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Review Article



# Beyond the Role of CD55 as a Complement Component

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**Conflict of Interest**
The authors declare no potential conflicts of interest.

**Abbreviations**
CHAPLE, CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy; EGF, epidermal growth factor; MS, multiple sclerosis; NK, natural killer; PNH, paroxysmal nocturnal hemoglobinuria; RA, rheumatoid arthritis

**Author Contributions**
Conceptualization: Lim JC, Kim LK; Funding acquisition: Lim JC, Kim LK; Supervision: Kim LK; Writing - original draft: Dho SH; Writing - review & editing: Dho SH, Lim JC, Kim LK.

## ABSTRACT

The complement is a part of the immune system that plays several roles in removing pathogens. Despite the importance of the complement system, the exact role of each component has been overlooked because the complement system was thought to be a nonspecific humoral immune mechanism that worked against pathogens. Decay-accelerating factor (DAF or CD55) is a known inhibitor of the complement system and has recently attracted substantial attention due to its role in various diseases, such as cancer, protein-losing enteropathy, and malaria. Some protein-losing enteropathy cases are caused by CD55 deficiency, which leads to complement hyperactivation, malabsorption, and angiopathic thrombosis. In addition, CD55 has been reported to be an essential host receptor for infection by the malaria parasite. Moreover, CD55 is a ligand of the seven-span transmembrane receptor CD97. Since CD55 is present in various cells, the functional role of CD55 has been expanded by showing that CD55 is associated with a variety of diseases, including cancer, malaria, protein-losing enteropathy, paroxysmal nocturnal hemoglobinuria, and autoimmune diseases. This review summarizes the current understanding of CD55 and the role of CD55 in these diseases. It also provides insight into the development of novel drugs for the diagnosis and treatment of diseases associated with CD55.

**Keywords:** CD55; Complement; Cancer; Malaria; Immunotherapy

## INTRODUCTION

In the past decade, immunotherapies have demonstrated therapeutic efficacy for many diseases, but they have received a lot of attention recently, especially for cancer. Most cancer immunotherapies are T cell modulatory therapies, including an immune checkpoint blockade that involves an anti-cytotoxic T-lymphocyte-associated protein 4 antibody (ipilimumab) and an anti-programmed cell death 1 antibody (pembrolizumab) as well as chimeric antigen receptor T cell therapy that modifies patient T cells to target tumor cells (1,2).

Other types of immune cells have been relatively overlooked for their role in immunotherapies, including the complement system, which has been increasingly ignored because it is only considered an effector system that potentiates antibody-dependent cellular cytotoxicity in immunotherapy (3). However, it is notable that the complement system is a

first defense in the response to pathogens or unwanted host elements (4). Additionally, since cancer cells are potential targets of the complement as well, the complement system may control tumor growth (3).

The complement is made up of more than 30 protein factors and is composed of the classical, lectin, and alternative pathways that are organized according to the target (5) (**Fig. 1**). The classical pathway is launched by the binding of immune complexes, such as IgG and IgM, to C1q (6). The lectin and alternative pathways are initiated upon binding of microbiotic surface substances, such as carbohydrates or proteases (7). C3 is a principal component of all complement pathways and auto-activated by immune complexes or microbiotic surfaces. The converged C3 molecule is cleaved into C3b (opsonin) and C3a (anaphylatoxin). C3 convertase produces large amounts of C3b that is a component of C5 convertase. C5 convertase splits C5 to C5a and C5b, and it finally forms a membrane attack complex (**Fig. 1**).

Because excessive activation of complement leads to cellular damage, tight regulation is necessary for maintaining the complement system. Regulation of the complement system is managed by CD55, CD59, factor H, C1-inhibitor, complement receptor 1, C4b-binding protein, clusterin, and vitronectin (8).

