Abstract. Signal regulatory protein α (SIRPα), also known as cluster of differentiation (CD)172a or Src homology 2 domain-containing phosphatase substrate-1, is a cell surface receptor expressed on myeloid and hematopoietic stem cells and neurons. Accumulating data suggests an important role of SIRPα in cell signaling as a negative regulator of the phosphatidylinositol 3-kinase signaling and mitogen-activated protein kinase pathways. In various cancers, including prostate, breast and liver, as well as astrocytoma and myeloid malignancies, downregulation of SIRPα is frequently observed, resulting in activation of these downstream signaling pathways. In turn, cell proliferation, transformation, migration and invasion may occur. Recently, it has been reported that blocking CD47, an anti-phagocytic signal expressed on tumor cells and an SIRPα ligand, may serve as a promising therapeutic approach, particular for the treatment of acute myeloid leukemia. In the present review, the current findings on SIRPα are summarized, with particular focus on its role in cancer.

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1. Introduction

The signal regulatory protein (SIRP) family consists of an inhibitory receptor, SIRPα, an activating receptor, SIRPβ [also known as cluster of differentiation (CD)172b] and a non-signaling receptor, SIRPγ (also known as CD172g) (1,2). SIRPα, also known as CD172a or Src homology 2 (SH2) domain-containing phosphatase substrate-1, is a cell surface receptor expressed predominantly in monocytes, granulocytes, dendritic cells and hematopoietic stem cells (3). SIRPα, SIRPβ and SIRPγ have distinct expression patterns, with SIRPα expressed in myeloid cells and neurons, SIRPβ expressed in macrophages and neutrophils, and SIRPγ expressed in lymphocytes and natural killer cells (1). SIRPα has two distinct isoforms, SIRPα1 and SIRPα2. SIRPα2, also termed brain immunoglobulin-like molecule with tyrosine-based activation motifs (4), shares structural similarity with SIRPα1. In fact, SIRPα1 and SIRPα2 are structurally identical except for their N-terminal immunoglobulin (Ig)-like domain (IgV), which is critical for binding to CD47. As SIRPα is established as an immunoreceptor harboring an IgV domain (5,6), it is generally considered as SIRPα1 unless noted otherwise. SIRPα is the most characterized member of the human SIRP family. The present review summarizes recent progress in the analysis of SIRPα function and the role of this molecule in cancer, introducing data from recent analyses by our group in leukemia cell lines.

2. SIRPα function

The functions of SIRPα1 and SIRPα2 are fundamentally similar; both exert a marked suppressive effect on the anchorage-independent growth of cells (7). In addition, the binding of SIRPα to its ligand, CD47, transduces a downregulation signal that inhibits cell phagocytosis (2). Overexpression of SIRPα may lead to reduced responsiveness to tyrosine kinase ligands, including epidermal growth factor (EGF), platelet-derived growth factor and insulin (3). Several reports have demonstrated that downregulation of SIRPα resulted in activation of downstream pathways (8-11). However, this remains controversial as it has also been reported that when SIRPα was transfected into either murine NIH3T3 or rat Rat1 fibroblasts expressing insulin receptor, it augmented insulin-stimulated phosphorylation of mitogen-activated protein kinase (MAPK) (12). Thus, the role of SIRPα may
depend on its expression level or on the cell type in which it is expressed (12).

3. CD47, an anticancer therapeutic target

As there are previous reviews on the relationships between CD47 and SIRPα (2,13), how CD47 modulates the function of SIRPα is only briefly discussed here. CD47 is a membrane protein expressed in nearly all cell types (2). The Ig domain of CD47 and the N-terminal Ig domain of SIRPα may bind directly, and this binding is reportedly sufficient for mediating transcellular bidirectional signaling via the respective cytoplasmic regions (14). In particular, the binding of SIRPα to CD47 promotes tyrosine phosphorylation of the cytoplasmic region of SIRPα (15).

