A γδ T–cell Imprint in a Rare Skin Tumor

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In-depth immune profiling can guide the development and targeting of cancer immunotherapies. In this issue, Gherardin and colleagues find a strong signature of γδ T cells in the immune infiltrate of Merkel cell carcinoma that correlates with a more favorable prognosis and heightened responsiveness to checkpoint inhibitors. This may lead to future γδ T cell–targeted immunotherapies.

See article by Gherardin et al., p. 612

Merkel cell carcinoma (MCC) is a rare cancer that arises in skin neuroendocrine cells (1). It is caused by either Merkel cell polyomavirus (MCPyV) or UV damage. MCPyV MCCs exhibit a low mutation burden, whereas abundant mutations in UV damage–associated MCCs result in the expression of neoantigens. MCC is quite aggressive, with high rates of metastases and a 5-year overall survival rate of ∼50%. The primary therapy for MCC is local excision. In recent years, anti–PD-1 and anti–PD-L1 immunotherapies have emerged as promising new treatments. As successfully designing new immunotherapeuties relies on detailed knowledge of a cancer's immune profile, Gherardin and colleagues characterize the immune infiltrate of MCC at high resolution and find an unusual γδ T–cell imprint that correlates with better response. This finding may guide the future development of MCC immunotherapies (2).

Using multiplex-immunohistochemistry/immunofluorescence, Gherardin and colleagues analyze 58 MCC specimens and find that at least 20% of infiltrating T cells are γδ T cells in almost half of the specimens. γδ T cells mainly reside in peripheral tissues, including the skin, where they sense tissue damage and promote immune responses and wound healing (3, 4). Based on Vδ gene segment usage, γδ T cells comprise three main groups: Vδ1, which encompass most tissue γδ T cells; Vδ2, which are mainly circulating; and Vδ3, which represent a minority of tissue γδ T cells. All γδ T cells recognize nonpeptidic ligands that are presented by nonclassic MHC molecules, MHC-like molecules, or butyrophilin-like proteins (BTNL; ref. 5).

Gherardin and colleagues analyze multiple tumor samples by bulk RNA sequencing (RNA-seq), showing a correlation between the presence of a γδ T–cell signature and prolonged survival. They use single-cell RNA-seq to show that MCC γδ T cells are predominantly of the Vδ1 type and include two major clusters. The largest cluster expresses genes encoding cytotoxic mediators (granzymes and perforin), natural killer (NK)–cell receptors (NKG2E and NKp46), and proteins indicative of exhaustion (TIM3, PD1, LAG3, and CTLA4) and tissue residency (CD103). The less prominent cluster expresses NK-cell receptors and CD69, which indicates activation, but there are no transcripts intimating exhaustion or residency. Whether these γδ T–cell populations are developmentally related and have distinct effects on disease progression was not addressed. T-cell receptor (TCR) repertoire analysis indicates that γδ T cells are oligoclonal, suggesting antigen-driven expansion. Expression of the four most dominant γδ TCR clonotypes isolated from one tumor in reporter cells shows that one clone recognizes the nonclassic MHC molecule MR1, which presents riboflavin derivatives. A second clone recognizes CD1c, which presents glycolipids. Among all patients studied, four undergoing immune-checkpoint blockade are shown to have more tumor-infiltrating γδ T cells; three of them had a complete response, suggesting that the beneficial effect of the treatment may be partly due to γδ T cells.

The study by Gherardin and colleagues shows that γδ T cells are biomarkers predictive of better prognosis and attractive candidates for future immunotherapies. It also raises important questions: (i) Do tumor ligands activate γδ T cells through TCRs, NK-cell receptors, or other cell-surface molecules? (ii) Do tumor γδ T cells recognize BTNLs in addition to MR1 and CD1c? (iii) Which pathways induce activation, exhaustion, and tissue residency phenotypes? (iv) Do immune-checkpoint inhibitors affect γδ T–cell exhaustion? (v) Are resident γδ T cells present in the tissue before the tumor evolves? Answering these questions will help design strategies to enhance γδ T–cell responses across many cancer types.

Authors' Disclosures

M. Colonna reports personal fees from NGM Biotechnology during the conduct of the study. No disclosures were reported by the other author.

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