstract

CD36 is an integral membrane protein primarily known for its function as a fatty acid transporter, yet also playing other biological roles from lipid metabolism to inflammation modulation. These pleiotropic effects are explained by the existence of multiple different ligands and the extensive distribution in numerous cell types. Moreover, the receptor is related to various pathologies and it may prove to be a good target for prospective therapeutic strategies. In the neurovascular unit (NVU), CD36 is expressed in cells like microglia, microvascular endothelial cells, astrocytes and neurons. In the normal brain, CD36 was proven to be involved in phagocytosis of apoptotic cells, oro-sensory detection of dietary lipids, and fatty acid transport across the blood brain barrier (BBB). CD36 was also acknowledged as a potentially important player in central nervous system (CNS) disorders, such as Alzheimer Disease-associated vascular dysfunction and oxidative stress and the neuroinflammatory response in stroke. Despite continuous efforts, the therapeutic arsenal for such diseases is still scarce and there is an increasing interest in discovering new molecular targets for more specific therapeutic approaches. In this review, we summarize the role of CD36 in the normal function of the NVU and in several CNS disorders, focusing on the dysregulation of the NVU and the potential therapeutic modulation.

KEYWORDS

Alzheimer Disease, CD36, neuroinflammation, neurovascular unit, oxidative stress, stroke, vascular dysfunction

Abbreviations: AD, Alzheimer Disease; ApoE4, apolipoprotein E4; BBB, blood-brain barrier; BEC, brain endothelial cells; CAA, cerebral amyloid angiopathy; CNS, central nervous system; CSF, colony-stimulating factor; FA, fatty acids; FAT, fatty acid translocase; HDL, high density lipoprotein; LXR, liver x receptors; NINDS, National Institute of Neurological Disorders and Stroke; NVU, neurovascular unit; oxLDL, oxidized low density lipoprotein; PD, Parkinson Disease; Pgp, permeability glycoprotein 1; PI3K, phosphoinositide 3 kinase; ROS, reactive oxygen species; SRB1, scavenger receptor class B member 1; SVD, small vessel disease; TLR, toll-like receptor; TSP, thrombospondins.

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1 | INTRODUCTION

Recent advances in neuroscience have drawn attention to a series of malfunctioning processes in the ageing neurovascular unit (NVU), acting as potential risk factors for age-related neurodegeneration. The term "neurovascular unit" was first mentioned in a report of the Stroke Progress Review Group, a group formed in 2001 and tasked to summarize progress and provide recommendations for the National Institute of Neurological Disorders and Stroke (NINDS) (Grotta, 2013) (for review see (Iadecola, 2017)). Throughout the years, several definitions and features of NVU have been used by the scientific community (Table 1).

Comprised of parenchymal cells such as neurons, astrocytes and microglia, as well as endothelial cells with their tight junctions, basal lamina, associated pericytes and the anatomical and chemical interactions between them, NVU is responsible for "sensing" the microenvironment of the brain and triggering the needed vasodilation or vasoconstriction responses (Figure 1) (Muoio et al., 2014; Netto et al., 2018). The continuous endothelial layer lining the blood vessels of the central nervous system (CNS) holds unique properties which regulate the exchange of molecules between the blood and the brain, building the blood–brain barrier (BBB).

The organization and interplay among neurons, glia, and blood vessels have fostered the concept of the neuro- vascular unit (NVU) as a distinctive structural and functional entity within the central nervous system that is worthy of study in its own right.

