IGSF8 is a novel innate immune checkpoint and cancer immunotherapy target

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Background Loss of MHC-I antigen presentation is often associated with T-cell excluded tumors, and represents a common mechanism of both primary and acquired resistance to immune checkpoint blockade (ICB) treatment. MHC-I normally acts as a marker of ‘self’ and cells that lack MHC-I are recognized and killed by innate immunity. In this study, we investigated the mechanism of innate immune evasion in tumors with MHC-I antigen presentation defects.

Methods Integrating functional genomics, big data, and artificial intelligence, we discovered that IGSF8 expressed on cancer cells is an evolutionarily conserved innate immune checkpoint. IGSF8 is normally expressed in neuronal tissues and is not essential in vitro or in vivo. However, knockout of IGSF8 in B16-F10 melanoma cell line decreased tumor growth in vivo. For clinical relevance of IGSF8 in tumor immunity, we analyzed genomics, transcriptomics, and clinical data from The Cancer Genome Atlas (TCGA). We developed an antibody (GV20–0251) against IGSF8 and tested its function to induce immune cell killing of cancer cells in vitro and inhibit tumor growth in vivo.

Results IGSF8 has receptors on both natural killer (NK) cells and dendritic cells (DC) to strongly suppress NK cytotoxicity and antigen presentation. In the TCGA tumor profiles, IGSF8 has highest mRNA expression in melanoma and is significantly overexpressed in many cancer types. IGSF8 also shows frequent copy number amplifications. In addition, IGSF8 expression is associated with low antigen presentation, low immune infiltration, and worse overall survival in patients with low MHC class I expression. Immunohistochemistry staining of various cancers showed that IGSF8 expression was primarily observed in malignant cells with low MHC-I.

We developed a cross-species reactive antibody against IGSF8 (GV20–0251) which blocks IGSF8 interaction with NK and DC. Flow cytometry of the tumor infiltrating CD45+ cells revealed that IGSF8 inhibition significantly increased NK and dendritic cell infiltration. GV20–0251 enhances NK killing of cancer cells in vitro and increases antigen presentation, NK-mediated cytotoxicity, and T cell signaling in vivo. In multiple syngeneic tumor models (B16-F10, CT26, LLC and EMT6), anti-IGSF8 shows single-agent efficacy and is synergistic with anti-PD1 in controlling tumor growth.

Conclusions IGSF8 is a novel innate immune checkpoint and cancer immunotherapy target. A phase 1 study is ongoing to explore the IGSF8 inhibitor GV20–0251 in patients with advanced or metastatic solid tumors (NCT05669430).

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