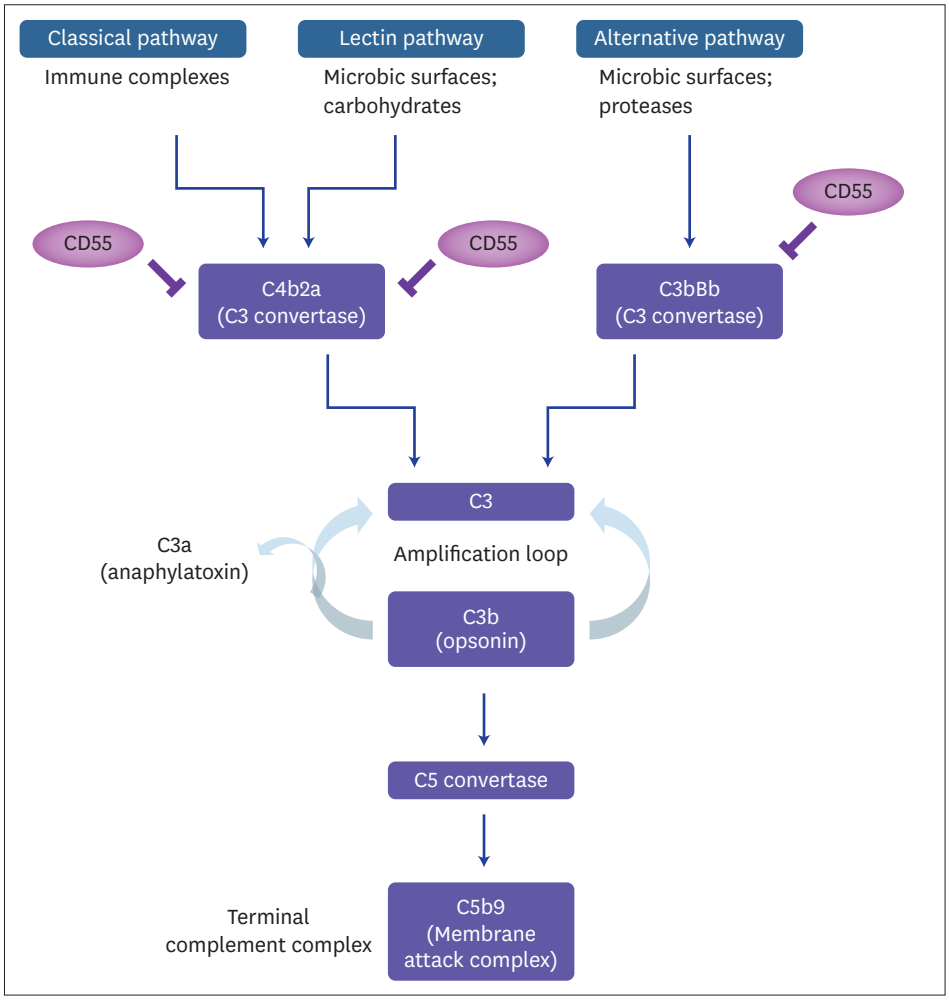


**Figure 1.** Simplified complement system.


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Among these complement regulatory proteins, we focused our study on CD55 since we realized that CD55 can be extended far beyond the complement inhibitor, and there have been recent interesting findings concerning CD55. The primary function of CD55 is to inactivate C3 convertases by dissociating them into their constituent proteins as well as preventing their assembly (5,9), which prevents formation of the membrane attack complex (**Fig. 1**). Moreover, CD55 has recently come into the spotlight. Ozen et al. (10) and Kurolap et al. (11) found that loss of function mutations in CD55 results in abnormal complement activation, angiopathic thrombosis, and ultimately protein-losing enteropathy. Additionally, CD55-deficient erythrocytes were refractory to infection with the malaria parasite (12). The importance of CD55 is underscored by the fact that several human diseases are associated with CD55 (5). In this study, we discuss the role of CD55 in cancer and other diseases.

## CD55

CD55 was isolated as a complement inhibitor from human erythrocytes in 1969 by Hoffmann (13). Since then, CD55 has been characterized as a glycosylphosphatidylinositol-linked membrane protein and has been broadly detected in blood, stroma, epithelial, and endothelial cells (14-16). Additionally, soluble CD55, which was generated by alternative splicing (17) or matrix metalloproteinase-7 (18), is distributed in plasma, urine, saliva, tears, and synovial fluids (15). Glycosylphosphatidylinositol-linked CD55 is regarded as the major form of CD55 rather than soluble CD55 (19).