The ultrastructural and molecular changes of NVU cellular components and especially of the BBB, represent one of the prerequisites of vascular dysfunction, in turn leading to cognitive impairment. Endothelial dysfunction is one of the major determinants of the structural and functional alterations of the brain microenvironment and has an increased likelihood to end in cerebral small vessel disease (SVD) (Poggesi et al., 2016). The permeability of BBB increases with age, and leakage of serum albumin can be identified in vascular dementia as well as in severe white-matter lesions (Simpson et al., 2007). Moreover, brain endothelial cells (BEC) are extremely sensitive and react to a large array of circulating

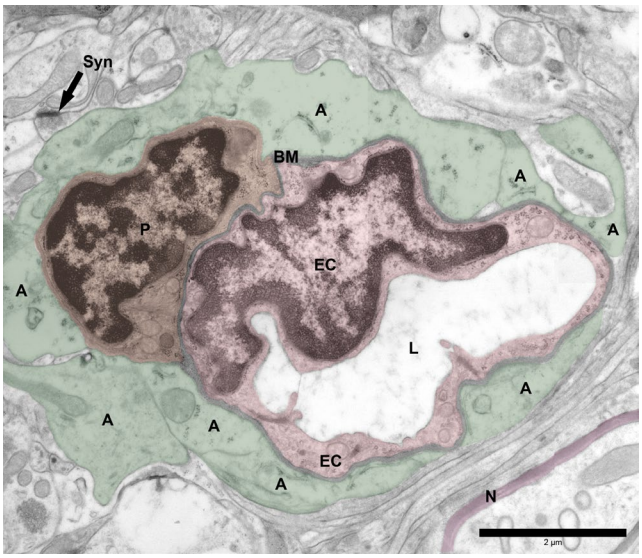

FIGURE 1 Electron micrograph showing the components of the NVU and the intimate connections between them: A – astrocyte, BM – basement membrane, EC – endothelial cell, L – lumen, N – neuron, P – pericyte, Syn – synapse

TABLE 1 Evolution of definitions and features of the neurovascular unit (NVU)

Definition	Features	References
NVU as "the organization and interplay among neurons, glia and blood vessels"	• distinctive structural and functional entity within the central nervous system • involves multiple cell types, microvasculatures and various genomic/proteomic/ionic functional entities	Lin et al., (2005)
NVU as "the intimate relationship between the brain and its vessels"	• important role in the coupling between neural activity and blood flow	Iadecola, (2017)
NVU as "a relatively recent concept in neuroscience that broadly describes the relationship between brain cells and their blood vessels"	• comprised of neurons, perivascular astrocytes, microglia, pericytes, endothelial cells (EC) and the basement membrane (BM) • intimate and complex associations are shared between the components of NVU, leading to their classification as a single functioning unit • responsible for the maintenance of a highly selective BBB, cerebral homeostasis, as well as the control of cerebral blood flow (CBF)	Bell et al., (2019)
NVU as "the strict anatomical/functional interaction occurring between neurons, glial cells and brain vessels"	• fundamental role in coupling the energy demand of activated brain regions with regional cerebral blood flow • includes the BBB • active role in neuroinflammation • participates to the glymphatic system	Giorgi et al., (2020)

molecules, which can induce transcriptional changes in BEC and further impact the structure and function of the brain, increasing the likelihood of neurodegenerative disease (Chen et al., 2020). Additionally, the BBB multidrug resistance decreases with ageing in a region-specific manner, eventually leading to a poor clearance of neurotoxic compounds and accumulation of oxidative stress products, this too promoting neurodegenerative disease (Whitton, 2007).

Despite constant progress in neurosciences, the therapeutic armamentarium against both ageing and neurodegenerative diseases is still limited. Therefore, one of the major aims is to extend the view on the underlying pathophysiological mechanisms by discovering new molecular players that could be specifically targeted and modulated by drugs.

So far, only a handful of molecular targets were shown to take part in the progression of BBB damage, neuronal degeneration, neuroinflammation and immune cell infiltration. Mutated genes or malfunctioning cellular transporters/receptors have been highlighted as contributing to BBB dysregulation (Sweeney et al., 2019). For example, apolipoprotein E4 (ApoE4) is a well-known risk factor in Alzheimer Disease (AD), being involved in BBB disruption, age-related cognitive decline and altered clearance at NVU level (Chia-Chen et al., 2013). Furthermore, permeability glycoprotein 1 (Pgp) is an ATP-dependent efflux pump found in the NVU which can contribute to dysfunctions of the BBB in neurodegenerative diseases like Parkinson's disease (Bartels et al., 2008; Kortekaas et al., 2005). Yet another example is CD36, shown to be essential to the pathogenesis of cerebrovascular oxidative stress and neurovascular dysfunction (Park et al., 2011).

