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SIRP/CD47 Signaling in Neurological Disorders

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Abstract

Microglia play important roles in the process of neuronal injury and recovery. Numerous surface receptors have been described to regulate microglial activation. These receptors tightly mediate normal microglial functions including cell mobility, phagocytosis, and production of inflammatory mediators or trophic factors. In recent years, significant progresses have been achieved for understanding the signaling mechanisms underlying these receptors. Their specific roles in neurological diseases have been documented. This review will focus on the signal regulatory protein (SIRP) and its ligand CD47, two surface receptors expressed on microglia and other cells in the central nervous system (CNS) such as neurons. We will discuss the involvement of SIRP/CD47 signaling in microglial activation and in the interplay between microglia and other CNS cells. Current studies reveal the importance of CD47 and SIRP α in the process of neuroinflammation in the CNS disorders. The dual and contradictory role of CD47 suggests that targeting the SIRP α /CD47 signaling may achieve different effects depending on disease stage.

1. Introduction

About 20 years ago, microglia were first regarded as a distinct cell population in the central nervous system (CNS) with almost the same functions as peripheral macrophages (Barron, 1995). Nowadays, accumulating studies have highlighted the importance of microglia in CNS health and in the short and long-term progress of CNS diseases. On the one hand, microglial activation benefits the injured tissue by cleaning cell debris and reconstructing tissue integrity (Hanisch and Kettenmann, 2007; Lalancette-Hebert et al., 2007; Thored et al., 2009). On the other hand, excessive microglial activation may lead to secondary damage

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Author Disclosure Statement

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and impair CNS repair by releasing a bunch of harmful substances, including nitric oxide (NO), reactive oxygen species (ROS), and proinflammatory cytokines (Hu et al., 2014a). Due to their janus-like roles, microglia are well-regulated by a variety of mechanisms so that they can be promptly switched on as the first responders to noxious stimuli and rapidly turned off to avoid unwanted effects. Many surface recognition receptors on microglia have been identified to sense the “turning on” or “turning off” signals released from other CNS cells and play critical role in modulating microglial responses in many CNS injuries and neurodegenerative diseases (Hu et al., 2014b).

The signal regulatory protein (SIRP, also known as CD172) and its ligand CD47 (also known as integrin-associated protein), are both expressed on the surface of microglia as well as on other types of CNS cells. Accumulating evidence documents that the interaction between SIRP and CD47 is important in mediating the cell-cell communication in the CNS. In this manuscript, we will discuss the functions of SIRP and CD47 in microglial activity and in the interplay between microglia and other CNS cells. The current understanding of the SIRP and CD47 signaling will also be reviewed.

1. Signal regulatory protein (SIRP) family

The SIRP is a family of surface receptors. The SIRP family consists of SIRP α , SIRP β , and SIRP γ as well as some other closely related proteins. Among them, SIRP α and SIRP β 1 are mainly expressed on myeloid cells and have been detected on microglia (Gaikwad et al., 2009; Gitik et al., 2011). Interestingly, SIRP α and SIRP β 1 may play opposite roles on regulating microglial activities.

1.1 Functions of SIRP α in microglia and other CNS cells

SIRP α (also known as SHPS-1, p84 and BIT) is expressed on a variety of myeloid cells. The activation of SIRP α has been related to the inhibition of cell activities, including the blunting of cytokine production (Kong et al., 2007; Latour et al., 2001; Smith et al., 2003), reduced monocyte adhesion to the extracellular matrix (Liu et al., 2005), reduced phagocytosis (Ide et al., 2007; Janssen et al., 2008; Latour et al., 2001; Oldenburg et al., 2000), and arrest of maturation of dendritic cells (Latour et al., 2001). In addition to these negative regulatory functions, a few positive effects of SIRP α have also been reported. For instance, engagement of SIRP α on monocytes mediates the transmigration of these cells across the endothelial lining of the blood-brain barrier (BBB) (de Vries et al., 2002). Ligation of SIRP α has also been shown to induce NO production from macrophages (Alblas et al., 2005). The expression of SIRP α on microglia is evident with immunohistochemical staining (Gitik et al., 2011). SIRP α is known to inhibit microglial phagocytic activity because the engulfment of myelin is augmented when microglial SIRP α is blocked with antibodies or knocked down by SIRP α -shRNA (Gitik et al., 2011). This inhibitory property of SIRP α is thought to be critical for the maintenance of myelin integrity under normal conditions or following mild brain damage. However, the inhibitory property of SIRP α may be disadvantageous in massive brain injuries or degeneration when rapid clearance of damaged myelin is essential.