Majeti et al (25), demonstrated that CD47 was expressed at higher levels on acute myeloid leukemia (AML) stem cells than on their normal counterparts. They also revealed that increased CD47 expression predicted worse overall survival in adult AML patients, and that monoclonal antibodies directed against CD47 enabled phagocytosis of AML leukemia stem cells and inhibited their engraftment in vivo (25). Recently, Chen et al (20) reported that macrophages were notably more efficient at phagocytosis of hematopoietic tumor cells compared with non-hematopoietic tumor cells in response to SIRPα-CD47 blockade (20). They also revealed that

<table>
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<th>Tissue</th>
<th>Expression</th>
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<td>Prostate cancer</td>
<td>Downregulated in prostate cancer tissues and cell lines</td>
<td>SIRPα overexpression resulted in a decrease in the number of live prostate cancer cells, while SIRPα silencing increased prostate cancer proliferation.</td>
<td>(30)</td>
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<td>Brain cancer</td>
<td>Expressed in 8 of 9 astrocytoma cell lines and 7 of 10 primary brain tumor biopsies</td>
<td>Reduced cell transformation, migration and invasion, and enhanced apoptosis following DNA damage.</td>
<td>(33,34)</td>
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<tr>
<td>Breast cancer</td>
<td>Downregulated in breast cancer tissues</td>
<td>Overexpression of Src homology 2 domain-containing phosphatase substrate-1 (SIRPα) resulted in suppression of anchorage-independent cell growth in soft agar, and in peritoneal dissemination in nude mice. Forced expression of SIRPα specifically suppressed anchorage-independent growth of the breast cancer cell lines, Hs578T and MCF7.</td>
<td>(7,35)</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Lower expression in hepatocellular carcinoma tissues than in matched normal tissues</td>
<td>Overexpression of SIRPα1 resulted in a decrease in hepatocellular carcinoma cell number. SIRPα1-transfected Huh7 cells exhibited reduced cell migration and invasion in a manner that was dependent on SIRPα1/SHP-2 complex formation.</td>
<td>(36,37)</td>
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<tr>
<td>Myeloid malignancies</td>
<td>Significantly suppressed in the majority of myeloid malignancies</td>
<td>Downregulation of SIRPα resulted in β-catenin upregulation. Thus SIRPα downregulation may contribute to the biology of cancer through β-catenin upregulation. In SIRPα1-suppressed myeloid K562 cells, significant phosphorylation of extracellular signal-regulated kinase Akt and GSK-3β (on Ser9) resulted in inactivation of GSK-3β leading to the induction of β-catenin.</td>
<td>(8,38)</td>
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SIRP, signal regulatory protein; GSK, glycogen synthesis kinase.

Table I. Expression and functions of SIRPα in various cancers.
SIRPα-CD47 blockade was strictly dependent on signaling lymphocytic activation molecule 7. In solid tumors, a moderate increase in CD47 expression has been detected compared with normal tissues, and CD47 transcript expression correlated with adverse prognosis (26). However, inhibition of CD47 function led to tumor cell phagocytosis and elimination (27). Mice harboring leiomyosarcoma, a smooth muscle tumor, have reportedly exhibited significantly reduced primary tumor size following treatment with anti-CD47 antibodies (27). In pancreatic neuroendocrine tumors (28) and small lung cell cancer (29), blocking CD47 signaling inhibited xenograft tumor growth. Although these studies were at the preclinical investigation stage, clinical trials of anti-CD47 antibodies are underway in solid and hematological malignancies (23).

4. SIRPα in cancer

Although SIRPα is widely expressed in numerous tissues, SIRPα downregulation has been reported in various cancers (Table I). In general, SIRPα downregulation may result in the activation of downstream signaling pathways that ultimately leads to the augmentation of cancer cell growth. For instance, downregulation of SIRPα expression has been reported in prostate cancer tissues and cell lines; and SIRPα overexpression resulted in a reduction in the number of live prostate cancer cells, whereas SIRPα silencing increased prostate cancer cell proliferation (30).

