

Implications of CD47 in Tumor Biology

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Cancer is a leading cause of death worldwide. Despite treatment advances, high rates of tumor recurrence emphasize the need for new therapeutic strategies. Tumors often acquire mechanisms to avoid detection by the immune system, allowing them to develop and metastasize. Immunotherapy is a type of treatment designed to overcome these mechanisms by reactivating the immune system to eliminate tumors. CD47 is a cell surface protein and marker of “self” expressed on cells throughout the body and prevents them from being “eaten” by cells of the immune system. CD47 has also been described to have immune-independent functions in normal and malignant cells which could contribute to tumor growth and progression.

CD47

immune checkpoint inhibitors

non-small cell lung cancer

1. CD47 Is a Ubiquitously Expressed Transmembrane Protein Upregulated in Cancer

CD47, also known as integrin-associated protein (IAP), is a 50 kDa cell surface protein with an IgV-like extracellular N terminal domain, five transmembrane domains, and a C-terminal cytoplasmic tail with four isoforms [\[1\]](#). Structurally, the IgV-like extracellular domain is composed of two beta-sheets linked by a cysteine bridge and tethers CD47 to the cell membrane [\[2\]\[3\]](#). A number of post-translational modifications on CD47 have been identified, including ubiquitination, phosphorylation, and glycosylation, as well as pyroglutamate and heparan sulfate modifications that alter its structure, expression, localization, and function [\[2\]\[4\]\[5\]\[6\]\[7\]\[8\]](#). The extracellular domain of CD47 binds to multiple ligands, while the cytoplasmic domain associates with Gi and other proteins [\[9\]\[10\]](#). These interactions transduce signals that regulate a plethora of cellular processes in diverse cell types as summarized below [\[11\]\[12\]](#) (**Figure 1**).

