IGSF8 is an Innate Immune Checkpoint and Cancer Immunotherapy Target

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Resistance to Immune-Checkpoints and innate immunity

- Over 65% of tumors have antigen presentation defects and these tumors are often immune cold and don’t respond to immunotherapy
- Innate immune Natural Killer (NK) cells normally kill cells with antigen presentation defects
- Why aren’t tumors with MHC-I defects killed by NK cells?

Garrido et al, Curr Opin Immunol 2016
Zaretsky et al, NEJM 2016
IGSF8 was discovered through antibody AI ranking and CRISPR screens

CRISPR screen in cancer cells grown in syngeneic mouse tumors

CRISPR screens of cancer cells co-cultured with primary NK cells
IGSF8 is overexpressed in solid tumors (TCGA)
IGSF8 is amplified in various solid tumors (TCGA)
IGSF8 mRNA expression is correlated with cold tumor markers

<table>
<thead>
<tr>
<th>CD8 T cells</th>
<th>Cytolytic activity</th>
<th>PDL1</th>
<th>Antigen presentation</th>
<th>Autophagy factors known to degrade MHC I protein complex</th>
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<tbody>
<tr>
<td>CD8A</td>
<td>CD8B</td>
<td>GZMA</td>
<td>GZMB</td>
<td>PRF1</td>
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<tr>
<td>CD274</td>
<td>B2M</td>
<td>NBR1</td>
<td>SYVN1</td>
<td>TMEM129</td>
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<td>SND1</td>
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- Spearman correlation with IGSF8

<table>
<thead>
<tr>
<th>Endometrium</th>
<th>Prostate</th>
<th>Thyroid</th>
<th>Breast</th>
<th>Rectum</th>
<th>Liver</th>
<th>Colon</th>
<th>Bladder</th>
<th>Lung (squamous)</th>
<th>Lung (adenoc.)</th>
<th>Head and Neck</th>
<th>Esophagus</th>
<th>Gastric</th>
<th>Melanoma</th>
<th>Glioma (low grade)</th>
<th>Ovary</th>
<th>Adrenal</th>
<th>Testis</th>
<th>Pancreas</th>
<th>Thymus</th>
<th>Sarcoma</th>
<th>Renal (papillary)</th>
<th>Renal (clear cell)</th>
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- p<0.05
- p>0.05
High IGSF8 mRNA is associated with poor survival and non-response to ICI

Riaz et al., 2017
IGSF8 has receptors on both NK cells and Dendritic Cells (DCs) in human and mouse.
Anti-IGSF8 leads to potent tumor growth inhibition across multiple tumor models as single agent and in combination.
Anti-IGSF8 prolongs survival in B16 model and increases T, NK and dendritic cells infiltration
Conclusions

- IGSF8 is highly expressed on cancer cells

- Anti-IGSF8 enhances NK killing, antigen presentation, and turns immune-cold tumors hot

- Anti-IGSF8 shows monotherapy efficacy and is synergistic with anti-PD1 in multiple syngeneic tumor models (including some known to resist to anti-PD1)

- The IGSF8 inhibitor, GV20-0251 is currently explored in a phase 1 study in patients with advanced or metastatic solid tumors (NCT05669430)