MUCOSAL-ASSOCIATED INVARIANT T (MAIT) CELL REGULATION NETWORKS IN ANTI-TUMOR IMMUNITY

¹Benjamin Ruf*, ²Vanessa Catania, ²Noemi Kedei, ²Simon Wabitsch, ²Chi Ma, ²Laurence Diggs, ²Qianfei Zhang, ²Bernd Heinrich, ²Varun Subramanyam, ²Linda Cui, ²Shunsuke Sakai, ²Sangmi Oh, ³Merrill Stovroff, ²Clifton Barry III, ²Daniel Barber, ³Alexander Kroemer, ²Farouze Korangy, ²Tim Greten. ¹National Institutes of Health (NIH), Bethesda, MD, United States; ²NIH, Bethesda, MD, United States; ³Georgetown University Medical Center, Washington, DC, United States

Background MAIT cells are MR1-restricted innate-like T cells that recognize non-peptide antigens including riboflavin derivatives. They account for up to 10 % of circulating T cells, but they are further enriched at mucosal sites and the liver. On one hand, altered MAIT number and function have been reported in liver cancer with MAITs correlating with poor clinical outcome. On the other hand, we recently demonstrated that MAIT cells can potentially have anti-tumor activity suggesting them as a novel target for cancer immunotherapy. Yet, the cellular and humoral factors that determine MAIT cell fate in the context of malignancies remain largely unknown.

Methods Highly multiplexed immunofluorescence-based CODEX imaging and high-dimensional flow cytometry was used to analyze MAIT cell infiltration and phenotype in human HCC samples. We recently developed an experimental framework to manipulate MAIT cells in vivo using VitaminB2 synthesis pathway-derived antigen 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) in combination with Toll-like receptor 9 agonist CpG. Next, we used murine models of orthotopic primary liver cancer and liver metastasis across two different mouse strains, to assess anti-tumor activity of MAIT cells. A series of pharmacological depletion experiments and genomic knockout mouse strains were used to identify additional effector immune cells and humoral factors mediating the anti-tumor effect.

Results Using flow cytometry and spatially resolved analysis of multiplexed CODEX microscopy images, we found impaired infiltration and altered phenotype of MAIT cells in human HCC tumors compared to unaffected liver tissue. Thus, we sought out to experimentally increase MAIT cell infiltration into liver cancers using murine models. Co-administration of 5-OP-RU + CpG induced a strong systemic in vivo expansion and activation of MAIT cells with Th1/NK-like polarization. We found MAIT cells to be potent orchestrators of anti-tumor function in vivo when activated by a combination of 5-OP-RU + CpG. MAIT-directed 5-OP-RU/CpG showed pronounced and consistent anti-tumor activity against different models of liver cancer and prolonged mouse survival. Importantly, such tumor inhibition was absent in MAIT-deficient MR1 k.o. mice but not dependent on MR1 expression on tumor cells. Additional pharmacological depletion studies/genomic k.o. models helped to identify antigen presenting cells, downstream effector cells as well as co-stimulatory cytokines as critical components needed for MAIT-induced tumor suppression.

Conclusions MAIT cells are important players in cancer immunology and represent an attractive novel target for cancer immunotherapy. Fine-tuned, context-dependent mechanisms determine MAIT-cell fate in vivo as they undergo a phenotypic switch upon 5-OP-RU and CpG treatment enabling them to exert potent anti-tumor function.

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