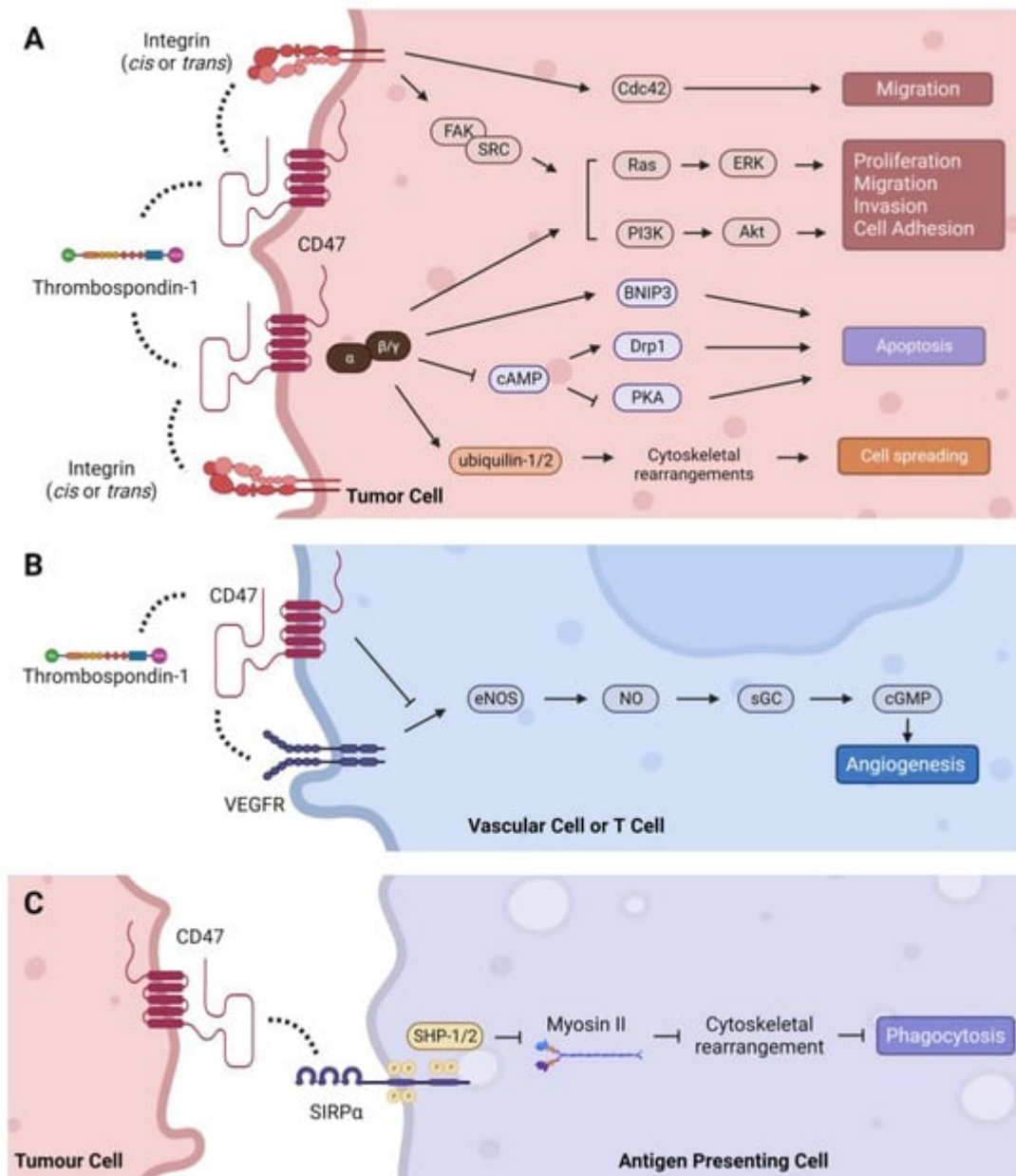


Figure 1. Intracellular signaling pathways regulated by CD47. **(A)** TSP-1 can indirectly activate integrin signaling through CD47 to stimulate Cdc42, as well as the Ras/ERK and PI3K/Akt pathways via FAK/SRC to regulate tumor-promoting processes such as cell proliferation, migration, invasion, and adhesion. CD47 signals through G_i proteins to promote cell proliferation through the PI3K/Akt pathway and cell spreading via direct association with ubiquilins. CD47-G_i interaction also regulates apoptosis by inhibiting cAMP-dependent signaling pathways, and CD47 can induce apoptosis directly through its interaction with BNIP3. **(B)** TSP-1 mediated inhibition of angiogenesis is CD47-dependent. Binding of TSP-1 to CD47 causes CD47 to dissociate from VEGFR2 and inhibits phosphorylation of VEGFR2, thereby suppressing the angiogenesis pathway. **(C)** CD47 binding to SIRP α initiates a signaling cascade that inhibits phagocytosis in macrophages and dendritic cells. Dashed lines indicate protein interactions.

CD47 is expressed in cells and tissues throughout the body, with relatively high levels on cells derived from the hematopoietic system including erythrocytes (red blood cells, RBCs) and hematopoietic stem and progenitor cells [1][13][14][15][16][17][18]. CD47 is also expressed as a >250 kDa proteoglycan on T cells, endothelial cells, and vascular smooth muscle cells [4]. Oldenborg and colleagues reported CD47 as a “marker of self” after discovering that RBCs lacking CD47 were eliminated by splenic macrophages [15]. Subsequent studies found that CD47 expression on RBCs decreases over their lifetime to mark aged cells for phagocytic clearance [14][19]. Regulation of platelet homeostasis via CD47 expression has also been described [20]. Upon recognition of its role in inhibiting phagocytosis, akin to CD31 disabling phagocytosis of viable cells, CD47 was later coined a “don’t eat me” signal [21]. CD47 is upregulated in many malignancies, and the first observations of cancer-associated CD47 overexpression were made in ovarian cancer [22][23]. Since then, CD47 expression has been described in various tumor types including NSCLC and SCLC, with numerous studies reporting its association with tumor stage and patient survival.