CD36, also known as fatty acid translocase (FAT) or scavenger receptor class B member 1 (SRB1), is an integral membrane glycoprotein with two transmembrane domains and both termini in the cytoplasm (Febbraio et al., 2001). At tissue level, CD36 is highly expressed in heart muscle, adipose tissue and bone marrow, has medium expression levels in breast and skin, but can also be found in the small intestine and even brain. CD36 was detected on the surface of various cell types such as platelets, monocytes, adipocytes, myocytes, hepatocytes, enterocytes, retinal and mammary epithelial cells, endothelial cells of the microvasculature (Mitchell et al., 2011), as well as neurons (Glezer et al., 2009). At subcellular level, CD36 is mostly found in lipid rafts, membrane microdomains known as caveolae – where it colocalizes with caveolin-1 (Febbraio et al., 2001), or in mitochondria (Campbell et al., 2004). The signal transduction processes that occur in these regions involve molecular and functional interactions between CD36 and either Src-family kinases or integrins. The outcome of the signalling cascade can be phosphorylation of downstream receptors, cytoskeletal rearrangement during phagocytosis and cell migration or even apoptosis mediated by thrombospondins 1 and 2. On the other hand, mutations in the cytoplasmic tail of CD36 can render it incapable of complexing with integrins and thereby inhibit signal transduction (Lawler & Lawler, 2012).

Depending on tissue distribution and binding affinity, the functions of CD36 can are highly variable, but can include lipid uptake, long-chain fatty acid (FA) metabolism, cholesterol efflux and homeostasis, adhesion and transduction in inflammation, as well as phagocytosis and endocytosis (Abumrad et al., 2005). CD36 has proven to be a candidate gene for the development of atherosclerotic lesions (Kuchibhotla et al., 2008). Putative ligands for CD36 are long-chain fatty acids, lipoproteins (oxidized low density lipoproteins – *oxLDL*, high density lipoproteins – *HDL*), thrombospondin-1, advance glycation endproducts, chondroitin sulfate, pathogenic agents such as *Plasmodium falciparum* and, most recently, amyloid-beta (Husemann et al., 2002; Park et al., 2013).

In the brain, CD36 gene and protein expression have not been extensively analysed outside the context of its function as a FA transporter (Mitchell et al., 2011). However, recent studies brought into focus the potential involvement in brain tissue homeostasis (Bruce et al., 2017).

The aim of this review is to characterize the role of CD36 in both normal and pathological NVU by highlighting its potential involvement in neuroinflammation, neurovascular dysfunction and neurodegeneration.

2 | CD36 EXPRESSION IN THE NVU

Due to the anatomical particularities of the NVU, such as the tight junctions formed by endothelial cells, circulating molecules from plasma are more likely to use transcellular routes instead of undergoing paracellular diffusion (Dalvi et al., 2014; Daneman & Prat, 2015). Although neurons are not in direct contact with the vascular compartment, there is a strong relationship between local neural activity and subsequent changes in cerebral blood flow, known as neurovascular coupling (Pasley & Freeman, 2008).

For example, the accumulation of blood triglycerides triggers a possible response in the NVU that has been linked to cerebrovascular inflammation and vascular dementia. Microvascular endothelial cells and astrocytes appear to have increased lipid droplet formation and accumulation when exposed to products of triglyceride-rich lipoprotein hydrolysis; moreover, cell stress pathways are also activated and culminate in the production of inflammatory cytokines, thus promoting neurovascular injury and inflammation (Lee et al., 2017). Lipid accumulation and development of neurodegenerative disorders can also be induced by downregulation of nuclear receptors that play a role in the control of cholesterol homeostasis, such as liver x receptors (LXRα and β) in astrocytes and

microglia (Czuba et al., 2017). In line with previous reports, we have recently documented the accumulation of lipid droplets in the basement membrane of the brain capillaries of aged mice, resulting in possible alterations of the BBB (Ceafalan et al., 2019). The molecular mechanisms of these processes are still under investigation and might rely on the activity of lipid transporters such as CD36.

