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CD55 in cancer: Complementing functions in a non-canonical manner

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Abstract

CD55, or decay accelerating factor, is a membrane lipid microdomain-associated, GPI-anchored protein implicated in the shielding of cells from complement-mediated attack via accelerating decay of C3 and C5. Loss of CD55 is associated with a number of pathologies due to hyperactivation of the complement system. CD55 is also implicated in cancer progression thought to be driven via its role in cell shielding mechanisms. We now appreciate that CD55 can signal intracellularly to promote malignant transformation, cancer progression, cell survival, angiogenesis, and inhibition of apoptosis. Outside-in signaling via CD55 is mediated by signaling pathways including JNK, JAK/STAT, MAPK/NF-κB, and LCK. Moreover, CD55 is enriched in the cancer stem cell (CSC) niche of multiple tumors including breast, ovarian, cervical, and can be induced by chemotherapeutics and hypoxic environments. CSCs are implicated in tumor recurrence and chemoresistance. Here, we review the unexpected roles of CD55 in cancer including the roles of canonical and noncanonical pathways that CD55 orchestrates. We will highlight opportunities for therapeutic targeting CD55 and gaps in the field that require more in-depth mechanistic insights.

Keywords

CD55; DAF; Decay accelerating factor; Cancer stem cell; Complement pathway

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Author contributions section

Rashmi Bharti: Conceptualization, methodology and writing – original draft, **Goutam Dey:** Conceptualization, methodology, writing – original draft, **Feng Lin:** Formal analysis and editing, **Justin Lathia:** Formal analysis and editing, **Ofer Reizes:** Resources, supervision, conceptualization, investigation, funding acquisition, writing – review & editing and approval of final draft.

Declaration of competing interest

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1. Introduction

The complement system is part of the innate and adaptive immune systems, participating in the formation of membrane attack complexes on foreign target cells. The complement cascade involves over 30 proteins that can be activated by three distinct pathways: (I) Classical pathway, (II) Lectin pathway, and (III) Alternative pathway [1]. In the classical pathway, immunoglobulins bind to antigens on target cells (Fig. 1A). This binding event activates and recruits the C1 complex proteins: C1q, C1r, and C1s. The C1 complex cleaves C2 and C4 by serine protease activities and ultimately assembles the C3 convertase (C4b2a). The lectin pathway is activated after mannose-binding lectin (MBL), ficolins, or MBL-associated serine proteases bind to certain carbohydrates, which constitute C3 convertase. The alternative pathway occurs spontaneously by hydrolysis of the internal C3 thioester bond, ultimately forming a different C3 convertase (C3bBb) after interacting with other complement proteins. C3 and C5 convertases sequentially cleave their respective complement components in the activation cascade, which ultimately assembles the membrane attack complex (MAC), leading to pore formation and subsequent lysis and/or damage of the target cells. CD55, also known as decay-accelerating factor (DAF), protects cells from complement-mediated attack by degrading the C3 and C5 convertase necessary for downstream formation of the MAC [2]. CD55 is a glycophosphatidylinositol (GPI)-anchored cell surface glycoprotein with a molecular weight that varies from between 50 and 100 kDa depending on cell type. CD55 was first discovered in 1969 on the cell surface of an erythrocyte [3]. From then, multiple studies have focused on the role of CD55 in immune surveillance. Structural analysis defined CD55 as a cell surface membrane protein associated in lipid microdomains due to its C-terminal GPI linkage, processed in the endoplasmic reticulum. Of the 2300 publications that focus on CD55, the majority focus on the canonical roles in regulation of complement. CD55 is associated with various diseases including angiopathic thrombosis [4], protein-losing enteropathy [5], complement hyperactivation [4], paroxysmal nocturnal hemoglobinuria [6], and certain autoimmune disorders [7]. More recently, CD55 has been implicated in cancer progression, cancer stem cells, and chemoresistance. Given the emergent functions of CD55 in cancer, here we focus on these new roles in cancer and therapeutic opportunities that target its signaling axis.

1.1. CD55 structure and cellular localization

Mature CD55 has three domains: (I) consensus repeat domains consist of four short consensus repeat (SCR) domains e.g. SCR-1, SCR-2, SCR-3 and SCR-4; (ii) O-linked carbohydrate domain having a serine/threonine/proline-rich region, and (iii) GPI anchor [42]. The SCR-2, 3, and 4 domains play a key role in the attenuation of complement-mediated cytotoxicity.