1.2 Function of SIRP β 1 in microglial phagocytosis

In contrast to the negative functions of SIRP α discussed above, the activation of SIRP β 1 usually leads to cell activation. SIRP β 1 has been shown to positively regulate macrophage phagocytosis (Hayashi et al., 2004) and neutrophil migration (Liu et al., 2005). The expression of SIRP β 1 on microglia was upregulated in APP transgenic mice and in Alzheimer's disease (AD) patients (Gaikwad et al., 2009). Activation of SIRP β 1 on microglia by cross-linking antibodies induces reorganization of cytoskeletal proteins and increased microglial phagocytosis of microsphere beads, neural debris, and fibrillary A β . In contrast, lentiviral knockdown of SIRP β 1 impairs microglial phagocytosis of neural cell debris and A β . These findings support the hypothesis that ligation of SIRP β 1 triggers microglial phagocytosis. Interestingly, SIRP β 1 activation suppresses LPS-induced gene transcription of tumor necrosis factor α (TNF α) and nitric oxide synthase-2 in microglia, suggesting that the impact of SIRP β 1 on microglia might not be a simple binary function such as activation or suppression, but rather a subtler directional regulation geared toward maximizing the beneficial effects of microglia.

2. CD47 – the ligand of SIRP α

CD47 is the first documented ligand for SIRP α . Some other soluble factors (surfactant proteins A and D) are also shown to bind to SIRP α in competition with CD47; however, these factors are highly specific to lung tissues (Janssen et al., 2008). CD47 is a cell surface transmembrane glycoprotein that is ubiquitously expressed in most cell types. Both SIRP and CD47 are members of the immunoglobulin superfamily and have one or more immunoglobulin superfamily (IgSF) structural domains.

2.1 SIRP α and CD47 interaction

Structural and mutagenesis studies have provided clues for the structural requirements for SIRP α -CD47 interactions. The extracellular region of SIRP α contains three IgSF domains: one membrane distal IgV domain (N-terminal) and two membrane proximal IgC domains. The N-terminal IgV domain of SIRP α is responsible for binding to CD47 (de Vries et al., 2002; Vernon-Wilson et al., 2000). For CD47, the extracellular IgV-like fold is responsible for its interaction with SIRP α as well as its association with α 3 integrin (Gaikwad et al., 2009). In the SIRP α /CD47 complex, four loop structures (BC, C'D, DE, FG loops) at the end of the IgV domain of SIRP α comprise the interface with CD47 structures (BC and FG loops, C' strand surrounding the FG loop, N-terminal pyroglutamic acid) (Hatherley et al., 2008). The CD47/SIRP α interface is highly convoluted, extensive, and well fitted, better resembling that of specific antigen-antibody interactions than that of moderate-affinity IgSF domain-mediated cell-surface interactions. However, this binding model based on domain-domain structures may be oversimplified; the true protein interactions may involve the formation of higher order structures, such as dimerization of SIRP α or CD47. Lee et al. reported that cell surface SIRP α dimerizes in cis mainly through the membrane proximal IgC domains (Lee et al., 2010). Although subsequent studies suggested that dimerization of SIRP α may be independent of CD47 binding, it is likely that SIRP α dimers on the cell surface act as a bivalent receptor that can bind two CD47 molecules. This adds a new dimension to the sophisticated interactions between SIRP α and CD47.

