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REVIEW

Role of ADAM17 as a regulatory checkpoint of CD16A in NK cells and as a potential target for cancer immunotherapy

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Abstract

Human NK cell antitumor activities involve Ab-dependent cell-mediated cytotoxicity (ADCC), which is a key mechanism of action for several clinically successful tumor-targeting therapeutic mAbs. Human NK cells exclusively recognize these Abs by the Fcγ receptor CD16A (FcγRIIIA), one of their most potent activating receptors. Unlike other activating receptors on NK cells, CD16A undergoes a rapid down-regulation in expression by a proteolytic process following NK cell activation with various stimuli. In this review, the role of a disintegrin and metalloproteinase-17 (ADAM17) in CD16A cleavage and as a regulatory checkpoint is discussed. Several studies have examined the effects of inhibiting ADAM17 or CD16A cleavage directly during NK cell engagement of Ab-coated tumor cells, which resulted in strengthened Ab tethering, decreased tumor cell detachment, and enhanced CD16A signaling and cytokine production. However, the effects of either manipulation on ADCC have varied between studies, which may be due to dissimilar assays and the contribution of different killing processes by NK cells. Of importance is that NK cells under various circumstances, including in the tumor microenvironment of patients, down-regulate CD16A and this appears to impair their function. Considerable progress has been made in the development of ADAM17 inhibitors, including human mAbs that have advantages of high specificity and increased half-life in vivo. These inhibitors may provide a therapeutic means of increasing ADCC potency and/or antitumor cytokine production by NK cells in an immunosuppressive tumor microenvironment, and if used in combination with tumor-targeting Abs or NK cell-based adoptive immunotherapies may improve their efficacy.

KEYWORDS
ADAM17, antibody, immunotherapy

1 | CD16A-MEDIATED ADCC BY HUMAN NK CELLS

NK cells are a very heterogeneous population of lymphocytes of the innate immune system.[1] They mediate direct and indirect cytolytic activities against tumor cells and virus-infected cells without prior sensitization and release various immune-modulating cytokines, as described in more detail in other reviews.[2–5] Direct target cell killing (natural cytotoxicity) by NK cells is tightly controlled by numerous activating and inhibitory receptors.[2,5] NK cells also mediate indirect killing by recognizing Ab-opsonized target cells, referred to as ADCC.[3,4] IgG Abs are recognized by leukocytes that express receptors for the Fc portion of the Ab, referred to as a FcγR. In humans, there are 3 classes of FcγRs: FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16).[6,7] The latter preferentially recognizes IgG1 and IgG3, and consists of two isoforms (CD16A and CD16B) that are encoded by 2 highly homologous genes.[6] CD16B is primarily expressed by neutrophils and CD16A is expressed at high levels by mature NK cells in the peripheral blood. CD16A is the sole activating FcγR on NK cells and upon binding to Ab-opsonized target cells induces NK cell degranulation and the release of their lytic components, as well as the production of various cytokines and chemokines (Fig. 1). CD16A has a low to intermediate affinity for IgG that varies between its allelic variants. For instance, CD16A with a valine at position 176 (position 158 if amino acid enumeration does not include the signal sequence) has a higher affinity for IgG than the allelic variant CD16A with a phenylalanine at position

Abbreviations: ADAM17, a disintegrin and metalloproteinase-17; ADCC, antibody-dependent cell-mediated cytotoxicity; MMPs, matrix metalloproteinases; TACE, TNFα converting enzyme

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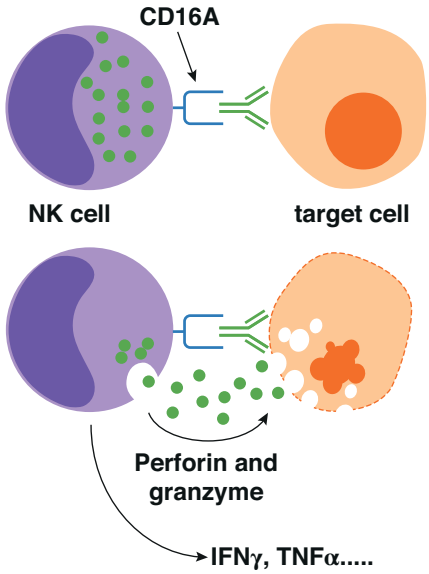

