Impairment of IgG Fc functions promotes tumor progression and suppresses NK cell antitumor actions

ABSTRACT

Natural killer (NK) cells mediate antibody dependent cytotoxic killing of cancer cells via cross-linking FcγR on NK cells with IgG-Fc. Studies have shown that the single-hinge cleaved IgGs (scIgGs) have dysfunctional Fc and failed engagement with FcγRs on immune cells. However, little is known about how scIgGs impact on antitumor immunity in the tumor microenvironment. In this study, we revealed a significant association of tumor scIgGs with tumor progression and poor outcomes of breast cancer patients (n = 547). Using multiple mouse tumor models, we demonstrated that tumor scIgGs reduced NK cell cytotoxic activities and resulted in aggressive tumor progression. We further showed that an anti-hinge specific monoclonal antibody (AHA) rescued the dysfunctional Fc in scIgGs by providing a functional Fc and restored NK cell cytotoxic activity. These findings point to a novel immunotherapeutic strategy to enhance Fc engagement with FcγRs for activation of anticancer immunity.