

## Immunology

**Major Finding:** Tissue-resident memory T cells and tumor-infiltrating lymphocytes (TIL) partitioned into two types.

**Concept:** One type resembled terminally exhausted cells; the other resembled progenitor-exhausted cells.

**Impact:** Insight into TIL heterogeneity may aid progress toward harnessing TILs for immunotherapy.

## TUMOR-INFILTRATING T CELLS MIMIC TISSUE-RESIDENT T-CELL HETEROGENEITY

Circulating CD8<sup>+</sup> T cells come in different types that vary with regard to function and memory potential, but whether tissue-resident memory T (T<sub>rm</sub>) cells—which resemble tumor-infiltrating lymphocytes (TIL) in some regards—also exhibit this property has not been established. Using a mouse model of lymphocytic choriomeningitis virus (LCMV) infection, Milner and colleagues found evidence for marked intertemporal and intratemporal heterogeneity in antigen-specific antiviral T<sub>rm</sub> cells in the small-intestine intraepithelial lymphocyte population. Early in viral infection, effector T cell-like T<sub>rm</sub> cells high in BLIMP1 and low in ID3 (BLIMP1<sup>hi</sup>ID3<sup>lo</sup>) predominated, whereas memory T cell-like BLIMP1<sup>lo</sup>ID3<sup>hi</sup> T<sub>rm</sub> cells became more prevalent as infection progressed. The T<sub>rm</sub> cell types defined by their expression of the transcriptional regulators BLIMP1 and ID3 also had unique transcriptional profiles and differed in other ways: BLIMP1<sup>lo</sup>ID3<sup>hi</sup> T<sub>rm</sub> cells had enhanced cytokine production and secondary memory potential compared with BLIMP1<sup>hi</sup>ID3<sup>lo</sup> T<sub>rm</sub> cells. Notably, the memory T cell-like BLIMP1<sup>lo</sup>ID3<sup>hi</sup> T<sub>rm</sub> cells were more multifunctional, possessing greater multipotency and the ability to give rise to both circulating and resident T-cell populations

upon reinfection. Extending this analysis to a mouse model of melanoma revealed similarly delineated tumor-infiltrating T-cell types, with BLIMP1<sup>hi</sup>ID3<sup>lo</sup> CD8<sup>+</sup> TILs (similar to the tissue-resident effector T cell-like T<sub>rm</sub> cells observed early in infection) exhibiting effector-like behavior and BLIMP1<sup>lo</sup>ID3<sup>hi</sup> CD8<sup>+</sup> TILs (similar to the tissue-resident memory T cell-like T<sub>rm</sub> cells observed later in infection) exhibiting memory-like behavior. Transcriptomic analysis showed that the effector-like CD8<sup>+</sup> TILs had gene-expression signatures akin to those of terminally exhausted T cells, whereas the memory-like CD8<sup>+</sup> TILs had gene-expression signatures more similar to progenitor-exhausted T cells. In summary, this work identifies T<sub>rm</sub>-cell heterogeneity that carries functional consequences, and this heterogeneity appears to extend to TILs, providing insight into the roles of cells that are critical for antitumor immunity. ■

Milner JJ, Toma C, He Z, Kurd NS, Nguyen QP, McDonald B, et al. Heterogenous populations of tissue-resident CD8<sup>+</sup> T cells are generated in response to infection and malignancy. *Immunity* 2020;52:808–24.E7.

## Colorectal Cancer

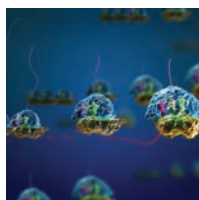
**Major Finding:** Colorectal cancer cells lost biosynthetic capabilities in an irreversible differentiation process.

**Mechanism:** Elevated RNA polymerase I subunit A activity was necessary to sustain the cancer stem cell phenotype.

**Impact:** Capacity for biosynthesis defines stemness of colorectal cancer cells in an LGR5-independent manner.

## DIFFERENTIATION OF CANCER STEM CELLS HALTS PROTEIN AND rRNA SYNTHESIS

Colorectal cancers depend on populations of cancer stem cells (CSC), which are typically defined by expression of the G-protein coupled receptor LGR5. However, not all colorectal cancers contain LGR5-expressing cells, raising questions about whether LGR5<sup>+</sup> colorectal cancers simply have CSCs that are not defined by LGR5 expression or do not require CSCs at all. Using patient-derived xenografts and fresh surgical specimens, Morral, Stanisavljevic, and colleagues found that colorectal cancers exhibited zonation patterns in their synthesis of protein and rRNA, with the vast majority of these biomolecules being produced by cells in limited niches near the stroma. However, proximity to the stroma alone was not sufficient to induce production of protein or rRNA by colorectal cancer cells. Further investigation revealed that fully differentiated colorectal cancer cells were characterized by low rates of rRNA and protein synthesis and reduced numbers of ribosomes, and these cells functioned by retaining proteins that had been produced prior to the loss of protein-synthesis machinery. Additionally, the colorectal cancer cells capable of producing rRNA and protein had increased levels



of RNA polymerase I subunit A (POLR1A), which is responsible for the transcription of rRNA-encoding genes. POLR1A<sup>hi</sup> protein- and rRNA-producing colorectal cancer cells were required to fuel tumor growth, whereas LGR5<sup>+</sup> cells were dispensable. Notably, although short-term (two days) forced differentiation of colorectal cancer cells in tumoroids grown *in vitro* was reversible, long-term (seven days) differentiation was not reversible and led to sustained low POLR1A levels and downregulation of biosynthesis-related genes. Experiments in which these tumoroids were xenografted into mice confirmed that this phenomenon also occurred *in vivo*. Together, these results support the notion that the capacity for biosynthesis defines CSC status regardless of LGR5 expression, an observation that may be used to develop CSC-targeting therapies for colorectal cancer. ■

Morral C, Stanisavljevic J, Hernando-Momblona X, Mereu E, Alvarez-Varela A, Cortina C, et al. Zonation of ribosomal DNA transcription defines a stem cell hierarchy in colorectal cancer. *Cell Stem Cell* 2020;26:845–61.e12.