The GPI anchor tethers CD55 to the outer leaflet of the cell membrane at lipid raft microdomains. The C-terminal ca.30 amino acids of the pro-CD55 protein contain the GPI trafficking code and are cleaved during processing. CD55 post-translational GPI anchor processing occurs in the ER and is modified within the Golgi apparatus prior to transport to the cell membrane and partition in microdomains. Lipid rafts are dynamic structures composed of sphingolipid and cholesterol [43] that are randomly distributed at the cell

surface. Lipid rafts regulate the distribution of cell surface receptors and proteins providing a platform for concentrating receptors, acting as signaling hubs. The role and function of lipid rafts remains under investigation. However, the prevailing understanding of lipid raft function is that it facilitates signaling hubs including TCR (T-Cell receptor), RAS, Hedgehog, EGFR (Epidermal growth factor receptor), and Insulin Receptor [44]. Nagaraj reported that CD55 can maintain the integrity of the lipid raft, as genetic deletion leads to structural changes and loss of integrity of the microdomains [45]. CD55 also localizes to the surface of extracellular vesicles such as exosomes where it can prevent complement-mediated attack [46]. While primarily localized to the cell surface, soluble CD55 isoforms have been identified that lack the C terminal GPI anchorage domain formed via alternative splicing [47]. These soluble isoforms of CD55 are distributed in the extracellular matrix, plasma, urine, and bodily fluids, suggesting alternate complement independent functions.

1.2. CD55 and its receptor

Cell-surface CD55 is a ligand for CD97, a member of the epidermal growth factor seven-span transmembrane (EGF-7TM) receptor family. CD97 is composed of an extracellular domain (α-subunit) and a 7TM transmembrane domain (β-subunit) [48]. The interaction between CD55 and the α-subunit of CD97 and leads to activation of intracellular signaling sufficient to activate T-cells [49]. CD97 is present on the cell surface of multiple cell types including immune cells, epithelial cells, hematopoietic stem cells, and muscular cells [36]. Moreover, CD97 is highly expressed in many cancers including pancreatic, cervical, colon, thyroid, and oral cancer, as well as various leukemias [50]. In glioblastoma, CD97 was found to be upregulated and targeted by DAF-Fc, a CD55 fusion protein that blocks the interaction between cell-surface DAF and CD97 and may inhibit cancer cell invasion and migration [51]. Indeed, CD55 can stimulate CD97 to trigger downstream signaling and modulate cancer metastasis [52]. Activated CD97 in co-ordination with GRK6 (G protein-coupled receptor kinase 6) leads to upregulation downstream matrix metalloproteinases, MMP-2 and MMP-9 in hepatocellular carcinoma cells (Fig. 1B). Notably, in colorectal cancer cells, CD97 promotes stabilization of glycogen synthase kinase-3 beta, adenomatous polyposis coli and β-Catenin complex (GSK3β -APC -β-Catenin) [53]. $CD55^{-}$ CD97 axis facilitates β-Catenin entry to the nucleus and bind with TCF transcription factor to increase gene expression of CCND1, MYC, and Matrix metalloproteinase 7 (MMP7) to drive oncogenesis. In normal erythrocytes, CD97 promotes degradation of GSK3β -APC-β-Catenin complex resulting inactivation of this pathway (Fig. 1B).

CD55 can signal via a CD97 independent mechanism. Various report point to induction of CD55 expression that is sufficient to activate intracellular signaling. In osteoclasts, CD55 can regulate bone formation via a CD97 independent mechanism. The findings of Bongjin et al. indicate that CD55 activates Rac and Rho GTPas to support bone resporption [54]. The findings are similar to those of Saygin et al. showing CD55 activity does not depend on CD97 as CD55 is sufficient to activate JNK/LCK via LIME/ROR2 [37].