The *CD55* gene is located on chromosome 1q32 within a locus encoding for other regulators for complement activation (8). The gene expands on a 40 kb-long fragment and contains 11 exons (8). The CD55 protein has a C-terminal glycosylphosphatidylinositol anchor, an O-glycosylated serine/threonine/proline-rich region and multiple copies of approximately 60 amino acid N-terminal short consensus repeat domains (5). Even though the calculated molecular weight of the CD55 protein is 43 kDa, the observed molecular weight of mature CD55 varies between 50 to 100 kDa depending on the cell type (8). Different sizes of CD55 might be caused by alternative splicing (17,20) or different glycosylation patterns (21).

CD55 inhibits early complement activation by accelerating the degradation of C3 convertase, which is a central molecule that regulates the complement cascade (**Fig. 1**). In addition, CD55 prevents the assembly of C3 convertase (C3bBb) by dissociation of Bb from fixed C3b and ultimately inhibits complement activation (22). Since complement activation is the first defense in response to a virus, the addition of CD55 to the viral envelope has proven to be a promising complement-resistant viral vector for gene therapy (5,23). In addition, CD55 also suppresses T cells (24) via a complement-independent pathway. It is known that CD55 is a ligand for CD97, which is expressed on monocytes and granulocytes, and their interaction promotes T and B cell proliferation (25). Furthermore, CD55 also inhibits natural killer (NK) cells (8,26). These facts suggest that CD55 regulates both innate and adaptive immune responses (27).

## CD55 AND ITS RECEPTOR CD97

CD55 has an additional role: it acts as a binding partner for CD97 (5), which is widely expressed in monocytes, granulocytes, lymphocytes, macrophage, dendritic cells, and

smooth muscle cells (28). CD97 is also found in a broad range of tumors, including thyroid cancer (29,30), colorectal cancer (31), glioblastoma (32), gallbladder cancer (33), cervical cancer (34), pancreatic cancer (35), gastric cancer (35), oral cancer (36), and esophageal cancer (8,35). Similar to upregulated CD97 facilitating migration of lymphocytes to inflammation sites, CD97 also promotes migration and invasion of cancer cells (37). Furthermore, CD97 stimulates angiogenesis through binding the integrin counter receptor α5β1 in endothelial cells (38). As expected, increased CD97 expression is associated with a poor prognosis in patients with rectal adenocarcinoma (39), glioblastoma (32), gallbladder carcinoma (33), and cervical squamous cell carcinoma (34).

The *CD97* gene is situated on chromosome 19p13.1 and consists of 18 exons spanning 12 kb (40). The CD97 protein is an epidermal growth factor (EGF)-seven-span transmembrane protein and binds to its ligand, CD55, through an EGF domain region (28,41). The binding of CD97 and CD55 is characterized by a rapid off-rate, a low affinity, and calcium dependence (42). The binding between CD97 and CD55 proteins is involved in cancer dedifferentiation, invasion, migration, and metastasis (43). Additionally, it has been suggested that CD97-CD55 interaction leads to pathogenesis for multiple sclerosis (MS) (28) and rheumatoid arthritis (RA) (44).

## DISEASES ASSOCIATED WITH CD55

The importance of CD55 is highlighted by the fact that CD55 is associated with several diseases, including cancer (45), malaria (12), protein-losing enteropathy (46), paroxysmal nocturnal hemoglobinuria (47), MS (28), and RA (44).

### CD55 and cancer

Overexpression of complement regulatory proteins, such as CD55, CD59, and factor H, has been shown to prevent complement-dependent cytotoxicity in cancer cells (45). Therefore, blockade of the complement regulatory proteins has been suggested to overcome the limitation of the therapeutic potential of anticancer antibodies (48).