FIGURE 1 Ab-dependent cell-mediated cytotoxicity (ADCC) by human NK cells. Tumor-targeting therapeutic mAbs are solely recognized by the Fcγ receptor CD16A (FcγRIIIA) on human NK cells, which induces their activation and release of cytotoxic components and various immune-modulating cytokines

176.[8,9] Incidentally, the latter is the dominant allele in humans.[10] Clinical analyses have revealed a positive correlation between the efficacy of tumor-targeting therapeutic mAbs and CD16A binding affinity. Patients homozygous for the higher affinity CD16A valine allele (CD16A-176V/V) had an improved clinical outcome after treatment with antitumor mAbs compared to those with heterozygous (CD16A-176V/F) or homozygous (CD16A-176F/F) genotypes containing the lower affinity CD16A F allele.[3] These findings suggest that increasing the attachment strength between NK cells and Ab-opsonized tumor cells increases killing.

2 | REGULATION OF CD16A SURFACE DENSITY BY ADAM17

Unlike other activating receptors expressed by NK cells, CD16A surface expression undergoes a rapid down-regulation within minutes when induced by the engagement of Ab-coated target cells, through other activating receptors, and by various cytokines.[11–15] Trinchieri et al. initially reported that CD16A is rapidly down-regulated in expression upon NK cell activation with a phorbol ester.[16] Others subsequently showed that CD16A release by NK cells was mediated by a metalloprotease.[11,17,18] Both allelic variants of CD16A undergo this cleavage process upon NK cell activation.[19] There has been some controversy, however, in the proteolytic mechanism involved. Some studies have suggested the role of matrix metalloproteinases (MMPs),[20,21] such as membrane-type 6 MMP.[14] More recently, several studies have shown that highly selective inhibitors of ADAM17, also referred to as TNF-α converting enzyme (TACE), block CD16A cleavage upon NK cell activation by various means.[12,13,15,19,22] Moreover, Tsukerman et al. reported that NK cells obtained from a patient lacking ADAM17 expression did not down-regulate CD16A during ADCC.[23] The mouse homologue of this receptor is not down-regulated by a proteolytic process following leukocyte activation and therefore the role of ADAM17 cannot be further established using normal mice.[12]

Unlike CD16A, which is a transmembrane protein, CD16B is linked to the plasma membrane via a GPI anchor.[24,25] CD16B is also cleaved from the cell surface following neutrophil activation,[26–31] this was found to be blocked ex vivo and in cancer patients by selective ADAM17 inhibitors and is also prevented in ADAM17-deficient cells.[12] Taken together, the above findings provide strong evidence that ADAM17 is the primary protease involved in CD16 cleavage. Moreover, soluble CD16 occurs at high levels in the plasma of healthy individuals,[11,12,27,32] establishing that its cleavage is a physiological process.

ADAM17 is a member of the adamalysin subfamily of the metzincin metalloproteinase superfamily, which contain a conserved methionine amino acid adjacent to a zinc-binding motif in the catalytic region of the proteases.[33,34] The ADAMs are type-1 transmembrane proteins with distinct modular domains that include an N-terminus metalloproteinase domain, disintegrin-like domain, cysteine-rich domain, an epidermal growth factor domain, which ADAM17 happens to lack, and transmembrane and cytoplasmic regions.[35] More than 20 ADAMs have been identified in humans, although 12 are proteolytically active.[34] ADAM17 is constitutively expressed on the surface of NK cells,[13,15,22] and it cleaves its substrates typically in a *cis* manner at an extracellular location proximal to the cell membrane.[35] A single cleavage site has been identified in CD16A released from activated human NK cells, located between alanine-195 and valine-196[19] (Fig. 2). A synthesized peptide of CD16A was also cleaved by recombinant ADAM17 at the same location.[15] Three cleavage sites in very close proximity were identified in the membrane proximal region of CD16B released from activated neutrophils.[19] This variability in which CD16B is cleaved may be the result of the receptor's GPI linkage to the plasma membrane, perhaps causing fluctuation in its interaction with the catalytic domain of ADAM17. ADAM17 does not require a strict consensus sequence in its substrates and instead tends to prefer a cleavage region of sufficient physical length with an α-helical conformation.[36–38] We have shown that either truncating the length of the membrane proximal cleavage region of CD16A (data unpublished) or substituting the serine at position 197 adjacent to the ADAM17 cleavage site for a proline (referred to as CD16A-S197P, Fig. 2) completely disrupts its cleavage in cell-based assays.[19]