1.2.1. CD55 and cancer—Since its discovery, CD55 has been implicated in diverse biological and pathophysiological states (Fig. 2). There is a growing appreciation that CD55 has an essential role in cancer. Specific roles and molecular mechanisms of CD55 in

prostate, ovarian, cervical, glioma, breast, colorectal, lung, and thyroid cancers, as well as in non-Hodgkin lymphoma, renal chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and acute myeloid leukemia (AML) are summarized in Table 1. Where studied, CD55 is implicated as a promoter of cancer cell survival and metastasis. CD55 gene and protein expression is induced via multiple growth factors and cytokines across a wide spectrum of cancers. Epidermal growth factor (EGF) can induce CD55 mRNA and protein expression via the p42/44 MAPK pathway in HT-29 colon cancer cells [55]. Likewise, vascular endothelial growth factor (VEGF) is able to induce CD55 expression in HUVEC cells [32]. Cytokines such as TNF-α, IL-6, and IL-1β treatment all increase CD55 expression in Hep3B hepatoma cells [56]. Induction of CD55 is implicated in tumorigenesis and disruption of CD55 leads to anti-cancer effects multiple cancers including ovarian [37], cervical [57], breast [58], prostate [34], and gastric [59] cancers, as well as in leukemia [60]. CD55 gene expression can be impacted by SNPs. Zhang and colleagues found that rs2564978 SNP in the promoter region of CD55 is associated with non-small cell lung cancer and regulates promoter activity [61]. As such, CD55 variants may provide alternate modes of regulation in cancer.

The expected role, based on Occam's razor, would suggest the canonical role for CD55 in protection of cancer cells from complement mediated lysis [62] and indeed several studies support this proposal, including in response to hypoxia [63]. However, our findings and others indicate that CD55 can utilize noncanonical- or noncomplement-mediated signaling in promoting cancer proliferation, chemoresistance, and metastasis. Saygin and colleagues study indicates that CD55 triggers a bi-furcating and non-complement signaling pathway in ovarian cancer cells [37]. Detailed mechanistic analysis reveals that CD55 interacts with membrane associated adaptor proteins, LIME and ROR2 and transmits its signaling to JNK pathway resulting in increased expression of NANOG, SOX2, and OCT4 known to be master regulators self-renewal. This complex noncanonical CD55 signaling network is essential for cancer stem cell maintenance in endometrioid subtype of ovarian cancer. CD55 also transmits it signal to the nucleus via CD55-LIME-LCK pathway leading to altered DNA repair gene genes such as BRCA1 and MLH1. This altered expression of DNA repair genes and stem cells regulators NANOG, SOX2, and OCT4 is sufficient to drive platinum resistance in ovarian cancer cells [37]. The findings point to an unappreciated role for CD55 in outside-in signaling.

2. CD55 and oncogenic signaling pathway

The prevailing hypothesis for CD55 cancer promotion is via blockade of complement-mediated pathway [2]. However, it has become apparent the cell surface CD55 is a driver of multiple intracellular oncogenic pathways including malignant transformation, cell survival, stem cell enrichment, and chemoresistance via outside-in signaling (Fig. 1B).

2.1. Activation of tyrosine kinase pathways

CD55 is implicated in activation LCK and FYN, members of the SRC family of non-receptor tyrosine kinases. The SRC tyrosine kinase family is a subgroup tyrosine kinase superfamily and implicated in cancer progression, cell growth, and differentiation [73].

Membrane bound CD55 is reported to promote phosphorylation of the non-receptor tyrosine tyrosine kinase proteins, LCK and FYN in Jurkat cells [74]. These tyrosine kinases promote tumorigenesis and chemoresistance in multiple cancers [74]. In ovarian cancer, CD55 is sufficient to activate LCK kinase by promoting autophosphorylation at tyrosine 394 [37]. As a result, DNA repair genes are induced. As CD55 is a GPI-anchored protein the communication with intracellular signaling pathways requires an adapter protein. In endometrioid ovarian cancer we determined the LIME adapter protein is sufficient to link CD55 to intracellular activation of LCK and downstream signaling [37]. The available data indicates that CD55 engages LIME in lipid rafts. However, the mechanism of outside-in signaling via CD55 to LIME remains to be investigated.

CD55 is implicated in decidualization during embryonic development in a p-SRC dependent pathways. CD55 leads to activation of cell proliferation and anti-apoptosis events essential steps during decidualization [75]. Low levels of CD55 results in abnormal decidualization and contributes to miscarriage. Mechanistically, downregulation of CD55 inhibits p-SRC and activates ERK pathway. In parallel, disruption of CD55 leads to suppression of EGFR, STAT3 and FOXO1 gene expression. Collectively, these studies point to a CD55 can signal in a noncanonical complement independent mechanism.