CD55 has been much more broadly studied than other complement regulatory proteins in cancer, at least in part because it is frequently up-regulated in a wide range of cancer types (8). For example, several studies have reported a correlation between CD55 expression and malignancies in lung cancer (49), colorectal cancer (21,50,51), gastric cancer (52), breast cancer (53), ovarian cancer (54), leukemia (55), prostate cancer (56), and cervical cancer (34). Furthermore, enhanced expression of CD55 indicates a worse prognosis in colorectal cancer (57) and breast cancer (53). It is plausible that increased expression of CD55 could decrease complement activation, inhibit complement-mediated lysis of cancer cells, and ultimately increase tumor progression. In addition, CD55 could promote tumor initiation and growth by inhibiting NK cells (8,26). Importantly, there is evidence that inhibition of CD55 is a highly effective treatment strategy. Inhibition of CD55 attenuates the growth of prostate cancer (56,58,59), cervical cancer (60,61), breast cancer (58), gastric cancer (62), and leukemia (59). Additionally, CD97 promotes migration, invasion, and metastasis of cancers by binding its ligand CD55 (39,41). Not only CD55 but also CD97 was found to be overexpressed in thyroid cancer (63), gastric cancer (64), and colorectal cancer (65).

The factor leading to CD55 expression has been studied in cancer cells. It has been reported that low molecular weight factors, such as cytokines and growth factors, induce

overexpression of CD55 in cancer (8). CD55 is induced by cytokines, IL-1β, and IL-4 in human intestinal epithelial cells (66,67). Additionally, TNF-α, IL-6, and IL-1β caused increased expression of CD55 in human hepatoma cells (68). One of the growth factors, EGF, also induced expression of CD55 via the mitogen-activated protein kinase pathway (69). Furthermore, expression of CD55 was increased by exposure to vascular endothelial growth factor (VEGF) in human umbilical vein endothelial cells (70).

After considering these findings, CD55 could be a target for cancer therapy. Indeed, CD55 inhibition has increased the anti-tumor activity of other antineoplastic agents, such as rituximab (71), trastuzumab, and pertuzumab (72). Notably, we showed that a novel monoclonal anti-CD55 antibody and radionuclide-labeled monoclonal anti-CD55 antibody are promising theranostic agents for colorectal cancer and pleural metastatic lung cancer, respectively (our unpublished data).

Although it is likely that CD55 promotes tumorigenesis, it is not clear that 1) an anti-CD55 antibody is ineffective in lung cancer (49) and renal cancer cells (73); 2) inhibition of CD55 does not sensitize breast cancer cells to complement attack (59); and 3) loss of CD55 in breast carcinoma is associated with a worse prognosis (74). Therefore, we do not exclude the possibility that CD55 plays different roles in various cell types. Additionally, it is possible that the importance of CD55 in tumorigenesis has been overstated since CD55 could be compensated for by other complement regulatory proteins.

## CD55 and malaria

CD55 has been reported to be a receptor of several enteroviruses (75) and microorganisms to promote cellular attachment for infection (76). Interestingly, Egan et al. (12) showed that CD55 is an essential host receptor for infection by *Plasmodium falciparum,* which is a malaria parasite. They found that CD55-null erythrocytes were resistant to malaria because the malaria parasite failed to stick appropriately to the host erythrocyte surface (12). Therefore, CD55 blockade in erythrocytes could be a potential therapy used in malaria treatment. Notably, it should be considered that complement activation by inhibition of CD55 in red blood cells is not beneficial to the host. CD55 inhibition increases susceptibility to severe anemia, which possibly occurs due to the destruction of erythrocytes by the complement activation (77). Therefore, soluble forms of CD55 as a competitor to CD55 on the surface of erythrocytes have become an attractive target for the development of malaria therapeutics (78).

## CD55 and protein-losing enteropathy

A feature of the CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) syndrome is urinary protein loss that results in glomerular diseases, such as edema, hypogammaglobulinemia, and hypoalbuminemia (79). It has been suggested that glomerular diseases are linked to the complement system (80). Notably, CD55-deficient mice were susceptible to glomerular injury (46). Importantly, a homozygous frameshift in CD55 was identified by whole-exome sequencing analysis from patients with the CHAPLE syndrome (11). Additionally, flow cytometric studies showed there was a marked decrease in CD55 in the erythrocytes and granulocytes of CHAPLE syndrome patients (11). Until now, supportive management programs for the CHAPLE syndrome have included a low-fat and high-protein diet as well as medium-chain triglyceride supplementation. Even if the exact mechanism that causes the CHAPLE syndrome remains elusive, the response to the U.S. Food and Drug Administration (FDA) approved eculizumab, which is a monoclonal antibody for C5 that inhibits terminal

complement activation, attenuated the symptoms of protein-losing enteropathy in some forms of CHAPLE syndrome (11). These changes underscore the role of CD55 at least in some forms of the CHAPLE syndrome and suggest treatment with soluble CD55 could be a promising therapy for the disease.