Interestingly, although the extracellular regions of SIRP β 1 and SIRP α are highly homologous, CD47 can only bind to SIRP α (and SIRP γ), but not to SIRP β 1. Such specificity has been attributed to the complementary determining loops of the SIRPs, which allow slight sequence changes between members of the family to produce dramatic changes in binding affinity (Hatherley et al., 2008). SIRP β 1 is expressed on the cell surface as a disulfide-linked homodimer with bond formation mediated by Cys-320 in the membrane-proximal Ig loop (Liu et al., 2005). The ligand of SIRP β is still unknown.

2.2 SIRP α and CD47 signaling

As a general rule in the immunoglobulin superfamily, the receptors react with the “turning off” signal usually keep microglia rest by regulating through a cytoplasmic-domain immunoreceptor tyrosine-based inhibition motif (ITIM); while the receptors activate microglia regulate through a cytoplasmic-domain immunoreceptor tyrosine-based activation motif (ITAM) (Linnartz and Neumann, 2013). As a receptor recognizing the “off” signal, the cytoplasmic region of SIRP α contains two ITIM with four highly conserved tyrosine residues. Ligation of SIRP α by CD47 induces phosphorylation of these tyrosine residues. The two C-terminal tyrosine phosphorylation sites (Y⁴⁴⁹ and Y⁴⁷³) provide docking sites for inhibitory phosphatases SH2 domain-containing phosphatase (SHP)-1 or SHP-2 (Kharitonov et al., 1997). Interestingly, these phosphorylated tyrosine residues could also be the substrate of SHPs and serve as the dephosphorylation site for their catalytic domains. Surprisingly, in spite of their highly homologous structures, SHP-1 and SHP-2 perform opposing biological functions (Neel et al., 2003). (Figure 1) SHP-1 negatively regulates various signaling pathways to inhibit multiple cell functions; SHP-2, in contrast, positively regulates signaling events involved in cellular activities such as growth and migration. For example, SIRP α engagement has been shown to inhibit macrophage phagocytosis through the recruitment of SHP-1 (Ohnishi et al., 2005; Veillette et al., 1998; Yamao et al., 2002). In contrast, IGF-1 stimulation of vascular smooth muscle cells results in the phosphorylation of SIRP α and recruitment of SHP-2 as well as other downstream molecules, leading to enhanced cell survival (Shen et al., 2010). Fc γ receptor (Fc γ R) activation has been shown to stimulate the association between SHP-1 and SIRP α , which in turn inhibits Fc γ R- and complementary receptor-mediated phagocytosis (Gresham et al., 2000; Latour et al., 2001). Crosslinking of Fc γ Rs induces the association of Fgr, a member of the Src kinase family, with SIRP α . However, Fgr is not involved in the phosphorylation of SIRP α . Instead, it protects SIRP α from dephosphorylation, allowing the recruitment and docking of SHP-1. Fgr therefore inhibits the phagocytic activity of macrophages. These results demonstrate how functionally opposed signaling pathways are activated in phagocytes to fine-tune their responses to specific external signals.

In addition to SHPs, SIRP α was also shown to associate with two adaptor molecules (Src-kinase-associated protein of 55 kDa homologue (SKAP55hom/R) and Fyn-binding protein/SLP-76-associated protein of 130 kDa (FYB/SLAP-130), or a tyrosine kinase PYK2 (Timms et al., 1999). It is possible that SIRP α has scaffold-like functions to assemble multi-protein complexes. The function of these complexes is not clear, but might involve the transmission of adhesion-regulated signals or termination of these signals via SHP-1 recruitment.