2.2. NF-κB/MAPK pathways

NF-κB as well as MAPK pathways are essential for tumor cell survival and growth in many cancers. Mammalian hepatitis B X-interacting protein (HBXIP) is highly expressed in tumors and activates complement regulatory proteins including CD55 via in MAPK/NF-κB oncogenic pathways in breast cancer cells leading to the prevention of complement mediated attack [76]. In Chinese Hamster Ovary (CHO) cells, CD55 plays a critical role in transduction of LPS signaling. LPS directly binds to CD55 leading to activation of downstream signaling via translocation of NF-κB and phosphorylation of IκB-α. LPS treatment in a CD55 dependent manner increases the phosphorylation of p38 and MAPK [77]. LPS binding to CD55 and the mechanistic triggers from outside-in are questions that remain unresolved. Likewise, in bone marrow, CD55 plays a critical role in survival and function of osteoclasts cells independent of complement. Mechanistically CD55 associates with and activates the receptor activator of NF-κB (RANK) in osteoclast cells leading to Rac signaling pathway and modulation of RANK/c-Src/Syk complex formation [54].

2.3. JNK pathway

Jun N-terminal kinase (JNK) is a mitogen activated kinase abnormally expressed in many malignant states. We showed that CD55 can activate LIME/ROR2 pathway to activate intracellular JNK signaling in ovarian cancer cells [37]. Inhibition of CD55, suppresses JNK signaling axis and disrupts expression of the self-renewal transcription factors SOX2, OCT4, and NANOG. Likewise, blocking JNK disrupts CD55 mediated action of pluripotency. Whether CD55 can augment pluripotency at other cancer sites remains to be investigated. As ligands for CD55 remain unidentified, the mechanism of ROR2 engagement and activation provide an opportunity for future studies. Identification the mechanisms of CD55 activation should yield opportunities to uniquely target this pathways.

2.4. JAK/STAT3 signaling

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) is a critical signaling pathway activated by various cytokines and growth factors. JAK/STAT is implicated in various cellular processes such as cell growth, cell division, and cell death. In ovarian cancer cells, the JAK/STAT3 pathway plays a critical role in malignant transformation and cell survival. CD55 is sufficient to activate JAK/STAT3 signaling in a CD97 dependent manner in ovarian cancer cells [78]. Structurally, the EGF_{3-5} domain of CD97 at N-terminus binds with SCR-(1–3) domains of CD55 in antiparallel orientation [79]. However, further studies are needed to explore whether CD55 activates CD97 via autocrine or paracrine manner.

2.5. HER2 signaling

HER2 is a member of human epidermal growth factor receptor family. Overexpression of HER2 is essential for the growth of many cancers. The monoclonal antibody trastuzumab is used in the management of HER2 positive cancers including breast carcinoma [80]. CD55 can protect HER2-positive breast cancer cells from the cytolytic effect of trastuzumab [66]. Conversely, PIPLC treatment or knockdown of CD55 can enhance the effect of trastuzumab in breast and uterine serous carcinoma [66,81]. Mechanistically, HER2 antibody trastuzumab contains IgG1 Fc which induces complement dependent cytotoxicity in cancer cells. As such, these findings implicate canonical CD55 signaling in prevention of HER2 antibody mediated complement regulation [66].

2.6. Hypoxia

Hypoxia or a state of low oxygen that triggers reshaping of the tumor microenvironment and induces a protective signaling pathway in cancer cells [82]. Hypoxia promotes sustained angiogenesis leading to increased neovascularization to support tumor growth [83]. Recombinant CD55 treatment is reported to protect hypoxia-induced apoptotic impact in neuronal cells via inhibition of complement activation [63]. Detailed molecular analysis shows that CD55 results in attenuation of C3a, MAC, C3a-C3aR interaction and downregulation of caspase-3 in hypoxic neuronal cells. Likewise, in colorectal cancer cells, CACO-2 and T84, induction of hypoxia was found to induce CD55 mRNA and protein expression [84]. Chromatin immunoprecipitation assays confirmed that hypoxia-inducible factor 1-alpha (HIF-1α) binds to the promoter region of CD55 during hypoxic responses in Hela cells. Similarly, in neuroblastoma cells, CD55 is an essential target of HIF-2α, another member of HIF family. Thus, hypoxia regulated CD55 leads to augmentation of invasive and anti-adhesive properties of neuroblastoma cancer cells [36]. In complementary studies investigating hypoxia in colon cancer, Olcina and colleagues found that hypoxic cancer cells become resistant to complement-mediated toxicity via CD55 [85]. Indeed, in HCT-116 and CT-26 colon cancer cells, hypoxia is sufficient to induce CD55 protein expression leading to prevention of complement-mediated toxicity. Findings to date indicate CD55 engages intracellular signaling pathways to maintain pluripotency and augment chemoresistance.