## CD55 and paroxysmal nocturnal hemoglobinuria (PNH)

PNH is a disease characterized by the unusual susceptibility of red blood cells to the hemolytic activity of the complement and causes fatigue, smooth muscle dystonias, venous thrombosis, abdominal pain, intravascular hemolysis, and hemoglobinuria (81,82). Approximately 50% of PNH patients die of thrombosis of the hepatic and cerebral veins (47). PNH results from a mutation of the phosphatidylinositol glycan class A (*PIGA*) gene that is essential for the synthesis of glycosylphosphatidylinositol in a hematopoietic stem cell (47,82). Subsequently, blood cells lack glycosylphosphatidylinositol-linked CD55 and CD59 proteins that protect from the attack by the complement system (47). Similar to the CHAPLE syndrome, Eculizumab, which inhibits terminal complement activation, reduced PNH symptoms and improved the quality of patients' lives (47). These findings suggest soluble CD55 or CD59 might be another treatment option for PNH.

## CD55 and MS

A feature of MS is the presence of axonal loss and inflammatory demyelinating lesions in the central nervous system (28). CD55-CD97 interactions have been reported to be involved in the inflammatory processes in MS (28). CD55 is expressed in the lesions of vessel walls to protect against complement-mediated cellular damage and binds to CD97 on infiltrating leukocytes. (28). The role of CD55 in MS was further clarified by the fact that $CD55^{-/-}$ mice exhibited greater demyelination and inflammation in the central nervous system of experimental autoimmune encephalomyelitis, which is an inflammatory myelin-specific T cell-mediated disease model for MS (24,83). Indeed, augmenting CD55 levels *in vivo* ameliorated MS in CD55 transgenic mice (84). CD55 suppresses autoreactive T cell responses in the MS model and therefore, CD55 might be an effective therapy for MS and other T cell-mediated diseases (84).

## CD55 and autoimmune diseases including RA and vitiligo

RA is a chronic inflammatory autoimmune disease that affects multiple peripheral joints (44). As expected, complement activation is observed in the disease. A role for CD55-CD97 interaction has been suggested in pathogenesis of RA (44). Fibroblast-like synoviocytes that strongly express CD55 interact with high expression levels of CD97 in macrophages (44). It is likely that expression of CD55 is not a cause but the failure of RA to protect synovial tissue from activation of the complement. Depletion of CD55 exacerbated arthritic mouse model (85). Furthermore, CD55 preserved the synovial tissue from immune complex-mediated arthritis (85). These outcomes indicate that soluble CD55 may be a strategy to treat RA. Although it is likely that CD55 ameliorates RA, there is another report showing that depletion of CD55 leads to reduction of RA (86). The seemingly opposite result might be caused by the fact that CD55 plays a different role depending on cellular context. While Karpus et al. (85) looked into the effect of CD55 depletion in $Fcgr2b^{-/-}$ mice through knockdown of *Fcγr2b* gene related to lupus susceptibility, Hoek et al. (86) observed it using collagen-induced RA models.

Vitiligo is another autoimmune disorder characterized by progressive skin depigmentation. The symptoms of vitiligo are caused by an autoimmune response against epidermal melanocytes (87). Notably, CD55 expression was decreased in the skin of patients with vitiligo (88). Additionally, depletion of CD55 has been shown to aggravate the MRL/lpr murine

model of human systemic lupus erythematosus, which is another autoimmune disease (89). Similarly, Soluble CD55 inhibited the Arthus reaction *in vitro* and *in vivo* (5,90). Collectively, these findings suggest that CD55 could be a target for treating autoimmune diseases.

