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J Immunol 2005; 175:7781-7787; doi: 10.4049/jimmunol.175.12.7781

Supplementary Material

http://www.jimmunol.org/content/suppl/2005/12/06/175.12.7781.DC1

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Signal Regulatory Proteins in the Immune System

Ellen M. van Beek,* Fiona Cochrane,† A. Neil Barclay,† and Timo K. van den Berg†*

Signal regulatory proteins (SIRPs) constitute a family of transmembrane glycoproteins with extracellular Ig-like domains. Several SIRP family members have thus far been identified on myeloid and other cells in man, mouse, rat, and cattle. In the present study, we provide a description of the SIRP multigene family, including a number of previously undescribed SIRP genes, based on the complete genome sequences of various mammalian and bird species. We discuss this information in the context of the known immunological properties of the individual SIRP family members. Our analysis reveals SIRPs as a diverse multigene family of immune receptors, which includes inhibitory SIRPa, activating SIRPβ, nonsignaling SIRPγ, and soluble SIRPβ members. For each species, there appears to be a single inhibitory SIRPa member that, upon interaction with the "self" ligand CD47, controls "homeostatic" innate immune effector functions, such as host cell phagocytosis. The activating SIRPβ proteins show considerable variability in structure and number across species and do not bind CD47. Thus the SIRP family is a rapidly evolving gene family with important roles in immune regulation. The Journal of Immunology, 2005, 175: 7781–7787.

The signal regulatory protein (SIRPα; CD172 and SHPS) family belongs to an increasing number of families of membrane proteins involved in the regulation of leukocyte function. More especially, the SIRPs belong to a group of receptors that have members with closely related extracellular regions but different cytoplasmic regions giving contrasting types of signals—the "paired receptors" that are particularly common on NK cells but also present on many myeloid cells. These "paired receptors" include the killer Ig-like receptors, paired Ig-like receptor, Ly49, CD94/NKG2A, Ig-like transcript, dendritic cell immunoreceptor, and CD200R families (1–4). Some of these families have C-type lectin domains in their extracellular regions (e.g., Ly49 and CD94), but the most common domain type in the paired receptors and indeed all leukocyte membrane proteins is the Ig superfamily domain (IgSF) (5). The SIRPs are expressed mainly by immune cells and more especially myeloid cells. Their extracellular regions are typically composed of a single V-set and two C1-set IgSF domains, which, when compared with other members of the IgSF, display a particularly close structural relationship to rearranging AgRs (TCR and BCR). Based on these similarities, we have previously proposed an evolutionary relationship between AgRs and SIRPs (6). Moreover, it appears that the putative primordial AgR that formed the target for the critical transposition event (7) that led to the appearance, ~500 million years ago, of rearranging AgRs and thus adaptive immunity was possibly a SIRP-like molecule. Insight into the functional properties of SIRPs may provide clues about the innate origins of the adaptive immune system. As with many members of the other "paired receptors" mentioned above, SIRPs possess the potential to signal through cytoplasmic tails that contain either ITIMs (8) or transmembrane regions that have positively charged residues that allow an association with adaptor proteins, such as DAP12/KARAP, containing ITAMs (9).

The biochemically characterized SIRP members

To date, three distinct human SIRP family members have been characterized at the protein level (for structural features of SIRP family members, see Fig. 1A). The first and best characterized member of this SIRP family, SIRPa (also known as SHPS-1, BIT, MFR, CD172a, or p84), was originally identified in rat cells by its association with cytoplasmic tyrosine phosphatase Src homology region 2 domain-containing phosphatase (SHP)-2 (8) and was later shown to exist in other mammals, including humans, mice, and cattle (10–12). Two other SIRP family genes, SIRPβ1 (CD172b) and SIRPγ (CD172g), have been described in humans (11, 13–15). SIRPγ was originally described as SIRPβ2 (14), but as outlined in the accompanying letter, we believe the name SIRPγ is more suitable. In the mouse, two SIRPβ members (SIRPβ1 and SIRPβ2), which can both associate and signal via DAP12, have been characterized (16, 17). The SIRPβ1 was previously termed mouse SIRPβ3. However, protein sequences with similarity to the reported SIRPs are present in the genomes, and the availability of the complete genome sequences of various species and extensive expressed sequence tag (EST) data now permit characterization of the complete SIRP family in humans and other species. The hypothesis is that proteins related to the known SIRPs will have evolved by gene duplication and have related functions as already shown for SIRPγ, which has the same ligand (i.e., CD47).
as SIRPα (13, 15). Clearly, understanding the full range of genes in the SIRP family is essential for understanding its significance in the immune system.