2.7. Chemoresistance

Chemoresistance is a major clinical challenge for cancer chemotherapy. CD55 is reported to induce cisplatin resistance in endometrioid ovarian cancer [37]. Saygin and colleagues defined a molecular signaling pathway driven by CD55 that activates cisplatin resistance via activation of LCK. Subsequent signaling leads to induction of homologous recombination DNA damage repair proteins. Inhibition of CD55 or LCK is sufficient to sensitize endometrioid ovarian cancer cells to platinum [86]. These studies point to a noncanonical signaling function for CD55. However, in breast cancer, CD55 promotes chemoresistance in response to neoadjuvant chemotherapy by suppressing antitumor immunity, indicative of a canonical pathway [41]. Lu and colleagues found that CD55 inhibited a subset of infiltrating B cell population in the tumor microenvironment. They identified a B cell population as a ligand for the T-cell-specific cell surface receptor ICOS positive population (ICOSL + B cells). During chemotherapy, ICOSL + B cells enhance the efficacy of chemotherapy via C3 complement activation. Whereas CD55 overexpression inhibits C3 complement activation and the ICOSL + B cell population resulting in chemoresistance. This findings offers a novel mechanism of chemoresistance and rational to target CD55 for cancer therapy.

2.8. Prognostic value of CD55

High levels of CD55 are indicative of poor prognosis in breast cancer. In a clinical analysis of 74 breast cancer patients, CD55 was elevated in 50 patients and the increased expression correlated with significantly higher relapse rate. Likewise, CD55 and CD97 were elevated in the invasive front of rectal adenocarcinoma [87] and high levels of CD55 was correlated with severity of cancer and reduced survival rate in gastric carcinoma [72], gallbladder cancer [35], pancreatic cancer [88] and intrahepatic cholangiocarcinoma [89]. Mechanistically, in pre-clinical animal models high expression of CD55 in cancer cells can attenuate apoptotic induction and enhance tumor growth [90]. Increased expression of CD55 is associated with metastasis and recurrence of cancer and indicated poor prognosis in colorectal cancer. So CD55 inhibition may be sufficient to destroy cancer cells. These studies indicate CD55 may define a patient population for CD55 directed therapies.

2.9. CD55 and cancer stem cell maintenance

Tumors exhibit a high degree of cellular heterogeneity and plasticity, a hallmark of the malignant state that likely accounts for continued growth, chemoresistance, and metastatic potential [91]. The heterogeneity may arise as a result of relatively rare tumor-resident, self--renewing, and chemoresistant cancer stem cells (CSCs) [92]. CD55 can regulate and promote stemness in multiple cancer models [93]. In cervical cancer, human papillomavirus E6 protein is sufficient to augment $CD55^+$ populations [65]. This upregulation of $CD55^+$ populations leads to enhanced stemness, tumorigenicity, and radioresistance in cervical cancer cells. In endometroid epithelial ovarian cancer, CD55 modulates stemness phenotype by employing a non-complement mechanism. CD55 directly interacts with adaptor protein LIME and transmits its signal to ROR2. These signaling activates downstream JNK pathway that leads to upregulation of pluripotency genes NANOG, SOX2, and OCT4 and augments a cancer stemness phenotype [37]. Recently, non-canonical role of CD55 have been investigated in human neuroblastoma cancer models [94]. Amplification of MYCN

is associated with neuroblastoma progression. MYCN binds the CD55 promoter leading to increased gene expression. Knock-down of CD55 showed inhibition of JNK pathway, OCT4 and Nanog protein expression in neuroblastoma cells in a complement independent mechanism. Thus MYCN-CD55 axis noncanonically regulates stemness phenotype in the neuroblastoma cells in a similar manner to the findings by Saygin and colleagues [37].