Of interest is that ADAM17 induction can occur very quickly following leukocyte activation.[35] For most stimuli, serine and threonine kinase-dependent intracellular signaling pathways are involved, including PKC and the MAPKs.[39–42] The rapid activation of ADAM17 in leukocytes involves an increase in its intrinsic activity instead of an up-regulation in protease expression, but the targets of the kinases involved in this process remain an active area of debate. Various potential mechanisms of ADAM17 activation in leukocytes have been discussed in recent reviews.[35,43]

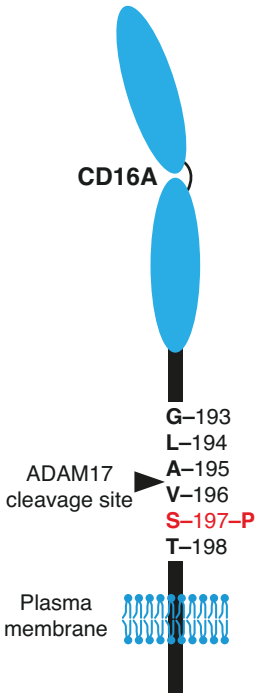

FIGURE 2 **CD16A is cleaved by ADAM17.** CD16A cleavage occurs at a specific extracellular location proximal to the cell membrane, as indicated. Exchange of serine-197 for a proline residue prevents CD16A cleavage by ADAM17

3 | ROLE OF CD16A CLEAVAGE IN NK CELL REGULATION

CD16A binds to IgG with low to intermediate affinity but achieves a higher binding avidity through multimeric interactions with Abs on target cells.[44] The rapid cleavage of CD16A by ADAM17 may provide a means of quickly decreasing its binding avidity to Ab-coated target cells. Of interest is that NK cells in the presence of an ADAM17 inhibitor or NK92 cells expressing CD16A-S197P demonstrated reduced mobility on an IgG-coated surface and decreased detachment from Ab-bound target cells.[45] These phenomena resemble the effects of blocking L-selectin cleavage on leukocyte attachment to endothelial cells. L-Selectin (CD62L) is also a low affinity receptor that is constitutively expressed at high levels by leukocytes,[46,47] and is a well described ADAM17 substrate.[35,47,48] Blocking its cleavage reduces leukocyte mobility on L-selectin ligands and increases their attachment to endothelial cells in vivo.[49–51]

CD16A associates with Fcγ (FcεRIγ) and/or CD3ζ chains and is perhaps the NK cell's most potent activating receptor.[3] Indeed, CD16A alone can trigger degranulation of resting human NK cells, whereas NKG2D and the natural cytotoxicity receptors induce NK cell activation by working together.[52,53] Inhibitory receptors transmit negative signals and dampen or counteract most activating receptors in NK cells, whereas CD16A is capable of overcoming inhibitory signals.[53,54] Several studies have shown that blocking CD16A cleavage can increase the intensity and duration of receptor signaling and the production of IFN-γ by NK cells.[13,22,45,55]

In contrast to the effects of blocking CD16A cleavage on Ab tethering and receptor signaling, the effects on ADCC by NK cells is less clear. Several studies have shown that blocking CD16A cleavage increases NK cell attachment to Ab-coated target cells, degranulation, and ADCC,[14,21,55,56] whereas others, including us, have reported that blocking CD16A cleavage either did not affect ADCC or decreased it.[13,22,45] For instance, Srpan et al. showed that blocking CD16A cleavage decreased the rate of NK cell detachment from Ab-bound tumor cells and as a result limited their ability to kill in a sequential (serial) manner.[45] This discrepancy between studies maybe the result of differences in the way the in vitro ADCC assays were performed, the NK cell to tumor cell ratios used, or in the killing process by individual NK cells. In addition to serial killing, an NK cell can kill surrounding cells in an indiscriminate manner referred to as bystander killing.[57,58] At this time, the effects of blocking ADAM17 or directly disrupting CD16A cleavage on the antitumor effector functions of NK cells in vivo and in the tumor microenvironment remain to be determined.