SHP-2, a ubiquitously expressed SH2-domain-containing tyrosine phosphatase, has been implicated in a variety of signal transduction pathways induced by cytokines, hormones and growth factors including EGF (31,32). It has been demonstrated that SIRPα receptor associates with SHP-2 to negatively regulate EGF receptor-mediated phosphatidylinositol 3-kinase (PI3K) signaling, resulting in reduced cell transformation, migration and invasion, and enhanced apoptosis following DNA damage in human glioblastoma cells (33). Transfection of SIRPα into the glioblastoma cell line, U87MG, has also been reported to inhibit cell migration and invasion on fibronectin (33). Additionally, it was revealed that SIRPα was expressed in 8 out of 9 astrocytoma cell lines and 7 out of 10 primary brain tumor biopsies (34).

Oshima et al (35), demonstrated that SIRPα was downregulated in breast cancer tissues compared with in matched normal tissues. In v-Src-transformed BALB/c3T3 cells, overexpression of SIRPα resulted in suppression of anchorage-independent cell growth in soft agar, as well as peritoneal dissemination in nude mice (35). Yamasaki et al (7), have also demonstrated that forced expression of SIRPα1 specifically suppressed anchorage-independent growth of the breast cancer cell lines, HS578T and MCF7.

In addition, SIRPα1 downregulation has been identified in hepatocellular carcinoma tissues and cells, and its overexpression in these cells resulted in a decrease in cellular growth (36,37). Furthermore, the treatment of SIRPα1-transfected Huh7 cells with EGF or hepatocyte growth factor induced tyrosine phosphorylation of SIRPα1 and its association with SHP-2, which was accompanied with reduced extracellular signal-regulated kinase (ERK) 1 phosphorylation (36,37). These SIRPα1-transfected Huh7 cells also exhibited reduced cell migration and invasion.

SIRPα expression has also been reported as significantly suppressed in the majority of myeloid malignancies (38). Notably, there was a lack of SIRPα1 expression in 4 out of 4 chronic myeloid leukemia patients and in 26 out of 59 AML patients analyzed, while there was significantly upregulated expression in normal myelomonocytic cells and in bone marrow hematopoietic stem/progenitor cells (38). Therefore, the suppressed expression is considered to serve a role in the pathogenesis of these cancers through aberrant signaling. Our group has previously reported that the expression of SIRPα1 correlated with the expression of myeloid transcription factor PU.1 in PU.1 transgenic K562 cells (39). As downregulation of PU.1 induces AML development (40,41), suppression of SIRPα1 expression induced by PU.1 downregulation may serve a role in the pathogenesis of AML. Additionally, our group has revealed that SIRPα1 downregulation resulted in β-catenin upregulation (8). Furthermore, it was identified that in SIRPα1-suppressed myeloid K562 cells, there was significant phosphorylation of ERK, Akt and glycogen synthesis kinase (GSK)-3β (on Ser9); these phosphorylations may have been responsible for inactivation of GSK-3β and thus the induction of β-catenin (8). As the induction of β-catenin is a hallmark of cancer (42), it is possible that SIRPα1 downregulation contributes to the biology of cancer through β-catenin upregulation. Our group has also observed that SIRPα1 downregulation leads to aberrant cell survival of serum-starved SIRPα1-knockdown cells (unpublished observations). The Ras-ERK-MAPK pathway (43,44) and PI3K/Akt signaling (45) are frequently activated in AML patient myeloblasts, contributing to proliferation, survival and drug resistance of these cells. Therefore, SIRPα1 downregulation may contribute to constitutive activation of these signaling pathways, ultimately resulting in the aberrant proliferation and survival of AML myeloblasts.

5. Conclusion

Increasing data suggests a role of SIRPα in immunity and various cancers. SIRPα downregulation may serve, at least in part, a role in the abnormal cell growth, invasion and survival of cancers through aberrant intracellular signaling. In addition, blocking CD47 ligand may be a promising therapeutic strategy, particularly against hematological malignancies. Further analysis of the SIRPα-CD47 axis may provide novel insight into cancer biology and aid the development of molecular-targeted therapies.

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References