A number of studies reported the expression of CD36 at all levels of the NVU and have made the first steps towards understanding the biological mechanisms that involve CD36 in either neuroprotection or neurovascular dysfunction (Glezer et al., 2009; Park et al., 2011; Sankar et al., 2018).

Although microglia is a transient component within the NVU, it can modulate various physiological or inflammatory processes, with the participation of scavenger receptors (Bell et al., 2019). The presence of CD36 on cultured microglia and microvascular endothelial cells from both mouse and human brain has been reported and associated with the synthesis of reactive oxygen species (ROS), which indicates possible roles of this receptor in homeostasis and neuropathology (Husemann et al., 2002; Park et al., 2013). Increasing evidence suggests the involvement of CD36, CD47 and integrins expressed by microglia in creating complexes that bind fibrillary proteins such as fibrillary amyloid-beta in AD, leading to proinflammatory response (Bamberger et al., 2003) and cerebral amyloid angiopathy (CAA), which, in turn, induces vascular oxidative stress, cerebrovascular dysfunction and subsequent cognitive deficits (Park et al., 2013). Additionally, interactions between CD36 and Toll-like receptors 4 and 6 (TLR4, TLR6) can culminate in the activation of microglia in processes of neuroinflammation and neurodegeneration (Shmuel-Galia et al., 2017).

On microvascular endothelial cells, CD36 colocalizes with CD31, an endothelial marker (Park et al., 2011). When expressed on these cells, CD36 mostly interacts with thrombospondins 1 and 2 (TSP-1, TSP-2), proteins that mediate cell-to-cell adhesion and cell-to-matrix interactions, by activating signalling pathways that end in endothelial cell apoptosis, hence its anti-angiogenic nature (Armstrong & Bornstein, 2003).

The expression of CD36 by astrocytes has been acknowledged so far to mediate both phagocytosis and inflammatory signalling through phosphoinositide 3 kinase (PI3K)/Akt signalling pathways (Sankar et al., 2018). In neurodegenerative diseases like AD, this decrease in astrocyte activity leads to impaired amyloid clearance (Sankar et al., 2018). Further investigation of the intimate collaboration between astrocytes and neurons is needed, since these cell types appear to be involved in lipid sensing and metabolism.

Uniquely positioned between endothelial cells, astrocytes and neurons, pericytes are a key component of the NVU – they integrate, coordinate and process signals from neighbouring cells in order to modulate the permeability of the BBB (Sweeney et al., 2016). Being directly in contact with the microvessels of the brain, pericytes also contribute to the optimal blood flow supply in the NVU and are involved in blood vessel formation, vessel maintenance and permeability, angiogenesis, clearance, and immune cell migration (McConnell et al., 2017). Pericyte damage has been previously reported in the neurovascular dysfunction associated with AD. To our knowledge, the expression of CD36 in brain pericytes has not been described yet. However, indirect evidence towards the role of CD36 on pericytes comes from a study on amyloid precursor protein (Tg2576) knockout mice, where pericyte damage was reported to amend after CD36 deletion, indicating CD36 as novel molecular target for cerebral amyloid angiopathy and other related conditions (Park et al., 2013).

Moreover, genes that encode CD36 appear to be constitutively expressed in specific neuronal cells. As shown using immunostaining and histochemistry, CD36 transcripts are to be found in brain regions involved in pheromone responses and reproductive behaviour (Glezer et al., 2009). Some of these regions are direct or indirect targets of the main olfactory bulb- and accessory olfactory bulb projections, including the dorsal taenia tecta, piriform cortex, bed nucleus of the stria terminalis, nucleus of the lateral olfactory tract, medial amygdaloid nucleus and posterolateral cortical amygdaloid nucleus. Other regions are involved in sight, such as the medial preoptic nucleus. Transitional regions where CD36 is expressed are the paraventricular thalamic nucleus, the rostral paraventricular nucleus of the hypothalamus, the ventral premammillary nucleus of the hypothalamus, lateral hypothalamic areas and the caudate putamen. By contrast, CD36 was not found to be expressed in the hippocampus, except for the pyramidal layer (Glezer et al., 2009; Xavier et al., 2016).

