Mystery Checkpoint Revealed: KIR3DL3 Finally Found a Ligand in HHLA2

Kerry S. Campbell

Inhibitory killer cell immunoglobulin–like receptors (iKIR) tolerize natural killer cells and some T cells upon detecting classical HLA class I molecules. In this issue, Bhatt and colleagues identify the B7 family member HHLA2 as an unanticipated ligand for a peculiar iKIR family member, KIR3DL3. These data establish a new inhibitory checkpoint pathway that may protect HHLA2^{+} tumor cells from immune attack.

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Inhibitory receptors provide checkpoints that regulate immune-cell functions. Antibodies blocking PD-1 and CTLA-4 inhibitory checkpoints reinvigorate antitumor T-cell responses to effectively treat cancer, but only some patients show durable responses. Therefore, significant research seeks to identify additional checkpoint pathways restraining robust antitumor immunity. Bhatt and colleagues provide evidence of a previously unknown ligand for the KIR3DL3 inhibitory receptor (1), revealing a novel checkpoint affecting natural killer (NK) and T cells.

Inhibitory killer cell immunoglobulin–like receptor (iKIR) family members are expressed on NK cells and some T cells. Recognition of classical HLA class I molecules by iKIRs tolerizes these lymphocytes toward normal healthy cells. *KIR* genes are differentially inherited in humans on chromosome 19q13.4. *KIR3DL3* is a "framework" *KIR* family gene that is inherited in all human haplotypes, suggesting it encodes a protein with important biological functions.

KIR3DL3 has unique properties among the iKIRs. First, most iKIRs have two cytoplasmic immunoreceptor tyrosine-based inhibitory motifs for inhibitory signaling, but KIR3DL3 has only one. Second, prominent promoter methylation more significantly limits *KIR3DL3* transcription, although mRNA and protein are detected in immature CD56^{bright} NK cells in healthy donor blood, especially in women, who also express KIR3DL3 on decidual NK cells in pregnancy (2). Third, *KIR3DL3* is one of the most polymorphic KIR genes, encoding at least 93 distinct polypeptide sequences with amino-acid variations throughout the protein (3). Fourth, although other iKIRs recognize classical HLA class I molecules, the ligand for KIR3DL3 has remained elusive.

Bhatt and colleagues solved this mystery, showing that the B7 family member HHLA2 (also known as B7-H7) is a KIR3DL3 ligand (1). HHLA2 is also a ligand for TMIGD2 (also known as CD28H and IGPR-1; ref. 4), which is a costimulatory receptor on T and NK cells, suggesting receptor signaling cross-talk with this ligand. Engagement of KIR3DL3 with HHLA2 effectively inhibited activation of a T-cell line and cytotoxicity by a NK-cell line. Monoclonal antibodies targeting KIR3DL3 and HHLA2 effectively blocked both receptor–ligand interactions and inhibitory function. Whereas some HHLA2-specific antibodies blocked both KIR3DL3 and TMIGD2 interactions with the ligand, others blocked only KIR3DL3. This importantly demonstrates the potential to develop therapeutics that only block the inhibitory checkpoint interactions. HHLA2 is expressed in renal cell carcinomas (RCC; ref. 4), and coexpression with PD-L1 significantly increases risk of disease progression and cancer-specific death (5). Bhatt and colleagues found distinct RCC regions expressing either HHLA2 or PD-L1, suggesting localized checkpoint regulation by KIR3DL3 and PD-1, respectively. KIR3DL3 was also upregulated on a small subset of activated T cells, which complements reported expression on activated and decidual NK cells (2). Notably, HHLA2 is expressed on trophoblast cells in decidual tissues (4), suggesting key roles for KIR3DL3/HHLA2 interactions in pregnancy, as well as cancer.

Despite these provocative new findings, numerous questions remain, including: (i) Are HHLA2 and KIR3DL3 coexpressed in tumor microenvironments, and do their interactions affect NK- and T-cell functions *in vivo*? (ii) What mechanisms regulate expression of KIR3DL3 and HHLA2? (iii) How does HHLA2 expression in tumors affect NK- and T-cell responses through signaling cross-talk between TMIGD2 and KIR3DL3? (iv) How do KIR3DL3 polymorphisms affect HHLA2 recognition and inhibitory function, and do allelic variations affect cancer risk? (v) In addition to cancer, how do KIR3DL3/HHLA2 interactions influence pregnancy? Nonetheless, if future preclinical studies continue to demonstrate importance of the KIR3DL3/HHLA2 inhibitory axis in tumors, blockade may prove to be a viable therapeutic path to treat cancer.

Author's Disclosures

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Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, Pennsylvania.

Corresponding Author: Kerry S. Campbell, Institute for Cancer Research, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111. Phone: 215-728-7761; Fax: 215-728-2412; E-mail: kerry.campbell@fccc.edu

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