2.2 Bidirectional signaling between SIRP α and CD47

Unique to SIRP α -CD47 signaling is that these two proteins may be coexpressed on the same cell and their ligation might mediate intercellular signaling in a bidirectional manner (Gaikwad et al., 2009). (Figure 1) This feature is especially important in the CNS where the expression of SIRP α and CD47 is largely overlapping (Gresham et al., 2000; Ohnishi et al., 2005). For instance, both SIRP α and CD47 are expressed on the surface of hippocampal neurons, with SIRP α present on the axon and dendrites and CD47 restricted to dendrites (Ohnishi et al., 2005). The CD47-SIRP α interaction between neighboring neurons plays an important role in neuronal network formation in the hippocampus (Murata et al., 2006). Similarly, CD47 and SIRP α are colocalized in microglia. Although SIRP α -CD47 signaling in microglia has not been thoroughly investigated, the individual roles of CD47 and SIRP α have been addressed. Interestingly, both SIRP α and CD47 participate in the phagocytic functions of microglia. As mentioned above, SIRP α inhibits microglial phagocytosis. CD47, however, works together with other surface receptors (CD36, integrin $\alpha_6\beta_1$, TLR4, TLR2 and scavenger receptor A) as a complex involved in microglial interactions with A β fibrils (Bamberger et al., 2003; Koenigsnecht and Landreth, 2004). The subsequent phagocytosis of A β fibrils and activation of intracellular signaling pathways leads to a proinflammatory response. Using acutely isolated microglia from mice of different ages, phagocytosis of A β fibrils has been shown to be prominent in young microglia (prepared from day 0 pups) in a CD47-dependent manner but is lost in aged microglia prepared from 6-month-old mice (Floden and Combs, 2011). This study suggests that dysfunctional CD47 might be responsible for the impaired phagocytic function of aged microglia. SIRP/CD47 signaling also play an instrumental role in cerebral infiltration of circulating monocytes. The interaction between the SIRP expressed on monocytes and CD47 on endothelial cells (ECs) promotes the transmigration of monocytes across the brain endothelial, which requires G1-protein activation instead of monocytes adhesion.(de Vries et al., 2002).

3. SIRP β 1 signaling through the transmembrane adaptor protein DAP12

Despite the similarity of the extracellular domains of SIRP α and SIRP β 1, the cytoplasmic domains differ greatly, leading to the activation of distinct downstream signaling cascades. SIRP 1 has a very short cytoplasmic region that lacks signaling motifs. It associates with DNAX activation protein 12 (DAP12), a dimeric adaptor protein containing an ITAM, through a basic amino acid residue in the transmembrane region. Engagement of SIRP 1 has been shown to activate the tyrosine kinase Syk, which subsequently activates mitogen-activated protein kinase (MAPK) and enhances microglial phagocytosis (Hayashi et al., 2004).

4. CD47 and SIRP α in neuroinflammation and CNS disorders

4.1 CD47 and SIRP α in experimental stroke and CNS injuries

A recent study documented an important role of SIRP α in the pathology of ischemic stroke. The infarct volume, neurological deficits, neuronal apoptosis, and oxidative stress after focal cerebral ischemia were all attenuated in SIRP α deficient mice (Wang et al., 2012). This study focused on the effect of SIRP α on neuronal stressors. Actually, SIRP α , together with

its ligand CD47, are also expressed by neurons and involved in neuronal apoptosis, neurite outgrowth, and synaptic activities (Gresham et al., 2000; Jiang et al., 1999; Wang et al., 2003). So far, the contribution of microglial SIRP α to ischemic stroke or other types of neurological disorders has not yet been addressed.

While the effect of SIRP in CNS injuries is relatively few, CD47 has been documented to be important in a variety of CNS injuries including ischemic and hemorrhagic brain injury, and spinal cord injury (SCI). A study using CD47 knockout mice suggests a deteriorate effect of CD47 in ischemic brain (Jin et al., 2009). The absence of the CD47 gene reduces brain infarct and swelling at acute stage after focal ischemic brain damage. Further study revealed that CD47 promotes matrix metalloproteinase-9 (MMP-9) upregulation after stroke and enhances the damage in BBB, resulting in increased inflammatory cell infiltration and aggravated neuroinflammation in the ischemic brain. *In vitro* studies further demonstrated that the engagement of CD47 upregulated vascular endothelial growth factor (VEGF) and MMP-9, two major neurovascular mediators, in brain endothelial cells and astrocytes, which could in turn contribute to CD47-mediated BBB damage after stroke (Xing et al., 2010).