3 | CD36 IN NORMAL BRAIN FUNCTION

As microglia in the human brain express low levels of CD36, it has been suggested that CD36 might be involved in the phagocytosis of apoptotic cells in the CNS, playing the role of a scavenger receptor (Coraci et al., 2002). However, CD36 is believed to have additional functions than leukocyte biology and could even be used in labelling specific brain circuits. Firstly, areas where CD36 mRNA is highly expressed, such as the ependymal cells lining the fourth ventricle, are probably associated with the well-described immune function of the lipid receptor (Gordon, 2002). Secondly, according to Glezer et al., the expression of CD36 in the mouse brain might be also associated with neural circuits involved in reproductive behaviour (Glezer et al., 2009).

Functional studies, using knockdown animal models, have placed CD36 in the context of various mechanisms related to lipid metabolism.

CD36 was shown to be involved in achieving nervous control of energy balance at the hypothalamic level. Several discrete neural networks in the hypothalamus were described as having the ability to detect variation of circulating long chain FA in order to regulate food intake in a phenomenon called "*lipid sensing*". The molecular mechanisms involved are still incompletely characterized, yet they seem to connect membrane components, such as CD36, with intracellular events such as FA oxidation or synthesis of diacyl-glycerol and ceramides (Cruciani-Guglielmacci & Fioramonti, 2019). Hypothalamic expression of CD36 in FA sensitive neurons seems to depend on the metabolic state of the organism, and it can vary depending on fasting/overfeeding periods. For example, expression of CD36 in the hypothalamus can decrease by 40% after 48 hr fasting periods or increase by 36% after 2 months of high fat diet (Moullé et al., 2012). Observations on CD36 depleted rats seem to indicate increased levels of plasma leptin and subcutaneous fat depositions, as well as an abnormal glucose tolerance in the case of CD36 deficiency in the ventromedial hypothalamus (Le Foll et al., 2013).

CD36 has been also studied in order to understand the mechanisms behind lipid supply for proper development, differentiation and metabolism of brain cells.

CD36 was described as a transporter for long-chain FA across BBB. However, in the case of CD36 deficient mice, there were no statistical differences in polyunsaturated FA concentrations recorded from different brain regions (cortex, hippocampus, cerebellum), as compared to wild-type mice, suggesting the existence of other mechanisms for maintaining brain FA concentrations (Song et al., 2010). Few phenotypical differences have been recorded in terms of cognitive performance - for example, although CD36 null mice seem to have a learning deficit (Abumrad et al., 2005), it is not yet clear whether the absence of brain CD36 has an influence on cognition.

Increasing evidence is highlighting the role of CD36 as a receptor in the olfactory and gustatory pathways (Julliard et al., 2017; Laugerette et al., 2005; Simons et al., 2011). For example, one model proposes the activation of phospholipase C via CD36 in neurons of the central olfactory areas, which leads to the generation of inositol 1,4,5-triphosphate, which induces calcium release from the endoplasmic reticulum, the depolarization of the plasma membrane via TRPM5 channels, culminating with neurotransmitter release (El-Yassimi et al., 2008). Similar mechanisms have been described for the taste buds (Gaillard et al., 2008), confirmed by the addition of CD36 inhibitors such as sulfo-N-succinimidyl oleate ester, which are associated with alterations of excitatory and inhibitory effects in neurons (Le Foll et al., 2013). In fact, CD36 is so important for calcium signalling that in circumvallate taste buds, lower levels of CD36 expression induced by high-fat diet have been associated with diminished sensitivity to fatty taste, which likely contributes to the progression of obesity (Zhang et al., 2011).