Novel genes related to the SIRPs were identified on the basis of sequence similarity and/or by systematic analysis of the regions of the genome where the known SIRP genes were present or regions syntenic to these in other species. Similarity searches were performed using the Basic Local Alignment Search Tool/Sequence Search and Alignment by Hashing algorithms in National Center for Biotechnology Information or Ensembl databases using the complete or partial sequences of known SIRPs. IgSF domains can often show considerable divergence even between species orthologs (the extracellular region of human CD4 shows only 53% amino acid sequence identity with its mouse counterpart) while unrelated domains may show ~20% identity as residues key for the domain fold are conserved (5). Therefore, a cutoff of 30% amino acid identity was used to search and identify related genes (see below).

The SIRP genes in humans and other primates

The genes of the three identified SIRPs in human, SIRPα, SIRPβ1, and SIRPγ, are clustered on chromosome 20p13 (Fig. 1B). Adjacent to the known human SIRP genes on chromosome 20, we have identified two additional SIRP genes and a pseudogene. Based on their structural properties, we termed these novel SIRP molecules, SIRPβ2, SIRPβ3 (for the pseudogene), and SIRPδ (Fig. 1A) (for nomenclature of the SIRP family, see the accompanying Brief Review). These novel SIRP family members are clearly more divergent than the three previously known SIRP molecules. In fact, SIRPα, SIRPβ1, and SIRPγ appear to form a subgroup that evolved relatively recently before the bifurcation of chimpanzee and man (see below). SIRPβ2 appears to encode a cell surface receptor composed of two extracellular IgSF V-type domains and, in analogy to SIRPβ1, a transmembrane region with a positively charged residue, suggesting a putative association with the adaptor

**FIGURE 1.** The SIRP family in man (Homo sapiens), chimpanzee (Pan troglodytes), rat (Rattus norvegicus), mouse (Mus musculus), and chicken (Gallus gallus). A, Schematic structures of SIRP family members. The existence of some SIRP proteins, including human SIRPα, SIRPβ1, and SIRPγ, rat SIRPα, mouse SIRPα, SIRPβ1, and SIRPβ2, is supported by direct biochemical evidence (see text for details), whereas that of the others is based on prediction. The gray and white circles represent V- and C1-set Ig domains, respectively. The Y-marked black and white squares represent ITIM and ITAM tyrosine residues, respectively. The positively charged lysine residues of the transmembrane regions of the SIRPβ members, which mediate or are proposed to mediate, an association with DAP12 are indicated with a “+”. In case of SIRPβ1, mSIRPβ1, and mSIRPβ2, an interaction with DAP12 is supported by direct evidence (16, 17, 38, 40) (www.ub.uni-heidelberg.de/archiv/4817); for the other SIRPβ members, it is proposed based on the presence and position of the transmembrane lysine residue. B, Genomic organization of the SIRP family. See supplementary Fig. 1 for database accession numbers and amino acid sequences.
protein DAP12. Consistent with this, SIRPβ2 is expressed by cells of the monocyte-macrophage lineage (as determined by PCR and analysis of EST data), and there is alternative splicing of the extracellular IgSF domains (E. M. Van Beek et al., unpublished observations). SIRPβ3p has an unusual extracellular region, with three NH2-terminal C1-type IgSF domains and two membrane proximal V-type IgSF domains. The human SIRPβ3p appears to be a pseudogene, but its orthologs in rodents (i.e., rat (r)SIRPβ3 and murine (m)SIRPβ3) appear functional (see below). Although gene prediction programs identify an open reading frame, there is no evidence (from, for example, EST) for expression. SIRPβ encodes a putatively secreted molecule with a single V-type IgSF domain. EST evidence suggests that SIRPβ may be expressed by sperm cells and in respiratory tissue (T. K. van den Berg, unpublished observations).

