Review > J Leukoc Biol. 2019 Jun;105(6):1297-1303. doi: 10.1002/JLB.2MR1218-501R.
Epub 2019 Feb 20.

Role of ADAM17 as a Regulatory Checkpoint of CD16A in NK Cells and as a Potential Target for Cancer Immunotherapy

Jianming Wu [1], Hemant K Mishra [1], Bruce Walcheck [1]

Affiliations + expand

PMID: 30786043 PMCID: PMC6792391 (available on 2020-06-01)
DOI: 10.1002/JLB.2MR1218-501R
Free PMC article

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.

Conflict of interest statement

Conflict of Interest Disclosure
The authors declare no conflict of interest