Additional data regarding the implications of CD36 in lipid metabolism come from Asian populations with natural CD36 deficiency, characterized by increased plasma triglyceride levels, decreased HDL, impaired glucose tolerance and delayed response of insulin secretion and blood pressure (Miyaoka et al., 2001). CD36 can be a gene associated with disordered FA metabolism, glucose intolerance and insulin resistance, as previously confirmed by quantitative trait loci mapping in spontaneously hypersensitive rats compared to normotensive control strains (Kadlecová et al., 2004). Altogether, any disruption in FA sensing has the potential to reduce the activity of brain reward systems, thus resulting in compensatory overeating behaviour and potentially lipid metabolism alterations (Volkow et al., 2011).

4 | CD36-RELATED NEUROINFLAMMATION, VASCULAR OXIDATIVE STRESS AND NEUROVASCULAR DYSFUNCTION IN ALZHEIMER DISEASE

AD is a neurodegenerative disease in which the pathological hallmarks are intracellular neurofibrillary tangles formed by the aggregation of tau protein and extracellular amyloid plaques containing amyloid-beta aggregates (Bloom, 2014). Vascular dysfunction is an important but often neglected feature of AD, that contributes to the alteration of the BBB (Jellinger, 2010). Amyloid-beta exerts several effects on the vessel wall, such as damage of the vessel cells and alteration of vasoreactivity (Deane et al., 2003; Thomas et al., 1996). Besides the parenchymal accumulation, amyloid-beta is also deposited in the wall of small and medium cerebral vessels, leading to amyloid angiopathy (Jellinger, 2010). Cerebral amyloid angiopathy can also occur independently of AD, sporadically or associated with specific gene mutations and it is an important cause of cerebral microbleeds, haemorrhagic stroke and cognitive impairment (Jellinger, 2010). Another key mechanism in AD pathophysiology is neuroinflammation, as it seems that several immunologic mechanisms are dysregulated, such as microglia activation by misfolded proteins and overexpression of pro-inflammatory cytokines, altogether amplifying the process of neurodegeneration (Minter et al., 2016).

The hypothesis that CD36 plays a role in the pathophysiology of AD emerged from studies showing that microglia express CD36 and that the receptor is activated by

amyloid-beta, thereby promoting the production of ROS (Bamberger et al., 2003; Coraci et al., 2002). Additionally, the interaction between CD36 expressed on cerebrovascular endothelial cells and amyloid-beta generates vascular oxidative stress, by activating the NADPH oxidase (Park et al., 2011). This process induces cerebrovascular dysfunction and alters the brain vasoreactivity (Park et al., 2011).

Another CD36-mediated oxidative stress response in AD models is induced by brain perivascular macrophages (Park et al., 2017). These cells are a distinct type of brain mononuclear cells involved in brain homeostasis and innate immunity that reside in the perivascular space, which are known to have an important role in the physiological clearance of amyloid-beta from the brain tissue (Faraco et al., 2017; Park et al., 2017). Brain perivascular macrophages express CD36 and are strong inducers of ROS (Faraco et al., 2017; Park et al., 2017). Numerous CD36-mediated interactions between amyloid-beta and perivascular macrophages occur in the perivascular space, leading to the production of large amounts of ROS, which in turn contributes to vascular dysfunction (Park et al., 2017). Moreover, the binding of amyloid-beta to CD36 expressed on the surface of macrophages activates the NLRP3-inflammasome complex, which promotes a pro-inflammatory response consisting in the secretion of pro-inflammatory cytokines (IL-1beta, IL-1alfa, IL-18), thus amplifying neuroinflammation (Sheedy et al., 2013).

In cerebral amyloid angiopathy, CD36 seems to play an important role not only in ROS production, but also in the deposition of amyloid-beta (Park et al., 2013). In CD36-null mice, the lack of the receptor has a protective role in regard to the accumulation of vascular amyloid, but does not influence the formation of parenchymal amyloid plaques (Park et al., 2013).