3. CD55 therapeutic strategies and future challenges

CD55 was first discovered in 1969 as a cell surface protein on erythrocytes. Since this discovery, over 2300 studies have been conducted to uncover the function, structure, and complexity of CD55 signaling. The effect of cell surface CD55 in complement regulation is well established. Here we provide a review of CD55 activity in non-complement or non-canonical functions such as activation of oncogenic signaling pathways. As a target, CD55 offers several pathways for cancer therapeutics. First, CD55 expression offers a pathway for disrupting cancer progression. SNP analysis has identified CD55 variants that may offer unexplored pathways for regulating CD55 expression in various cancers [61]. This may indicate opportunities to identify regulators of CD55 at the gene level. Second, blocking CD55 signaling has been reported to suppress stemness phenotype and chemoresistance in cancer cells [37]. These finding provide strong evidence for disrupting extracellular CD55 leads to improved outcomes in cancer therapy. Therapeutic approaches using monoclonal antibody targeting of CD55 have shown promising responses in inhibition of colorectal [40] and lung cancer [69]. Despite these promising approaches, to date, no small molecule inhibitor of CD55 protein is reported likely owing to limited understanding of engagement of CD55 with intracellular signaling pathways. A third approach could focus on CD55 activation of intracellular pathways. These include the pathways reviewed here such as ROR2/LIME/JNK, LCK, NF-KB, AKT, MAPK, JAK/STAT, and GSK-3β/β-Catenin pathways in cancer cells promoting cell proliferation, invasion/metastasis, increased stem cell formation, and chemoresistance. These downstream signaling pathways are well established and multiple drugs are in pre-clinical and in development though none are unique to CD55. We have much to learn about how CD55 triggers intracellular signaling, particularly in relation to the SCR domains, the Ser/Thr region, and whether GPI anchorage is necessary.

Finally, CD55 mediated signaling appears to be cell intrinsic for the most part and does not require engagement with CD97. Whether autocrine CD55 signaling via CD97 can occur remains to be investigated. Likewise, the existence of alternate splice forms of CD55 including a soluble variant that is expressed and detectable in the circulation indicates paracrine or hormonal role for CD55. Collectively, the data identify a need to improve our understanding of CD55 signaling in cancer and offers unique opportunities for silencing. These highlights the need of rigorous investigation of CD55 activated pathways for further development as a cancer therapy.

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Abbreviations:

DAF	Decay-accelerating factor
GPI	Glycosylphosphatidylinositol
LCK	Lymphocyte cell-specific protein-tyrosine kinase
JNK	c-Jun N-terminal kinases
MAPK	Mitogen-activated protein kinase
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
STAT	Signal transducer and activator of transcription
TCR	T Cell Receptor
EGF	Epidermal growth factor
VEGF	vascular endothelial growth factor
LIME	Lck-interacting transmembrane adapter 1
SCR	Short consensus repeat

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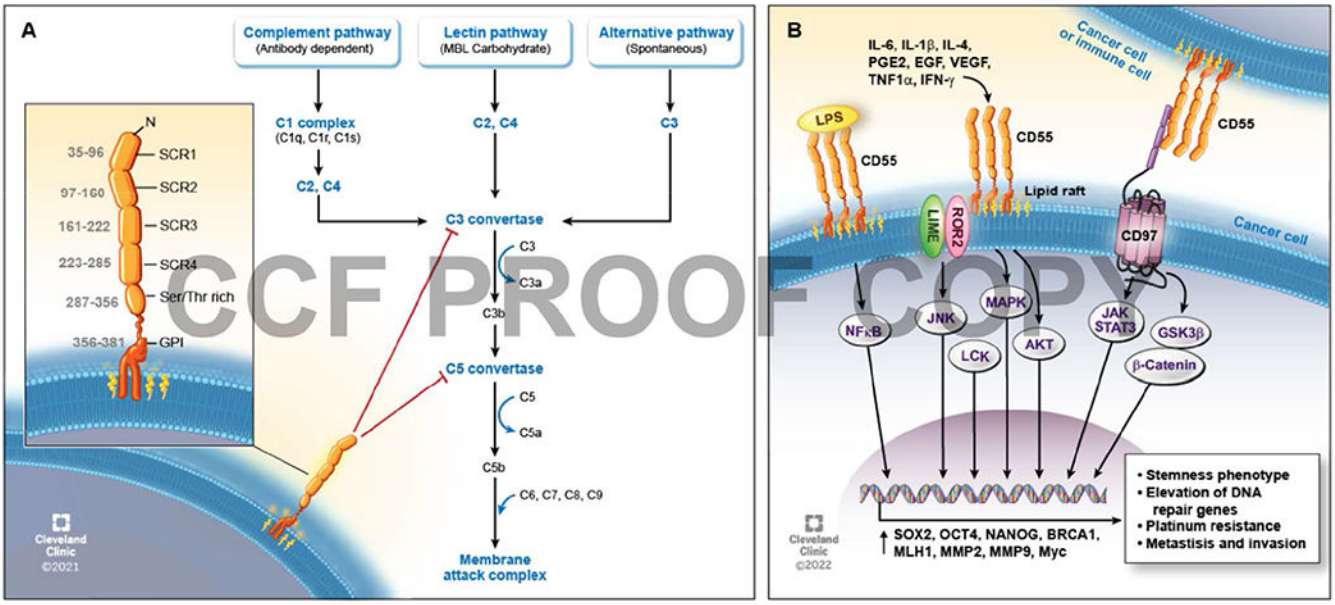