The human SIRP gene cluster is flanked by the dynorphin precursor (pDyn) gene, and this orientation is conserved in all species investigated where a SIRP cluster is found in a syntenic position in the genome. Outside the 20p13 SIRP cluster, we have not detected any other active human SIRP genes, apart from an intronless SIRPα gene (92% overall nucleotide identity) on chromosome 22, which probably represents a retrotransposon (Fig. 1A). Although this SIRPα-like gene has an open reading frame, the lack of evidence for transcription strongly suggests it to be a pseudogene (termed SIRPα2p). In the chimpanzee, the productive SIRPα gene is localized in a syntenic position on chromosome 23 while, the SIRPα like gene within the chimpanzee SIRP-gene cluster is most probably a pseudogene. This illustrates the difficulty in assigning specific species homologues and reflects how, as with many other “paired receptors,” these genes have been subject to extensive duplication, divergence, and loss. Furthermore, it seems possible that the chimpanzee SIRPβ1 does not contain a V-type Ig-like domain, but the latter could also be a sequencing error or a mistake of the gene prediction algorithm. Because expression data are lacking, as yet only genomic information has been used for the chimpanzees, and thus SIRP genes and their products are exclusively predicted here by gene prediction programs. One of the more important implications from the above is that there is only a single human SIRPα family member, suggesting indirectly that most of the additional human SIRPα sequences reported (11) probably represent polymorphic variants. In fact, our own findings (A. Van Elsas and T. K. van den Berg, unpublished observations) suggest that the most frequent SIRPα allotypes in the human population are represented by the two deposited SIRPα1 and SIRPα2/BIT sequences (SIRPα1 (National Center for Biotechnology Information Entrez protein accession no. CAA71403) and SIRPα2/BIT (protein accession no. NP_542970)).

The SIRP genes in rodents

In rodents, two clusters of SIRP genes are present (Fig. 1B). The SIRPα ortholog and rat and mouse SIRPβ3 (i.e., the orthologs of the human SIRPβ3p pseudogene) are in the first cluster (cluster I). Interestingly, these SIRPβ3 and mSIRPβ3 represent functional genes and not a pseudogene as in humans. Both have a C1-C1-C1-TM-Cyt structure and represent the only family member that lacks a typical V-set IgSF domain. However, in the rodent SIRPβ3 genes and primate SIRPβ3 pseudogene, there is evidence for the remains of two V-like sequences located between the third C1 domain exon and the TM region-encoding exon, suggesting that perhaps in early mammals there was a SIRP family member with a C1-C1-C1-V-V-TM-Cyt structure. Despite the low sequence similarity (~23%) between the C1-set domains of SIRPβ3 and the C1-set domains of, for example, SIRPα, a distant relationship can still be seen. It seems that a putative primordial SIRPβ3 arose by an incomplete duplication of the two tandem C1-set domains as present in the SIRPα, SIRPβ1, and SIRPγ subgroup genes. As compared with primates and chicken, the organization of SIRP genes in the rodent genome appears special in two aspects. Firstly, the rodent cluster I is uniquely flanked by the IL-1α and -1β genes, which is likewise the result of multiple translocations. Furthermore, there is a second cluster of SIRP genes (cluster II), which is located on corresponding regions of the rat chromosome 2q23 and mouse chromosome 3A1. Cluster II shows a relatively high degree of divergence among mice and rats. In mice, but not in rats, there is a SIRPβ member (SIRPβ1) representing the SIRPβ molecule described by Hayashi et al. (16). It is clear that this mSIRPβ1 is closely related to members of the primate SIRPα-SIRPβ1-SIRPγ subgroup as well as to the mouse SIRPα (all identities ~55%), but because the homologies among the members of the primate subgroup are considerably higher (~75%), they probably arose later (i.e., independently), and thus mSIRPβ1 cannot be considered a direct ortholog of any of these. However, because it contains the typical transmembrane lysine residue and can also associate with and signal via DAP12 (16), it may serve a function analogous to the primate SIRPβ1. The rodent rSIRPβ1, rSIRPβ2, rSIRPβ4, and mSIRPβ2 molecules, i.e., with variable numbers of only V-set IgSF domains and a transmembrane region with a charged lysine, are not particularly related to the primate SIRPβ2, which within the context of the whole SIRP family appears rather divergent. A phylogenetic tree for the individual V-like domains strongly suggests that the various SIRP members from cluster II arose independently in the rat and mouse lineage by either single or tandem V-like domain exon duplication events (Fig. 2). All this appears consistent with the translocation of a cluster I-derived SIRPα- or SIRPβ1-like founder gene giving rise to cluster II.