4 | ADAM17 AS A REGULATORY CHECKPOINT OF ADCC BY NK CELLS

Immune checkpoints are important for maintaining immune homeostasis to prevent excessive tissue damage while the immune system responds against its targets. ADAM17 appears to function as a regulatory checkpoint of CD16A, facilitating the detachment of NK cells from Ab-coated target cells and diminishing signal transduction by this potent activating receptor. Malignant cells, however, can exploit immune checkpoints to suppress antitumor immunity. This may be the case for ADAM17 on NK cells as well. For instance, cell surface levels of CD16A on NK cells can be down-regulated in the tumor microenvironment of patients, contributing to NK cell dysfunction.[59,60] CD16A down-regulation also occurs on circulating NK cells in individuals receiving tumor-targeting therapeutics Abs,[61,62] and by NK cells during their ex vivo expansion for adoptive transfer into cancer patients.[63] Blocking ADAM17 activity in these situations may enhance the effector functions of NK cells within the tumor microenvironment. Indeed, ADCC potency by NK cells has been shown to positively correlate with CD16A expression levels.[21,64,65] Blocking ADAM17 may also improve the therapeutic efficacy of expanded NK cells for adoptive transfer and tumor-targeting mAbs that induce ADCC. Similar to the effects of blocking L-selectin cleavage, which increases neutrophil attachment levels and binding strength to endothelial cells,[50,51] blocking CD16A cleavage may increase NK cell attachment levels and binding strength to Ab-coated target cells, which may increase the likelihood of killing the most resilient cancer cells in an immunosuppressive tumor microenvironment (Fig. 3).

Blocking ADAM17 could enhance the antitumor activity of NK cells in other ways as well. CD16A on NK cells has also been reported to mediate cell killing independent of Ab recognition, referred to as spontaneous cytotoxicity.[66,67] This occurs by CD16A interacting in a *cis* manner with the NK cell receptor CD2 that recognizes CD58 on particular target cells, such as melanoma cells.[67] Thus, blocking CD16A cleavage may also enhance NK cell killing of certain cancer

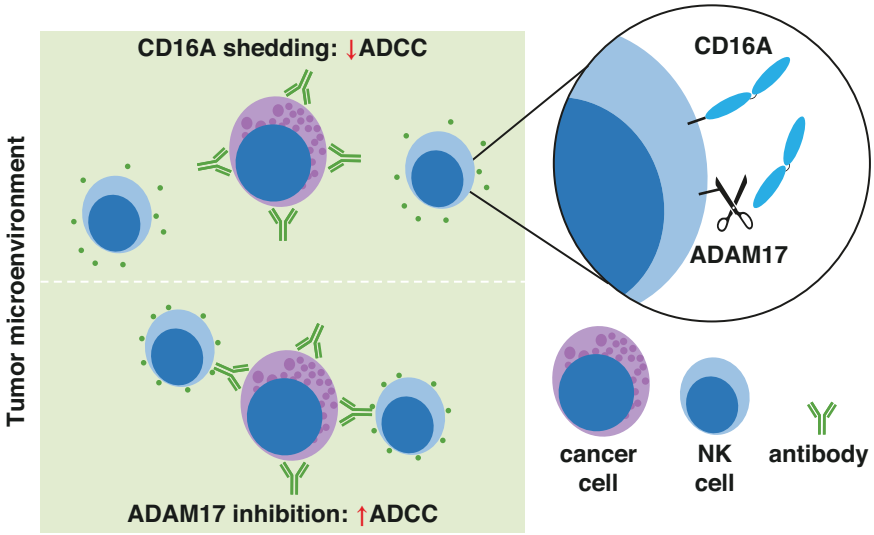

FIGURE 3 Illustration of CD16A cleavage in the tumor microenvironment and impairment of ADCC by NK cells. Blocking ADAM17 in NK cells may reduce CD16A down-regulation on tumor infiltrating NK cells and increase their ADCC potency

cells independent of ADCC. NKG2D is another activating receptor broadly expressed by all mature human NK cells and its ligands include MHC class I-related chain molecules A and B (MICA and MICB) and non-MHC-encoded UL16-binding proteins (ULBPs), which are widely expressed by tumor cells.[68] MICA and MICB are reported to be substrates of ADAM17 and their cleavage can impair NK cell activity.[69–71] Blocking ADAM17 may decrease the inhibitory effects of soluble NKG2D ligands and increase NKG2D binding to its ligands on tumor cells. In addition, ADAM17 has been shown to be overexpressed in cancer cells and cause their release of EGFR ligands and adhesion molecules that promote growth and metastasis.[72–76] Taken together, blocking ADAM17 activity may impair tumor cell growth and survival in various direct and indirect manners.