Fig. 1. Canonical and non-canonical function of CD55

(A) CD55 structure and its role in complement mediated pathway. **(B)** Non-complement role of CD55 signaling in cancer. CD55 can signal from outside in leading to activation of diverse oncogenic signaling pathways. Growth factors, cytokines, and prostaglandins augment or activate CD55 signaling. As a ligand for CD97, an epidermal growth factor seven-span transmembrane (EGF-7TM) receptor, CD55 can trigger intracellular signaling via Janus kinase/signal transducer and activator of transcription (JAK/STAT3) and GSK3β. These pathways can activate cascades that drive oncogenesis via Myc, resistance to chemotherapy via BRCA1 and MLH1, and CSC self-renewal via SOX2, OCT4, and NANOG.

Fig. 2.

Timeline of CD55 discovery [3, 8] [9] [10, 11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36–41]

Table 1

CD55 roles in diverse cancer sites.

Cancer	Role of CD55	Ref
Ovarian	•CD55 activates ROR2/JNK and LCK pathways to drive stemness phenotype and cisplatin resistance.	[37]
Endometrial/uterine	•CD55 is over-expressed in endometroid ovarian cancer.	[64]
Neuroblastoma	•High CD55 is associated with poor survival. CD55 is a HIF-2 alpha target gene	[36]
Cervical	•Short peptide targeting CD55 inhibits cervical cancer cell growth and induces apoptosis via BCL2/Caspase 3 pathway	[38]
	•HPV-E6 protein promotes enrichment of CD55 positive population and increases stemness phenotype, migration, and radio-resistance.	[65]
Prostate	•High level of CD55 observed in clinical specimens from advanced prostate cancer and CD55 knockdown inhibits tumor growth and metastasis.	[34]
Breast	•CD55 protects HER2 positive breast cancer cells from trastuzumab treatment.	[66]
	•High CD55 population is resistant to apoptosis with increased anti-apoptotic Bcl2 expression.	[67]
Colorectal	•Elevated level of CD55 is correlated with cancer progression. CD55 antibody attenuates cancer invasion, progression, and migration.	[40]
	•Cyclooxygenase-originated prostaglandin E2 (PGE2) induces CD55 through cAMP/protein kinase A pathway in colon cancer.	[68]
Lung	•CD55 expression is high in human non-small lung cancer tissue. Radiolabeled CD55 antibody suppress lung tumor growth and improves survivals in mouse model of metastatic lung cancer.	[69]
Thyroid	•CD55 protects the thyroid cancer cells from complement mediated attack.	[62]
Renal	•High CD55 is detected in renal cancer cells.	[70]
Non-Hodgkin lymphoma	•CD55 expression is high in bulky disease treated with rituximab. CD55 may predict the response of rituximab	[71]
Gastric tumor	•High level of CD55 detected and may be a potential prognostic marker	[72]
Squamous cell carcinoma (SCC)	•CD55 is induced by the activation by estrogen receptor in SCC cells.	[39]
Leukemia	•CD55 expression is high in Chronic myeloid leukemia (CML), Chronic lymphocytic leukemia (CLL) but inconsistent in other leukemias.	[26]