Subverting T_{reg}-mediated protection for tumors

By Kai-Jye Lou, Senior Writer

T_{reg} cells present a conundrum for cancer researchers—although these cells can suppress the antitumor immune response, depleting them can trigger severe inflammation and autoimmunity. Now, a team of researchers at **St. Jude Children's Research Hospital** has uncoupled these effects by targeting neuropilin 1–semaphorin 4A signaling, a pathway active in tumor-associated T_{reg} cells.¹

The results suggest that disrupting the neuropilin 1 (NRP1)–semaphorin 4A (SEMA4A) signaling axis could be used to treat tumors that respond poorly to immunotherapies designed to boost the antitumor immune response.

T_{reg} cells are mediators of peripheral tolerance and play a critical role in preventing pathological autoimmunity and inflammation.² However, tumors are known to induce the expansion of T_{reg} cells to protect themselves from the host immune system.³ Indeed, multiple groups have shown that T_{reg} cells limit the efficacy of cancer immunotherapies.^{4,5}

“We want to attack T_{reg} cells in cancer, but we know that broadly suppressing their activity or wiping them out could have devastating immunological consequences as patients with a mutation that renders them

deficient in these cells have severe autoimmunity,” said Dario Vignali, vice chair of the Department of Immunology at St. Jude Children's Research Hospital. “Thus, there is a strong therapeutic desire to manipulate T_{reg} cells in a manner that focuses the modulation on their activity in the tumor microenvironment.”

Vignali's group thus searched for molecules and pathways that T_{reg} cells use

in highly inflammatory settings such as the tumor microenvironment but not when maintaining immune system homeostasis.

The researchers used a series of transwell assay and transcriptome profiling studies to identify SEMA4A as a ligand that boosts T_{reg} cell function. A follow-up ELISA showed that SEMA4A interacted with

NRP1, a membrane-bound co-receptor expressed on T_{reg} cells whose function in the cells was previously unknown.

Mice with deletion of *Nrp1* in T_{reg} cells did not develop autoimmunity, but the *Nrp1*-deleted T_{reg} cells still maintained immune system homeostasis.

In mice, T_{reg} cell-restricted deletion of *Nrp1* resulted in a stronger antitumor immune response against injected cancer cells than no deletion. The *Nrp1*-deficient mice also showed less tumor growth and increased survival compared with nondeficient controls.

In wild-type mice injected with the cancer cells, SEMA4A- or NRP1-targeted antibodies decreased tumor growth compared with control antibodies.

Subsequent gene expression analysis on the T_{reg} cells revealed an *Nrp1*-induced transcriptional signature associated with enhanced T_{reg} cell function and survival. Inhibition of *Nrp1*-signaling blocked this signature.

Results were published in *Nature*.

“This study suggests it could be possible to target this neuropilin-semaphorin pathway with antibodies or soluble antagonists to eliminate T_{reg} cells that suppress the antitumor immune response without perturbing the T_{reg} cells that keep autoimmunity in check,” said Theresa Whiteside, a professor of pathology, immunology and otolaryngology at the **University of Pittsburgh Cancer Institute**.

Whiteside said that the study also presents a good model on how to search for pathways involved in the regulation of T_{reg} function in tumors and inflammatory settings.

“We were able to use our data to create a set of analytical fingerprints to indicate when this pathway is active in T_{reg} cells, and this allowed us to show that the tumor microenvironment encourages T_{reg} cells to exploit this pathway, thereby evading the host immune system,” added Vignali, who was the corresponding author. “We know from our study that removing NRP1 removes this fingerprint, which suggests there isn't a redundant pathway for this tumor-protective function in T_{reg} cells.”

Vignali said that targeting the SEMA4A-NRP1 pathway in T_{reg} cells could provide a new approach to limit T_{reg} cell function in tumors and make tumor cells visible to the host immune system, which could be useful in cases in which cancer immunotherapies have shown limited efficacy.

Determining applicability

Vignali said that his group still needs to determine how broadly the SEMA4A-NRP1 signaling pathway in T_{reg} cells is exploited by various tumors.

“There are enough data here to be excited about potential therapeutic possibilities and to warrant additional investigation of this pathway, but we need to first determine how broadly it is utilized in various cancers and in other inflammatory states,” he told *SciBX*.

Whiteside said that therapies based on targeting the SEMA4A-NRP1 pathway will likely need to be accompanied by a companion diagnostic to determine whether the pathway is active in a particular tumor.

She also thinks that there are likely to be other pathways that regulate the function of T_{reg} cells in the tumor as well as subpopulations of

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T_{reg} cells that suppress the antitumor immune response via different mechanisms. Moreover, she said other cell populations such as myeloid-derived suppressor cells are known to attenuate antitumor immunity and weaken the effect of immunotherapies.⁶

As a result, Whiteside thinks that targeting any one pathway may not be sufficient for controlling tumor-mediated immunosuppression.

Vignali said that the group now needs to run a more comprehensive set of studies to check for potential immunological consequences and side effects from targeting the SEMA4A-NRP1 pathway.

“Even though we show that inhibiting this pathway did not initiate an autoimmune response, we don’t yet know if inhibiting this pathway will exacerbate a pre-existing autoimmune response, which may be present in patients,” said Vignali. “Also, NRP1 is also expressed on neurons and is involved in their development, so we need to make sure blocking this pathway will not perturb these cells in an undesirable manner.”

Whiteside wanted to see studies to determine whether the SEMA4A-NRP1 pathway is active in metastatic tumors, which are the primary contributors to patient mortality in cancer and could have different characteristics than the primary tumor. Further along, she said, it will be important to determine whether compounds targeting the pathway will be

sufficient on their own or need to be combined with other cancer therapies.

St. Jude Children’s Research Hospital has filed for a patent covering the findings reported by Vignali’s group. The work is available for licensing.

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