SIRP genes in other species and the evolution of SIRPs

SIRP genes are broadly found among mammals and are not restricted to primates and rodents. We have also found SIRPs in dog (Canis familiaris), cow (Bos taurus) (10), pig (Sus scrofa), horse (Equus caballus), and the gray short-tailed opossum (Monodelphis domestica), a marsupial mammal. The full SIRP repertoire in these species can be described in detail once their genome sequences and expression data have become available, and this may provide further insight into the evolution of SIRPs in mammals.

Considering the evolutionary relationship of SIRPs with AgRs, which has previously led us to propose a common nonrearranging SIRP-like predecessor in early vertebrates (6), it was of interest to know whether nonmammalian vertebrates such as birds, reptiles, amphibians, and fish encode SIRP family members. The availability of the chicken, Xenopus, zebrafish, and fugu (pufferfish) genome sequences provided a means to explore this. In chicken, we found three family members, termed chicken (g)SIRPα, gSIRPγ, and gSIRPβ, which are encoded in a position syntenic to the mammalian cluster I. These chicken SIRP-like molecules are not obvious orthologs of the primate
SIRPα, SIRPγ, or SIRPδ genes but may still serve analogous functions. The presence of SIRPs with a V-C1-C1 structure as well as a gene with ITIMs (i.e., gSIRPα) suggests that these comprise perhaps the original ingredients of a primordial SIRP.

Of interest, our extensive searches have not provided evidence for the presence of typical SIRP family members in other major phylogenetic groups, including amphibians, fish, and invertebrates. Our analysis included the complete (draft) genome sequences of zebrafish (*Danio rerio*), Torafugu pufferfish (*Takifugu rubripes*), spotted green pufferfish (*Tetraodon nigroviridis*), clawed toad (*Xenopus tropicalis*), fruit fly (*Drosophila melanogaster*), mosquito (*Anopheles gambiae*), and helminth (*Caenorhabditis elegans*). The closest homologues of SIRPs that can be found by basic local alignment search tool searches in for instance the complete genomes of zebrafish and fugu are either AgR chains or members of the novel immune type receptor families (18) (at ~20–30% identity), which clearly represent related but distinct IgSF families. This apparent lack of SIRPs in the other major vertebrate groups (i.e., amphibians and fish) is perhaps surprising considering the previously suggested relationship between SIRPs and AgRs that predicted an ancient SIRP-like molecule in early (jawed) vertebrates (6). It seems likely that SIRP family members did indeed exist in early vertebrates and continued to exist in birds and mammals but were lost at some point(s) during fish and amphibian evolution or that they arose later. Clearly, it is more difficult to trace the evolution of proteins such as these as they are diverging very rapidly compared with, for example, cytosolic enzymes where phylogenetic analysis is simpler, and also it is likely that there has been extensive duplication and gene loss within the species making direct orthologs difficult to identify (see discussion above on mouse SIRPα1 and primate SIRPs).