2. Regulation of CD47 Expression in Cancer

Several mechanisms have been described to regulate CD47 transcription in cancer cells [24]. Expression of CD47 can be controlled by cytokines, oncogenes, and micro-RNAs (miRNA). In liver and breast cancer cells, TNF α induces CD47 expression through the transcriptional regulator, NF- κ B [25][26]. In melanoma models, CD47 expression was induced by IFN γ , although the exact mechanism remains to be elucidated [27][28]. Interleukins also appear to upregulate CD47 expression. IL-6 induced CD47 through STAT3 in hepatoma cells, and IL-1 β induced CD47 via NF- κ B in cervical cancer cells [29][30]. CD47 induction by IL-4, IL-7, and IL-13 has also been described, but how these interleukins stimulate CD47 transcription is unknown [30][31]. These immune-stimulating, pro-inflammatory cytokines may be physiologically programmed to induce CD47 expression, like PD-L1, as a negative feedback mechanism to prevent harmful overactivation of the immune response. Both MYC and HIF-1A oncogenes have been shown to directly bind the CD47 promoter and induce its transcription in breast, leukemia, and lymphoma models [32][33]. On the contrary, multiple miRNA have been shown to negatively regulate CD47 expression in several cancer types by degrading CD47 transcripts or blocking protein translation. These include miR-133a, miR-155, miR-192, miR-200a, miR-222, miR-340, and miR-708 [24]. Two recent studies established novel mechanisms of CD47 expression regulation by the oncogenic drivers, EGFR and KRAS. In NSCLC, KRAS was discovered to upregulate CD47 by suppressing miR-34a [34]. Specifically, KRAS-mediated activation of PI3K-AKT signaling led to the phosphorylation of STAT3 and its transcriptional repression of miR-34a, thereby relieving post-transcriptional inhibition of CD47 and increasing its expression. Similarly, EGFR was found to upregulate CD47 by stabilizing its expression. In glioblastoma models, EGFR activation induced c-Src-mediated phosphorylation of CD47, which prevented its interaction with the E3 ubiquitin ligase, TRIM21, and protected CD47 from ubiquitin-associated degradation [8].

3. CD47: Molecular Interactions, Signaling Pathways, and Malignant Phenotypes

CD47 regulates various signaling cascades by interacting with different proteins including those located intra- or extracellularly, within the plasma membrane or in the extracellular matrix (ECM). These interactions occur in either a cis (same cell) or trans (different cell) manner and are dependent upon CD47's IgV-like, transmembrane, and cytoplasmic tail domains. The most well characterized CD47 interaction partners include thrombospondin-1, integrins, and members of the signal-regulatory protein (SIRP) family, which signal through CD47 to promote various hallmarks of cancer.

3.1. Thrombospondin-1 (TSP-1)—Proliferation, Migration, Cell Death, and Angiogenesis

TSP-1 is an extracellular matrix (ECM) glycoprotein secreted by platelets, macrophages, dendritic cells, endothelial cells, smooth muscle cells, and epithelial cells in response to stress, as well as tumor and stromal cells in the TME. TSP-1 interacts with many proteins including integrins, collagen, fibrinogen, laminin, proteases, and growth factors to regulate diverse physiological processes such as vascular response to injury, inflammation, platelet activation, and ECM remodeling [35][36]. The cellular effects of TSP-1 are dependent on tissue-specific expression of its receptors and other interacting partners in the local environment. The C-terminal domain of TSP-1 binds the extracellular region of CD47 at picomolar concentrations to control motility, proliferation, and angiogenesis that influence the invasive and metastatic properties of cancer cells [35]. For example, CD47–TSP-1 interaction promoted tumor progression in a T cell lymphoma model by supporting proliferation, survival, and migration via activation of ERK, AKT and survivin signaling [37]. Similarly, antibody-mediated cross-linking of CD47 on T cells stimulates their activation and proliferation [38][39]. In contrast, TSP-1-induced cell death in leukemia, lung, breast, and colon cancer cell lines in a CD47-dependent, caspase-independent manner [40][41][42]. In non-malignant T cells, binding of CD47 by TSP-1 has been shown to induce caspase-independent apoptosis and stimulate migration, and to suppress activation-induced proliferation, CD69 expression, and IL-2 production, further illustrating the context-specific effects of CD47–TSP-1 interactions [4][43][44][45][46]. CD47–TSP-1 binding has also been implicated in mediating sensitivity to cancer therapies. Interaction of CD47 and TSP-1 blocked the escape of breast and colorectal cancer cells from chemotherapy-induced senescence and sensitized melanoma cells to radiotherapy in a cell autonomous manner [47][48]. CD47 blockade also protected mice from lethal whole-body irradiation that was associated with an increase in autophagy in surviving cells [49]. However, the specific mechanisms explaining these responses to therapy remain to be defined.

