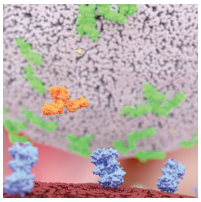
Immune Evasion

Major Finding: Cancer cells alter NK cell surface topology to block immune synapse formation and cytotoxicity.

Concept: Intratumoral dysregulation of serine metabolism alters sphingomyelin levels in NK cell membranes.

Impact: Increasing sphingomyelin production on NK cells may boost the efficacy of immune checkpoint blockade.

TUMOR CELLS ALTER NK CELL SURFACE TOPOLOGY FOR IMMUNE EVASION



Previous studies have suggested that membrane protrusions on natural killer (NK) cells may be a component of immune synapses, but whether tumor cells block these lytic immunologic synapses by altering NK cell surface topology has not been fully explored. To investigate if tumor cells evade immune-mediated lysis through altering NK cell surface topology, Zheng, Hou, and colleagues isolated NK cells from patients with liver cancer and showed that intratumoral NK cells have shorter and fewer cell membrane protrusions than those isolated from normal liver tissue or the peripheral blood of healthy donors. These intratumoral NK cells also did not bind or form immunologic synapses with liver cancer cells in coculture experiments. Single-cell analysis of NK cell membrane components revealed that intratumoral NK cells had significantly reduced sphingomyelin (SM) content, and inhibition of sphingomyelin synthase 1, the enzyme responsible for SM synthesis, in peripheral NK cells from healthy donors reduced both membrane protrusion size and number as well as prevented immune synapse formation with liver cancer cells. Additionally, the coculture of healthy peripheral NK cells with liver cancer cells revealed that reduced levels of serine, a precursor for SM synthesis, inhibited SM synthesis and subsequent protrusion formation, indicating that dysregulated serine metabolism in cancer cells mediates the reduction of SM levels in intratumoral NK cells. Furthermore, inhibition of SM catabolism led to increased SM levels, protrusion formation, synapse formation with liver cancer cells, and lytic activity of intratumoral NK cells, while blockade of both SM catabolism and Tim3, an immune checkpoint molecule upregulated on intratumoral NK cells, in a humanized mouse model of liver cancer demonstrated suppression of tumor growth better than either treatment alone. In conclusion, this study shows that cancer cells evade NK cell cytotoxicity by altering NK cell surface topology and suggests that targeting this mechanism can improve the antitumor efficacy of immunotherapies. ■

Zheng X, Hou Z, Qian Y, Zhang Y, Cui Q, Wang X, et al. Tumors evade immune cytotoxicity by altering the surface topology of NK cells. Nat Immunol 2023;24:802–13.

doi: 10.1158/2159-8290.CD-RW2023-052

Gastric Cancer

Major Finding: The driver event landscape of gastric cancer varies between ancestry, clinical subtype, and EBV infection status.

Concept: This large cohort revealed low-frequency driver genes, clonal mutations, and immune evasion mechanisms.

Impact: These results can improve diagnosis, treatment, and prevention in patients with gastric cancer.

DRIVER EVENTS OF GASTRIC CANCER DIFFER ACCORDING TO SUBTYPE AND ANCESTRY

Incidence rates of gastric cancer have been found to vary by region due to germline variants, environmental factors, and lifestyle factors. However, comprehensive molecular studies that evaluate somatic mutations and their associations with geographic and epidemiologic diversities are lacking. Totoki and colleagues, using 1,335 cases, conducted a study to evaluate the multiancestral landscape of driver events in gastric cancer and identified 77 significantly mutated genes (SMG). The intestinal subtype was found to be enriched for alterations in RTK/RAS and cell-cycle pathways, while the diffuse subtype of gastric cancer had more mutations in the cell adhesion pathway with characteristic SMGs that included *CDH1*, *RHOA*, *PIGR*, *SOX9*, *TGFBR2*, and *BAP1*. Moreover, *PD-L1*, *PD-L2*, and *JAK2* were more frequently amplified in Epstein–Barr virus (EBV)–positive cases, and mutations in *MDM2*, *CDKN2A*, *ARID2*, *PTEN*, and *MUC6* were more frequently altered in cases of European ancestry, while *TP53* alterations were more common in those of East Asian ancestry. Recurrent hotspot mutations were also noted in *TRIM49* and *ARHGAP5*, while *RB1* and *ARHGAP5* were noted as having a higher altered variant allele frequency but weak positive selection, suggesting these mutations may be clonal drivers of unidentified minor subtypes. Additionally, enriched inframe splicing alterations were found in *CDH1*, with a majority targeting localized extracellular domains, indicating these somatic mutations function as dominant-negative mutants. Furthermore, a comprehensive evaluation of pathogenic germline variants identified *ATM*, *PKHD1*, *APC*, and *SASH1* as more prevalent in those of European ancestry, with *BRCA2* and *ERCC6* being more frequent in those with East Asian ancestry. Furthermore, those with East Asian ancestry and the diffuse subtype demonstrated an association with germline variations in genes associated with alcohol consumption, suggesting a link between alcohol metabolism and the development of $RHOA^{Y42C}$ hotspot mutations. Finally, hypermutated cases of gastric cancer were found to harbor more mutations related to immune evasion. In summary, these results reveal the driver event landscape of gastric cancer as well as the association of these events with ancestry and clinical subtype, which can be used to improve clinical management of this disease. ■

Totoki Y, Saito-Adachi M, Shiraishi Y, Komura D, Nakamura H, Suzuki A, et al. Multiancestry genomic and transcriptomic analysis of gastric cancer. Nat Genet 2023;55:581–94.

doi: 10.1158/2159-8290.CD-RW2023-049