The functions of SIRP family members in immunity

The biochemically characterized SIRPs are all expressed by cells of the immune system with SIRPα also expressed on neurons...
(19, 20) (the relevant properties of human SIRPs are summarized in Table I). SIRPα is relatively ubiquitously expressed on myeloid cells, including macrophages, granulocytes, myeloid dendritic cells (DCs), mast cells, and their precursors, including hematopoietic stem cells (19–21). CD47, a broadly expressed transmembrane glycoprotein with a single Ig-like domain and five membrane spanning regions, functions as a cellular ligand for SIRPα (21, 22) with binding mediated through the NH2-terminal V-like domain of SIRPα (23). CD47 can itself signal, and hence, engagement can potentially give two-way signaling (24). The cytoplasmic region of SIRPα contains four ITIMs, which upon ligand binding become phosphorylated, and mediate recruitment and activation of the tyrosine phosphatases SHP-1 and SHP-2 (8, 11, 25). SHP-1 and SHP-2 can, in turn, dephosphorylate specific protein substrates and thereby regulate cellular functions, generally in a negative fashion. Probably the best documented role of SIRPα is its inhibitory role in the phagocytosis of host cells by macrophages (26). In particular, the ligation of SIRPα on macrophages by CD47 expressed on the host target cell generates an inhibitory signal mediated by SHP-1 that negatively regulates phagocytosis. The role of SIRPα in host cell phagocytosis is supported by in vivo studies with target cells from CD47-deficient mice (27, 28), as well as by using macrophages from SIRPα-mutant mice (26, 27). Mice that lack the SIRPα cytoplasmic domain are thrombocytopenic, which apparently results from an increased rate of clearance of circulating platelets (26, 27). Recent evidence also implies SIRPα in the clearance of aged erythrocytes (29). This strongly suggests that SIRPα acts to detect signals provided by “self,” in this case CD47 on host cells, to negatively control innate immune effector function against these cells. This is analogous to the “self” signals provided by MHC class I molecules to NK cells via Ig-like or Ly49 receptors. Another example of negative regulation through SIRPα is the inhibition of LPS-induced TNF-α production in macrophages (30). However, the role of SIRPα may be more complex than previously anticipated, and the molecule may not only provide negative signals. For instance, we have shown recently that engagement of SIRPα by CD47 in macrophages can promote the production of NO via the SIRPα-associated Janus kinase (JAK2), suggesting that SIRPα can also activate certain effector functions (31). Finally, there is the potential for a variety of other components, which can also bind to SIRPα, to regulate its signaling. These include the tyrosine kinases CSK and PYK2 and the adaptor molecules Grb2, FyB/SLAP-130, and SKAP55hom (11, 12, 25, 32). In fact, apart from the ITIMs, the SIRPα cytoplasmic tail contains two proline-rich regions that may form a docking site for the SH3 domains in some of these proteins. Thus, SIRPα does not only function as a typical inhibitory receptor but may also act as a scaffold for a variety of other signaling molecules at the plasma membrane.

Apart from the above, reported evidence suggests that SIRPα-CD47 interactions play a role in macrophage fusion to form multinucleated cells in vitro (33, 34). It remains to be established whether the SIRPα-CD47 interaction is also relevant for osteoclast fusion and multinucleated giant cell formation in vivo.

In addition to the regulatory functions in macrophages, interactions between CD47 on T cells and SIRPα on DCs have been shown to regulate, in a bidirectional fashion, DC and T cell activation. Furthermore, it seems that SIRPα provides signals that can modulate DC maturation (35). The contributions of the different signals are difficult to discern as these in vitro studies with human cells did not really clarify whether the effects observed were the result of agonistic or antagonistic action of the reagents used. Apart from this, it will be interesting to investigate more directly the possible role of SIRPα in adaptive immunity.

Finally, SIRPα appears to control myeloid cell migration. Studies using SIRPα-mutant mice provide evidence for a role of SIRPα in the emigration of Langerhans cells from the skin (36). Furthermore, interactions of SIRPα on monocytes or granulocytes with CD47 on endothelial or epithelial cells are important for transendothelial or epithelial migration (37–39). Collectively, these findings picture SIRPα as a versatile regulator of myeloid cell function.

SIRPβ1 was reported originally by Kharitonenkov et al. (11) in humans and is expressed on myeloid cells, including monocytes, granulocytes, and DCs (40–43). Interestingly, SIRPβ1, although closely related to SIRPα, does not appear to bind CD47 and lacks cytoplasmic ITIMs or any other recognizable cytosolic motifs for signaling. Instead, SIRPβ1 contains a transmembrane region with a positively charged lysine residue that mediates association with DAP12, an adaptor protein that carries an ITAM (41, 43). Phosphorylation of the DAP12 ITAM mediates recruitment of the protein tyrosine kinase Syk and consequent activation of the MAPK pathway that regulates various functions (9, 41, 43, 44). Triggering of the murine SIRPβ1 receptor, for instance, which also complexes with DAP12, promotes phagocytosis in macrophages (16). This indicates that mSIRPβ1 acts as an activating SIRP family member. Further evidence for the rapid evolution of this family of proteins is given by the differences in SIRPβ1 sequences from different mouse strains (16).