More recently, an association emerged between a genetic variation of the CD36 gene (specifically, the A allele in SNP s3211892), and a significant increase in the risk of AD (Šerý et al., 2017). The mechanism behind this association involves changes in cholesterol regulation, formation of ROS, with the subsequent induction of neuroinflammatory cascades.

5 | CD36-RELATED NEUROINFLAMMATION IN OTHER CNS DISORDERS

5.1 | Parkinson disease (PD)

In the last decade, it became clear that inflammation plays a significant role in the pathophysiology of PD. One study showed that alpha-synuclein activates microglia in a process that involves CD36, promoting a pro-inflammatory response early in the disease (Su et al., 2008). Aggregated alpha-synuclein binds to microglial CD36, which recruits Fyn-kinase, leading to NF-kB activation through PKCδ tyrosine phosphorylation and, subsequently, to NLRP3 inflammasome activation (Panicker et al., 2019).

5.2 | Prion diseases

An important component of prion diseases is the activation of microglia by the prions, accelerating progression of the disease by enabling a pro-inflammatory status (Kouadir et al., 2012). CD36 is one of the receptors involved in the binding of prions to microglia, inducing the activation of these cells (Kouadir et al., 2012).

5.3 | Ischemic stroke

In acute ischemic stroke, the inflammatory response triggered by the damaged tissue plays an essential role in the ischemic lesion expansion. Therefore, stroke neuroinflammation is an appealing field of research that requires modulation of molecular targets having the potential to limit these consequences. Microglia and peripheral immune cells that infiltrate the damaged tissue play key roles in this process.

One of the first studies that showed the involvement of CD36 in the pathophysiology of stroke in a mouse model highlighted that CD36 is overexpressed in microglia and macrophages located in the cerebral ischemic tissue and contributes to the formation of ROS in the early phase of stroke (Cho et al., 2005). Also, in CD36-null mice the infarcted area was smaller and there was a better post-stroke clinical recovery in comparison with the wild-type (Cho et al., 2005). These data suggest that CD36 inhibition could be a promising therapeutic option in acute ischemic stroke albeit dependent on the timing of treatment. In a hyperlipidemic mouse model, the post-stroke treatment with a CD36 inhibitor did not show any improvement in the stroke outcome, instead a chronic treatment with a preventive role before onset of the acute stroke led to reduced brain swelling and a certain degree of reduction of the infarct size (Kim et al., 2020).

Although encouraging, solving the involvement of CD36 in ischemic stroke is far from trivial, mainly because the receptor is involved in different cellular processes and in different steps of the cerebral ischemic cascade as we will further describe. CD36, in cooperation with TLR2/1, initiates the inflammatory process that occurs in cerebral ischemia (Abe et al., 2010). Thus, CD36 stands at the "gate" of the cerebral inflammatory response by sensing danger molecules produced during the ischemic process (Abe et al., 2010). Indirectly, CD36 expressed in brain cells also facilitates the accumulation and activation of inflammatory cells in the parenchymal tissue (Garcia-Bonilla et al., 2015). After an ischemic stroke, cerebral endothelial cells secrete CSF3, a colony-stimulating

factor that attracts and promotes the infiltration and activation of neutrophils and is responsible for the production of ROS in the brain (Garcia-Bonilla et al., 2015). The secretion of CSF3 from endothelial cells is mediated by CD36, which is probably activated by the danger molecules released in stroke (Garcia-Bonilla et al., 2015). Another study suggested that overexpression of CD36 in the ischemic brain under hyperlipidemic conditions is mainly due to infiltrating peripheral immune cells (Kim et al., 2012). Moreover, for the proinflammatory injury to occur, peripheral CD36 co-activates the MCP1/CCR2 complex along with CD36 expressed on brain cells (Kim et al., 2012). These data suggest a synergistic action of both peripheral and brain CD36 in regulating the immune processes that take place in stroke (Kim et al., 2012).