Studies in endothelial cell models have deduced a role for CD47 in regulating angiogenesis through the VEGFR2 signaling pathway [11][50]. First, CD47 was found to be essential for TSP-1-mediated inhibition of nitric oxide-stimulated responses in vascular cells [51]. It was later discovered that CD47 physically associates with VEGFR2 in endothelial and T cells, and that CD47 ligation by TSP-1 disrupts this physical interaction with VEGFR2, which inhibits its phosphorylation and downstream signaling [52][53]. It is unclear how the CD47–TSP-1–VEGFR2 axis influences angiogenesis in tumors because of conflicting findings in tumor models, which may be confounded by irregularities in tumor vasculature and the enigmatic role of nitric oxide in regulating tumor angiogenesis [54]. Studies in melanoma and breast tumors found that TSP-1 overexpression in cancer cells negatively regulated tumor blood flow in response to vasoactive agents in a CD47-dependent manner [55]. Recent studies reported that

disrupting the CD47–TSP-1 interaction reduced angiogenesis in neuroblastoma and glioblastoma models, but selectively depleting CD47 in stromal cells increased angiogenesis and tumor burden in a syngeneic prostate cancer model [56][57]. Furthermore, inhibition of CD47 normalized tumor vasculature in a multiple myeloma model, which was associated with reduced expression of pro-angiogenic factors, increased expression of anti-angiogenic factors, and tumor growth inhibition [58]. Thus, the effects of TSP-1-CD47 interactions on angiogenesis may be malignancy-dependent, and further studies are needed to fully understand them.

3.2. Integrins—Migration, Invasion, and Inflammation

CD47 was originally named integrin-associated protein (IAP) because it was discovered that it binds with several members of the integrin family of transmembrane receptors, including integrins $\alpha\beta3$, $\alpha11\beta3$, and $\alpha\beta1$ [10]. Subsequently, CD47 has been shown to interact with $\alpha5$, $\alpha4\beta1$, $\alpha6\beta1$, among others [50]. Integrins facilitate cellular attachment to the ECM via the actin cytoskeleton and regulate focal adhesion kinase (FAK), integrin-linked kinase (ILK), and SRC kinase signaling pathways including Ras-ERK, PI3K/AKT, and YAP/TAZ, which support tumor growth and progression [59]. Lateral (cis) interactions between CD47 and integrins form signaling complexes that can activate integrins and influence binding to ECM proteins [12][50]. They also promote migration and metastasis phenotypes in a seemingly cancer-specific manner [12], which may be explained by differences in integrin expression across cancer types. Interactions between CD47 and $\alpha\beta3$ enhanced binding of ovarian and breast cancer cells and spreading of melanoma cells on vitronectin-coated substrates, as well as chemotaxis of prostate cancer and melanoma cells towards collagen [60][61][62][63]. CD47- $\alpha4\beta1$ interactions stimulated adhesion in melanoma, lymphoma, and T cells, and promoted migration in B-cell leukemia models [64][65][66]. Notably, many of these processes are dependent on the ligation of CD47 by TSP-1, TSP-1-derived peptides (e.g., 4N1K), or anti-CD47 antibodies. In addition to these cancer cell-intrinsic effects, CD47–integrin interactions can influence tumor immunity by modifying the behavior of immune cells in the TME [10]. For instance, CD47-blocking antibodies inhibited CD23-stimulated secretion of several pro-inflammatory cytokines including TNF α , IL-1 β , and PGE2 from monocytes and IFN γ from T cells through a CD47– $\alpha\beta3$ complex [67]. Consistently, CD47 ligation with antibodies or 4N1K suppressed IL-12 release from monocytes and inhibited the transition of naive T cells to Th1 effector cells [68][69]. Additional mechanistic studies to investigate CD47–integrin interactions in different cancer models are needed to better understand the generalizability of their cellular effects.

