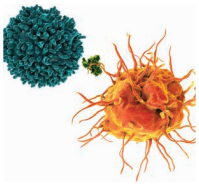
Immunology

Major Finding: TIM3 expression in dendritic cells inhibits antitumor immunity by regulating the inflammasome.

Concept: Loss of TIM3 in dendritic cells promoted a protective T-cell immune response in murine tumors.

Impact: Insights into TIM3 function in dendritic cells can guide future use of TIM3 blockade to enhance antitumor immunity.

TIM3 BLOCKADE IN DENDRITIC CELLS MAY POTENTIATE ANTITUMOR IMMUNITY



T-cell immunoglobulin and mucin-containing molecule 3 (TIM3) is implicated as an immune checkpoint molecule and is expressed on several different types of immune cells. However, exactly how therapeutic blockade of TIM3 might influence antitumor immunity is currently unknown. Using single-cell RNA sequencing and mouse models, Dixon, Tabaka, and colleagues demonstrated that loss of TIM3 on dendritic cells (DC), but not on T cells, promotes an antitumor immune response. Conditional knockout mice lacking TIM3 in $CD8^+$ T cells, both $CD8^+$ and $CD4^+$ T cells, or T regulatory cells had no change in the tumor burden of engrafted murine colon cancer cells. Single-cell RNA sequencing and flow cytometry analysis of cells from wild-type mice with colon tumors revealed the highest expression of TIM3 on DCs, as well as high expression on intratumoral monocytes and macrophages. Targeted deletion of TIM3 in DCs resulted in a reduction in tumor burden in mice engrafted with colon cancer, lung cancer, or melanoma cells. Subcutaneous engraftment of colon cancer cells into mice with conditional loss of TIM3 prevented DCs from expressing a regulatory program and increased the number of $PD\text{-}1^+$ tumor-infiltrating lymphocytes (TIL) found in tumors. Analysis of TILs showed an increased number of stem-like $CD8^+$ cells, memory precursor T cells, and cells entering the effector lineage, together indicating promotion of a protective immune response in tumors from mice where TIM3 expression on DCs is lost. Further single-cell RNA-sequencing analysis of DCs lacking TIM3 from murine tumors showed promotion of DC functionality and enhancement of antigen-specific antitumor immunity. Finally, TIM3 deletion in DCs resulted in accumulation of reactive oxygen species, activating the NLRP3 inflammasome. Blocking inflammasome activation either directly or via inhibition of downstream effector cytokines IL1β and IL18 reversed the antitumor effects of deletion of TIM3. These results highlight the potential of TIM3 blockade to harness inflammasome activity to boost antitumor immunity. ■

Dixon KO, Tabaka M, Schramm MA, Xiao S, Tang R, Dionne D, et al. TIM-3 restrains anti-tumour immunity by regulating inflammasome activation. Nature 2021;595:101–6.

Tumor Microenvironment

Major Finding: Macrophage embryonic lineage contributes to invasiveness and immune evasion at the onset of tumorigenesis.

Concept: Tissue-residing macrophages dominate early and then redistribute upon monocyte-derived macrophage infiltration.

Impact: Targeting tissue-resident macrophages could be a promising early therapeutic strategy for lung cancers.

TISSUE-RESIDENT MACROPHAGES HELP EARLY-STAGE LUNG TUMORS DEVELOP

Macrophages are an important component of the tumor microenvironment (TME), with roles in tumor immunity and response to immunotherapy. Therapeutic targeting of macrophages has significant potential, but current knowledge about the diversity and functions of tumor-associated macrophages is lacking. Using single-cell RNA sequencing, Casanova-Acebes, Dalla, and colleagues analyzed samples of tumor and nonmalignant lung from 35 people with early-stage non–small cell lung cancer along with samples from murine models of lung adenocarcinoma, finding four distinct clusters of monocytes and macrophages with differing gene expression profiles. Lineage tracing of these macrophage populations using two different murine models revealed distinct spatial and temporal distributions in the TME as well as different origins, with some being locally self-maintained tissue-resident macrophage (TRM) populations whereas others were monocyte-derived macrophages derived from adult hematopoietic stem cells in the bone marrow. Coculture of mouse adenocarcinoma cells with TRMs caused distinct transcriptional changes, promoted invasion and epithelial–mesenchymal transition, and increased the dispersion of tumor cells over time. Coculture of the same cells with monocyte-derived macrophages instead resulted in changes in genes associated with DNA replication and cell-cycle regulation. TRMs were located close to tumor cells in early-stage lung lesions along with an accumulation of T regulatory cells but were found increasingly at the TME periphery as tumors grew and the population of monocyte-derived macrophages increased. Specific depletion of TRMs using an engineered mouse model reduced regulatory T cells, promoted $CD8^+$ T-cell recruitment and reduced tumor growth and invasion. The authors suggest that TRMs play a key role in the progression of early-stage lung tumors and that targeting TRMs could be an effective therapeutic strategy for the treatment and prevention of these lesions. ■

Casanova-Acebes M, Dalla E, Leader AM, LeBerichel J, Nikolic J, Morales BM, et al. Tissue-resident macrophages provide a pro-tumorigenic niche to early NSCLC cells. Nature 2021 Jun 16 [Epub ahead of print].

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