However, not all data on the effects of CD36 overexpression is unfavourable, some suggesting an opposing, anti-inflammatory role of the receptor in certain situations. For instance, in the context of ischemic stroke, the activation of microglial PPAR-gamma by the antidiabetic drug rosiglitazone leads to the overexpression of CD36 on the surface of microglia, which facilitates the clearance of peripheral immune cells infiltrated in the brain, favouring the cessation of the inflammatory post-stroke process (Ballesteros et al., 2014). Another study highlights the positive anti-inflammatory effects of the infiltrated peripheral macrophages expressing CD36 in the later phase of the stroke, by assisting the phagocytosis of apoptotic cells and debris (Woo et al., 2016). Another process in which CD36 is involved is the post-ischemic glial scar formation, by favouring astrocyte activation and proliferation (Bao et al., 2012). This process cannot be precisely classified as either beneficial or harmful, because in the initial phase of the stroke it has a beneficial function, while later it becomes harmful, altering the local neuronal microenvironment.

5.4 | Haemorrhagic stroke

The previous mentioned role of PPAR-gamma-activated microglia that promotes phagocytosis via CD36 in ischemic stroke also applies to intracerebral haemorrhage, where CD36-mediated phagocytosis helps in the resolution of the hematoma (Zhao et al., 2007). Another study mentioned the beneficial role of microglia and infiltrated peripheral macrophages expressing CD36 in promoting hematoma absorption, while TLR4 activation mitigates this effect (Fang et al., 2014).

6 | THERAPEUTIC MODULATIONS OF CD36

In the last few years, CD36 has been garnering attention as a potential therapeutic target in AD. The signals mediated by CD36 and some of its ligands (amyloid-beta, oxLDL), the inflammatory response in atherosclerosis and AD and vascular amyloid deposition activate NADPH oxidase and culminate with vascular oxidative stress and cerebrovascular dysfunction. Additionally, CD36 is also involved in the microglia migration towards the amyloid-beta deposits by assembling hp130Cas complexes (Moullé et al., 2012). Potential therapeutic agents for AD should therefore be able to block the CD36 – amyloid-beta interactions in an attempt to stop the pathological processes promoted by amyloid-beta. Compounds such as ursolic acid or hexarelin, were shown to have this effect (Bulgarelli et al., 2009; Wilkinson et al., 2011).

Downregulation of CD36 might have a therapeutic effect in reducing the impact of stroke in hyperlipidemic subjects, as seen in the brain of ApoE knock-out mice. Post-stroke, these mice exhibited swelling and inflammation in the peri-infarct area, due to foam cell formation (Kim et al., 2008). Modulating the activity of CD36 positive microglia by either stimulation of PPAR-gamma by drugs such as rosiglitazone or blockage of TLR4 could represent another treatment option in patients with intracerebral haemorrhage in order to speed up the resolution of the inflammation and hematoma (Fang et al., 2014; Zhao et al., 2007).

Statins or similar antioxidants have been used to reduce the expression of CD36 and the uptake of oxLDL through inhibition of PI3K/Akt pathway in blood macrophages (Cho & Kim, 2009). Additional studies are required to monitor the effects of such pharmacologically active compounds in the NVU, in the context of stroke.

7 | CONCLUSIONS AND PERSPECTIVES

Although only few systemic effects of CD36 in the brain have been shown, there is increasing evidence of its potential involvement in neuroinflammation, neurovascular dysfunction and subsequent neurodegeneration. However, the intimate mechanisms mediating these effects are still a matter of investigation and future studies will surely bring further evidence for the importance of CD36 modulation in the prevention and treatment of various neurological diseases.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Laura Ceafalan had the idea for the article. Laura Ceafalan, Octavian Ioghen and Leona Chitoiu performed the literature search and data analysis, together with Mihaela Gherghiceanu. Mihaela Gherghiceanu provided the electron micrograph in Figure 1. Laura Ceafalan and Mihail Hinescu drafted and/or critically revised the work. The first draft of the manuscript was written by Octavian Ioghen and Leona Chitoiu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Peer Review

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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