3.3. SIRP α/γ —Phagocytosis and Tumor Immune Evasion

The SIRP family is a group of cell surface receptors primarily expressed on myeloid cells [70]. Of the three identified members, SIRP α binds CD47 with the highest affinity and is expressed on macrophages, dendritic cells, T cells, hematopoietic progenitor cells, and neurons [9]. Hatherley et al. identified five key residues (Y37D, D46K, E97K, E100K, E106K) in the extracellular domain of human CD47 that are critical for binding to SIRP α [2]. In addition, Gln-19 must be enzymatically modified to pyrrolidone carboxylic acid (pyroglutamate) for SIRP α to bind CD47 [6]. CD47–SIRP α interaction initiates a signaling cascade that inhibits phagocytosis, and this pathway has been the primary focus for developing CD47-targeted therapies. Upon CD47–SIRP α ligation, the intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM)-domain in the cytoplasmic tail of SIRP α is phosphorylated.

This recruits the inhibitory phosphatases, SHP-1 and SHP-2, which dephosphorylate myosin II, thereby preventing reorganization of the cytoskeleton that is required for phagocytosis to occur [71]. Consequently, antigen uptake and presentation by APCs and subsequent activation of the adaptive immune response is inhibited [72]. In addition to SIRP α , SIRP γ also binds to CD47 but with ten times lower affinity [73]. SIRP γ is expressed on NK cells and lymphocytes, and studies have shown that CD47–SIRP γ interactions positively regulate T cell transendothelial migration, T cell activation, and apoptosis of Jurkat cells, which could be undesirably impaired by CD47 blockade [73][74][75][76].

3.4. Intracellular Interactions and Signaling

Many of the interactions described above transduce extracellular signals to intracellular molecules bound to CD47's cytoplasmic tail to elicit associated cellular effects. Initially, CD47 was co-immunoprecipitated with heterotrimeric G α proteins in membranes isolated from platelets, melanoma, and ovarian cancer cells, which was reversible by the potent inhibitor of receptor–G α protein binding, pertussis toxin [77]. Evidence that CD47 activates G α proteins was provided by the finding that 4N1K ligation decreased intracellular cAMP levels [77]. Later studies found that CD47 interacts with two ubiquitin-related proteins involved in protein degradation, ubiquitin-1 and ubiquitin 2, via tethering to CD47 by G $\beta\gamma$ [78][79][80]. This interaction induced cytoskeletal rearrangements and enhanced spreading of Jurkat and ovarian cancer cells [79]. Subsequently, the CD47–G $\alpha\beta\gamma$ pathway was shown to activate PI3K/Akt signaling to induce proliferation in astrocytoma cells [81]. Additional cytoplasmic signaling cascades regulated by TSP-1–CD47-mediated G α activation and consequential reductions in cAMP levels include the phosphorylation of SYK and LYN and their interaction with FAK during platelet aggregation; phosphorylation of ERK during smooth muscle cell migration and T cell lymphoma migration and adhesion; and inhibition of PKA during apoptosis in activated T cells [37][65][82][83][84]. In addition to G α proteins, the cytoplasmic domain of CD47 has also been shown to directly interact with the BCL-2 family member, BNIP3, to induce a necrosis-like mode of caspase-independent T cell death upon CD47 ligation with TSP-1 [45]. Most recently, c-Src was reported to bind and phosphorylate CD47 in an EGFR-dependent manner, which led to CD47 stabilization and immune evasion in a glioblastoma model [8]. Besides these direct physical associations, CD47 has been discovered to indirectly interact with several other cytoplasmic proteins to regulate various cancer-relevant processes. These include interactions with Cdc42, Drp1, and guanylate cyclase (GC), as well as regulation of autophagy proteins that collectively influence cell death and survival, migration, invasion, and angiogenesis [11][49][50][85][86].

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