Table I. Immunological properties of characterized human SIRP family members

<table>
<thead>
<tr>
<th>Ligand</th>
<th>SIRPα</th>
<th>SIRPβ1</th>
<th>SIRPγ</th>
</tr>
</thead>
<tbody>
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<td>Signaling motifs</td>
<td>Four ITIMs; two proline-rich regions</td>
<td>Unknown</td>
<td>CD47</td>
</tr>
<tr>
<td>Signaling proteins</td>
<td>Lys in TM region</td>
<td>DAP12</td>
<td>None*</td>
</tr>
<tr>
<td>Function</td>
<td>Promotion of phagocytosis?</td>
<td>Mediates antigen presentation and T cell proliferation</td>
<td></td>
</tr>
</tbody>
</table>

* The cytoplasmic tail of SIRPγ comprises four amino acids with no known signaling motifs or interactions.

** The positive effect on phagocytosis is based on studies with the mouse mSIRPβ1, which also associates with DAP12 and may serve an analogous function.
SIRPγ, the third member of the human SIRP family, is expressed on T cells and activated NK cells (13–15). It can bind CD47, albeit with 10-fold lower affinity as compared with SIRPα (13). Moreover, SIRPγ-CD47 interaction mediates cell-cell adhesion and supports APC-T cell contact, enhancing Ag presentation, the consequent T cell proliferation, and cytokine secretion (15). It seems unlikely that SIRPγ itself generates intracellular signals because it does not have any recognizable signaling motifs. Instead, SIRPγ may trigger signaling of CD47 in APCs.

Concluding remarks

The SIRP family comprises multiple genes in mammals and birds. Similar to what is seen in various related families of leukocyte receptors, the genome includes SIRP family members with either inhibitory or activating signaling potential. Of interest, for each species analyzed, we have found only a single, relatively well-conserved, inhibitory SIRPα receptor member, which is consistent with a homeostatic function. Indeed, SIRPα is capable of recognizing “self” in the form of the broadly expressed surface marker CD47, and this negatively controls effector functions of innate immune cells, such as macrophages. It also seems possible that SIRPα-CD47 interactions regulate the induction of adaptive immune responses, but clearly more in vivo investigation is desired in this area.

In contrast to the single SIRPα, multiple SIRPβ-like molecules with putative activating potential appear to be present in the various species. For some SIRPβ-like members, which may associate with and signal via the adaptor molecule DAP12, there is evidence that they can trigger activation and phagocytosis in myeloid cells. The strong diversification, which has led to significant differences in SIRPβ composition, even among closely related species such as mouse and rat, is more in line with a function in host defense, perhaps even involving direct pathogen recognition. If so, the SIRP repertoire may have been shaped by the continuous molecular battle between host and pathogens. It is noteworthy in this context that essentially all poxviruses encode a homologue of CD47 termed vCD47. It seems feasible that vCD47 has, at least at some point during evolution, mediated poxvirus immune evasion by negative regulation of myeloid cell function via SIRPα. Of interest, very recent evidence indicates indeed that the myxoma virus vCD47 protein (also known as M128L), which is expressed on the surface of infected cells, is required for the production of a lethal infection in its natural host (i.e., the rabbit) and, at the same time, contributes to the suppression of macrophage activation (45). Although this study did not provide direct evidence for an interaction between vCD47 and SIRPα, it is clearly consistent with a possible role of vCD47-SIRPα interactions in virus-mediated immune evasion. Conversely, the generation of activating SIRPβ variants by duplication from SIRPα, particularly if they acquired a certain degree of specificity toward the viral CD47 molecule, would likewise have provided the host with a selective advantage. The precedent for this type of reaction has been shown with the Ly49 system. This family of NK-paired receptors in mice has extracellular lectin-like domains, and like SIRPs have forms with intracellular ITIMs (for inhibitory genes) such as Ly49I or associate with DAP12 (for activatory genes) such as Ly49H. These particular proteins bind the m157 viral product from mouse CMV and determine the susceptibility of mice toward virus infection (46, 47). It will clearly be of interest to further explore the interactions of SIRP family members with poxvirus vCD47 and other ligands expressed by pathogens.

Note added in proof. Recent evidence suggests that apoptosis of cells can be accompanied by a down-regulation of (functional) CD47 expression (48). As a result, the apoptotic cells will no longer provide an inhibitory signal for phagocytosis via SIRPα which will facilitate their uptake by macrophages. CD47 may thus act as a “viability” or “don’t eat me” signal to the phagocyte.

Acknowledgments

We thank Georg Kraal for critically reading the manuscript.

References