## CONCLUSION AND PERSPECTIVE

This review has described our current understanding of CD55. CD55 was undervalued since it was just thought to be an inhibitor of the complement system, which is a nonspecific immune response. In contrast, CD55 exerts other functions beyond its role as a complement inhibitor, such as a receptor for infection, acting as a ligand of CD97, and being an inhibitor of anti-tumor NK cell activity. In addition, CD55 has been extensively investigated in various diseases, including cancer, malaria, CHAPLE syndrome, paroxysmal nocturnal hemoglobinuria, MS, and autoimmune diseases. It is interesting that CD55 has both positive and negative effects in various diseases (**Fig. 2**). It is not surprising that the effects of CD55 on the immune system act as a so-called double-edged sword, which plays a contradictory role depending on the disease, but all situations need to be summarized and considered to understand the exact role of CD55. CD55 is a positive regulator of tumorigenesis and malarial infection, whereas it is a negative regulator of the CHAPLE syndrome, paroxysmal nocturnal hemoglobinuria, MS, and autoimmune diseases. These contradictory roles of CD55 for each disease will be studied more clearly and precisely in the future.

The role of CD97, which is a receptor of CD55, has yet to be studied in these diseases. It is likely that CD97 is involved in all the diseases associated with CD55. Therefore, a study of CD97 should also be performed with CD55.

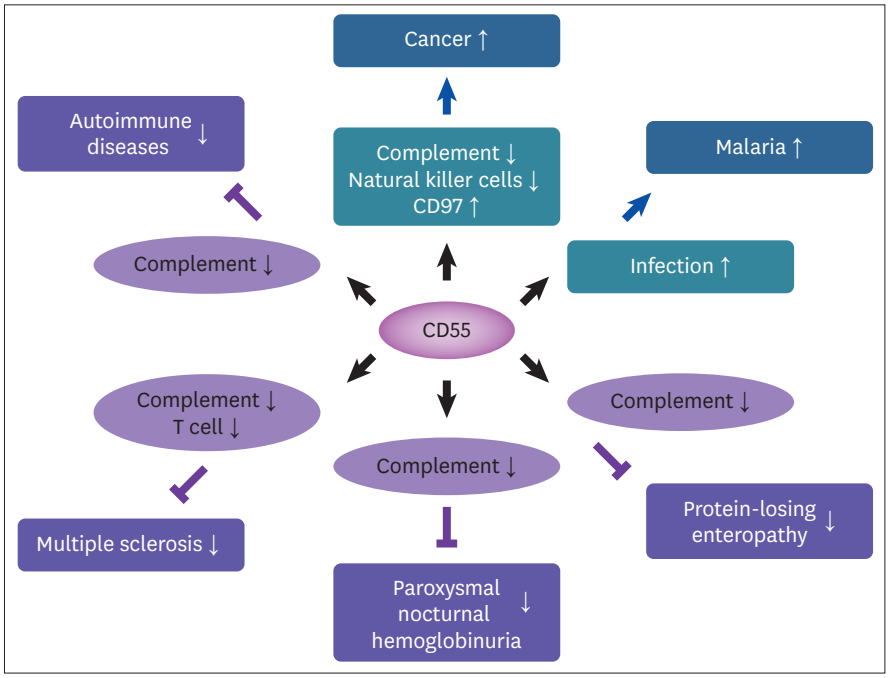


**Figure 2.** The role of CD55 in various diseases. CD55 acts as a positive (blue arrows) or negative (purple lines) regulator in disease.


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This review provides insight into preclinical and clinical potential of CD55, including the possibility of using CD55 as a biomarker for diagnosis and for treatment of diseases, including 1) CD55 being used for diagnosis of cancer; 2) CD55 inhibitors being used for targeted cancer therapy; 3) soluble CD55, which is a competitor for the CD55 receptor, being used to treat malaria; and 4) augmentation of CD55 could be used a therapy for the CHAPLE syndrome, paroxysmal nocturnal hemoglobinuria, MS, autoimmune diseases through inhibiting complement. Thus, inhibitors and neutralizing antibodies for CD55 should be developed and studied further for these diseases.

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