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A new humanized mouse tool reveals T-cell mediated tumor control

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Mice with a human immune system (HIS mice) have become an essential tool for studying human tumor biology and for the preclinical testing of tumor-fighting therapeutics. However, HIS mice have subpar T and B cell antigen-specific function compared with immunocompetent mice and humans, and more credible models of the human immune system are needed to guide the development of future therapies against cancers, including immunotherapies.

In a study published in *Communications Biology*, researchers show HIS mice can mount tumor-specific responses and demonstrate the important role of T cells in spontaneous regression of human B-cell lymphoma Raji.

The researchers from the biotech company Regeneron Pharmaceuticals used SRG and SRG-15 immunodeficient mice reconstituted with human fetal liver-derived CD34+ cells. They employed a combination of techniques including flow cytometry, single-cell RNA sequencing, cloning of T cell receptors, and in vitro assays, to provide new insights into the role of T cells and T-cell memory in tumor growth control in HIS mice. The team implanted Raji and Ramos tumors in the HIS mice, two common tumor-inducing tools to study tumor behavior in the lab. HIS-reconstituted mice implanted with Raji tumors began to develop tumors around 12 days post-implantation, and tumor regression could be observed starting two weeks after implantation. By contrast non-HIS mice show no tumor regression, indicating that the reconstituted immune system is responsible for tumor regression. The findings also show that HIS-reconstituted mice rechallenged with Raji cells after rejecting Raji tumor during the primary challenge did not develop tumors, indicating that Raji tumor elicits T-cell memory. Raji tumor progression occurred in mice with depleted CD4+/CD8+ cells, demonstrating that tumor control is largely T-cell-mediated. Additionally, the findings show that the response is specific against Raji tumors when compared to Ramos as mice implanted with Ramos showed tumor progression. Regardless, mice that previously cleared Raji tumors show some protection from Ramos showing slower progression. Single-cell RNA-seq analysis additionally revealed that tumor-infiltrating T cells were predominantly CD8+ T cells which are known for their cytotoxic role, while matching splenic T cells were predominantly naive CD4+ T cells.

Taken together, these findings suggest that researchers can use this model system to evaluate immune therapeutics that can enhance tumor-specific T-cell responses.

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