The involvement of CD47 in hemorrhagic stroke has also been investigated in a pig model of intracerebral hemorrhage (ICH). (Zhou et al., 2014) The expression of CD47 in the perihematomal white and grey matter is upregulated soon after ICH and such upregulation can last for at least 2 weeks. Increased expression of CD47 is observed in microglia/macrophages, neurons and oligodendrocytes. However, the exact roles of CD47 in these cells after ICH are still unknown.

Similar to the study in ischemic brain injury, targeted deletion of CD47 leads to protection in a model of SCI, as manifested by white matter sparing, decreased neutrophil extravasation and improved functional recovery (Myers et al., 2011). Further study revealed that the beneficial effects of CD47 ablation could be attributed to reduced endothelial cells-neutrophil interaction through CD47-SIRP α signaling. The knockout of CD47 also inhibits angiogenesis that mediated by CD47 interaction with its angiogenic ligand, thrombospondin-1 (TSP-1) (Benton et al., 2008) and results in improvements in penumbral microvasculature after SCI. This anti-angiogenic effect alone, however, can not lead to functional improvement as there is no significant behavioral improvement between TSP-1 knockout mice and wildtype mice.

Taken together, these studies highlight the importance of CD47-SIRP α signaling in the development of neuroinflammation after CNS injury.

4.2 CD47 and SIRP α in multiple sclerosis

In addition to the CNS injuries, CD47 is also important in CNS autoimmune diseases such as multiple sclerosis (MS). (Han et al., 2012) CD47 localizes in normal myelin and also in foamy macrophages and activated astrocytes around the active MS lesions. The expression of CD47 is downregulated in MS brain lesions. CD47 deficient mice are resistant to experimental autoimmune encephalomyelitis (EAE), a model of MS, together with an ameliorated inflammatory responses in T cells and other immune cells. Surprisingly, inhibition against CD47 with a monoclonal antibody at the peak of paralysis deteriorated

EAE severity in spite of ameliorated immune cell activation. In vitro assays demonstrate that blocking CD47 enhance myelin phagocytosis which is largely dependent on CD47/SIRP α binding. Therefore, lack of CD47 may promote demyelination by enhancing SIRP α -dependent phagocytosis of myelin. This study exemplifies the dual and contradictory effects of CD47 during neuroinflammation, which are likely caused by differential expression of CD47 in different cell types, location, and disease phase.

5. Future directions

Despite our increased understanding of SIRP α /CD47 interaction between CNS cells and their roles in CNS homeostasis and abnormalities, there are still unsolved questions in this field (Barclay and Van den Berg, 2014). First and foremost, current studies lack of a cell-specific view of SIRP α -CD47 interplay and the mobilization of downstream signaling mediators. In addition, the complexity of SIRP α /CD47 contribution to CNS injuries and disorders need to be further characterized and the underlying mechanisms need to be elucidated. For example, the previous study documented increased expression of CD47 in microglia/macrophage, neurons and oligodendrocytes after ICH. However, the cell specific function of CD47 is unknown and its downstream signaling is not clear. Secondly, it is still uncertain whether CD47 or SIRP α can be a therapeutic target for the treatment of CNS diseases. Indeed, the therapeutic role of CD47/SIRP α binding has been demonstrated in cancer therapy. A promising anti-cancer strategy depending on a unique CD47/SIRP α interaction between tumor cells and macrophages/microglia has been addressed (Weiskopf et al., 2013). However, in the CNS, both CD47 and SIRP α are widely expressed on various cells and actively involve in multiple cell activities. Moreover, CD47 and SIRP α may play janus roles in certain pathological events such as neuroinflammation (Han et al., 2012). It therefore would be important and challenging to decide whether modulating CD47/SIRP α signaling may have different effects depending on disease progress. In this regards, better characterization of cell-specific CD47/SIRP α interaction during different stages of certain disease would be necessary for the development successful treatment strategies targeting these molecules.