There have been broad efforts to develop ADAM17 inhibitors,[76,77] with a particular focus on preventing tumor cell growth and spread.[72–76] Initial efforts were on the development of selective small-molecule inhibitors. Although early toxicity issues have been addressed by improving their specificity, the small-molecule ADAM17 inhibitors have not been found to be clinically successful thus far. More recently there have been considerable advances in generating function-blocking Abs of ADAM17 that have greater specificity and a longer half-life in vivo.[78–83] For instance, MEDI3622 produced by Medimmune is noteworthy in that its epitope has been mapped to a surface loop unique to the catalytic domain of ADAM17, resulting in exquisite specificity and a potent inhibitory activity.[84] MEDI3622 was originally developed to impair EGFR-dependent tumor growth,[82] but recently has been shown to block CD16A cleavage from activated human NK cells and markedly enhance their production of IFN-γ during ADCC.[22] This occurred for NK cells exposed to different tumor cell lines and therapeutic Abs, and over a broad range of NK cell/target cell ratios. IFN-γ has broad antitumor effector functions, which includes recruiting innate and adaptive leukocytes, up-regulating ICAM-1 and MHC molecules on tumor cells to facilitate leukocyte attachment and activation, and suppressing cell proliferation and angiogenesis in tumors.[85–88]

5 | CONCLUDING REMARKS

CD16A is a potent activating receptor on NK cells and it has an exclusive role in their ADCC effector function. Of importance is that several clinically successful tumor-targeting Abs utilize ADCC as a primary mechanism of action.[3,89] However, despite having a significant impact on some malignancies, most cancer patients respond poorly or develop resistance to this therapy. As detailed above, ADAM17 embodies a regulatory checkpoint of CD16A in NK cells. Its activation results in rapid CD16A cleavage, which abates NK cell attachment to Ab-coated target cells and diminishes CD16A signaling. NK cells in the tumor microenvironment of patients have reduced levels of CD16A on their cell surface,[59,60] indicating increased ADAM17 activity and a dysregulation of this immune checkpoint. Checkpoint inhibitors for cancer immunotherapies are intended to promote a robust and durable immune response in immunosuppressive tumor microenvironments. Function blocking ADAM17 mAbs may be beneficial in part by diminishing CD16A down-regulation by tumor-infiltrating NK cells and maintaining their ADCC effector function (Fig. 3), and perhaps could be used in combination with tumor-targeting mAbs or adoptively transferred NK cells for treating diverse malignancies. As can be the case with targeting regulatory checkpoints, blocking ADAM17 for prolonged periods of time could have detrimental effects. Indeed, ADAM17 gene-targeting in mice and loss-of-function mutations in ADAM17 in humans can cause inflammatory diseases.[90,91] Another approach is to specifically block CD16A cleavage by expressing a non-cleavable version of the receptor, such as CD16A-S197P, in engineered NK cells. Various autologous and allogeneic NK cell platforms could be utilized, including expanded cord blood or peripheral blood NK cells, NK cell lines, and stem cell-derived NK cells, which offer different advantages.[92–94] A potential limitation of this approach is that NK cells expressing non-cleavable CD16A might be less efficient at serial killing of Ab-coated tumor cells in vivo. However, it is also possible that non-cleavable CD16A may further stabilize and increase NK cell attachment to tumor cells in the tumor microenvironment for more effective

killing of resilient cancer cells. This manipulation may also increase or extend CD16A signaling to boost NK cell activation and their degranulation for killing surrounding cancer cells and/or their production of antitumor cytokines. Moreover, for adoptive cell immunotherapies, lymphocytes are administered in large numbers to increase effector to target cell ratios, and under these conditions, serial killing may play less of a role in ADCC. None-the-less, there is much that needs to be elucidated about the potential benefits and detriments of blocking ADAM17 activity and CD16A cleavage on ADCC by NK cells in vivo.

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AUTHORSHIP

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DISCLOSURE

The authors declare no conflict of interest

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