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Abbreviation

Aβ	amyloid β
AD	Alzheimer's disease
CNS	central nervous system
IgSF	immunoglobulin superfamily
ICH	inintracerebral hemorrhage
DAP12	DNAX activation protein 12

ITAM	immunoreceptor tyrosine-based activation motif
ITIM	immunoreceptor tyrosine-based inhibition motif
MAPK	mitogen-activated protein kinase
MMP	matrix metalloproteinase
MS	multiple sclerosis
NO	nitric oxide
ROS	reactive oxygen species
SCI	spinal cord injury
SHP1	SH2 domain-containing phosphatase-1
SIRP	Signal regulatory protein
TNFα	tumor necrosis factor α

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Highlights

- SIRP and CD47 regulate microglial activation.
- SIRP and CD47 mediate the interplay between microglia and other CNS cells.
- CD47 and SIRP are important in neuroinflammation in the CNS disorders.
- CD47 and SIRP α may play janus roles in certain pathological events.
- Modulating CD47/SIRP α may have different effects depending on disease progress.

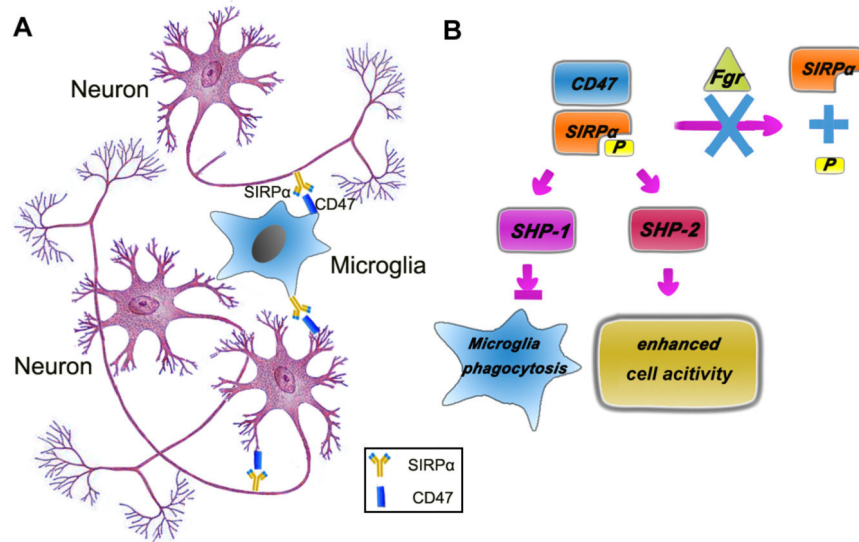


Figure. Cell-cell crosstalk through signal regulatory protein (SIRP) α -CD47 signaling
 A. Bidirectional signaling between SIRP α and CD47. SIRP α and CD47 may be coexpressed on the same cell and their ligation might mediate intercellular signaling in a bidirectional manner. SIRP α -CD47 binding between neighboring neurons enhances neuronal network formation in the hippocampus. Similarly, CD47 and SIRP α are colocalized in microglia. Although SIRP α -CD47 signaling in microglia has not been thoroughly investigated, the individual roles of CD47 and SIRP α have been addressed. Both SIRP α and CD47 participate in the phagocytic functions of microglia. B. SIRP signaling in microglia. The phosphorylation of SIRP α allows the recruitment and docking of SHP-1 and SHP-2. SHP-1 and SHP-2 perform opposing biological functions. SHP-1 negatively regulates various signaling pathways to inhibit multiple cell functions such as phagocytosis; SHP-2, in contrast, positively regulates signaling events involved in cellular activities such as growth and migration. Fgr, a member of the Src kinase family that can be activated by crosslinking of Fc γ receptor, inhibits the SIRP α dephosphorylation, allowing the recruitment and docking of SHP-1. Fgr therefore inhibits the phagocytic activity of microglia. *SHP1*, *SH2 domain-containing phosphatase-1*.