Beyond the Nobel: How Tumors Hijack Regulatory T Cells to Press the Immune "Brake"

Science study uncovers the EPO/EPOR axis as a key switch for cancer immune suppression through macrophage-Treg reprogramming

Regulatory T Cells in the Spotlight

The 2025 Nobel Prize in Physiology or Medicine honored the discovery of regulatory T cells (Tregs) — a milestone in immunology that reshaped the understanding of immune tolerance.

Since their identification by Shimon Sakaguchi in the 1990s as $CD25^{+}CD4^{+}$ cells expressing the transcription factor FOXP3, Tregs have been recognized as essential regulators of immune balance, safeguarding against autoimmunity by restraining excessive immune responses. Yet, within the tumor microenvironment (TME), the same mechanism of restraint becomes a liability. By restraining effector T cells and promoting an immunosuppressive milieu, Tregs help sustain so-called "cold" tumors, which remain resistant to immune checkpoint blockade and other immunotherapies.

The Nobel recognition has renewed focus on a pressing question in tumor immunology: How can Tregs be precisely modulated within tumors to release the immune brake and restore anti-tumor activity?

An Unexpected Immunosuppressive Switch: Tumor-Derived Erythropoietin

A recent *Science* paper from Stanford University offers an unexpected answer. In hepatocellular carcinoma (HCC) models, the researchers discovered that tumor cells can secrete erythropoietin (EPO) — a hormone classically associated with red blood cell production — to drive immune suppression.

Comparing noninflamed ("cold") and inflamed ("hot") tumors, the researchers found that EPO levels were markedly elevated in immune-resistant, cold tumors. Mechanistically, EPO acts on EPO receptors (EPOR) expressed by macrophages, reprogramming them toward an M2-like, Kupffer cell–like state.

These macrophages, in turn, promote Treg activation and polarization while inhibiting $CD8^{+}$ effector T-cell activation and recruitment, forming a self-reinforcing EPO–EPOR–macrophage–Treg circuit that protects the tumor from immune attack.

Decoding the Circuit: In Vivo Functional Dissection

To dissect this pathway experimentally, the authors performed a series of targeted *in vivo* depletion and blocking experiments, using functional-grade antibodies to selectively deplete defined immune cell populations or modulate key pathways.

These experiments — built on the use of Bio X Cell's high quality functional antibodies — enabled the team to dissect cellular dependencies within the TME with precision and reproducibility.

1. Tregs contribute to EPO-Mediated Immune Suppression

To confirm the role of Tregs downstream of EPO signaling, researchers depleted them using antibodies including anti-CD25 and anti-CTLA-4.

Method: C57BL/6 mice were orthotopically implanted with 3×10^6 Epo-overexpressing Hepa1-6 HCC cells. On days 14, 17, and 20 after implantation, mice received intraperitoneal injections of 2 mg/kg of anti-CD25 (clone PC-61.5.3) and anti-CTLA-4 (clone 9H10), or hamster polyclonal isotype control. Tumors and spleens were collected on day 21 for further analysis.

Result: Treg depletion led to significant regression of EPO^{OE} tumors, demonstrating that Treg cells contribute to EPO-mediated immune suppression.

2. $CD8^+$ T Cells as the Ultimate Antitumor Effectors

To determine whether the tumor control achieved by disrupting EPO signaling depends on T cells, the researchers selectively depleted $CD4^+$ and $CD8^+$ T cells.

Method: In *LysM-Cre* myeloid-specific EPOR-knockout mice bearing "cold" tumors generated by hydrodynamic tail vein injection (HDTV), mice were injected intraperitoneally with 4 mg/kg anti-CD8 (YTS169.4), anti-CD4 (GK1.5), or isotype control (LTF-2) twice for the first week and then weekly for a total of six doses. Overall survival was measured.

Result: Depletion of $CD8^+$ T cells abrogated the tumor regression observed after EPOR deletion and drastically shortened the survival, indicating that antitumor immunity unleashed by blocking the EPO/EPOR axis depends on CD8+ T cells.

3. EPO/EPOR Blockade Synergizes with PD-1 Inhibition

The study also examined whether interrupting EPO signaling could sensitize otherwise unresponsive tumors to immune checkpoint blockade.

Method: Following HDTV, mice received intraperitoneal injection of 10 mg/kg of anti-PD-1 (RMP1-14) or isotype control (2A3) every three days for a total of five doses. Tumor growth was assessed by bioluminescence imaging, and survival was recorded.

Result: While anti-PD-1 monotherapy was ineffective in "cold" tumors, combining EPOR ablation with PD-1 blockade showed profound synergy and achieved complete

tumor regression in all treated mice, indicating that EPO/EPOR signaling plays a central role in generating a noninflamed TME.

4. Excluding Erythroid-Derived Myeloid Cells as the Mediators

Since EPO also induces erythroid-differentiated myeloid cells (EDMCs) with pro-tumor activity, the authors assessed whether these cells contributed to the immunosuppressive phenotype.

Method: Two weeks after HDTV, mice received intraperitoneal injection of 2 mg/kg of anti-Ter-119 (TER-119) or isotype control every three days for a total of nine doses, alone or in combination with anti-PD-1.

Result: EDMC depletion did not improve survival or enhance PD-1 responsiveness, indicating that EPO-mediated immune suppression arises from macrophage reprogramming rather than erythroid progenitors.

Perspective

This *Science* study identified EPO/EPOR signaling as a previously unrecognized immunoregulatory axis that bridges macrophages, Tregs, and effector T cells. The findings suggest that targeting this axis may have application for the treatment of solid tumors by transforming “cold” tumors into “hot” tumors.

Mechanistic precision, enabled by antibody-based in vivo approaches, remains central to unraveling such complex cellular networks. Bio X Cell continues to support researchers worldwide with well-characterized functional antibodies, building the experimental foundations linking basic immunology to translational insight.

References

1. Press release. The Nobel Prize in Physiology or Medicine 2025.
2. Chiu, DK, *et al* (2025) Tumor-derived erythropoietin acts as immunosuppressive switch in cancer immunity. **Science.** 388(6745):eadr3026. doi: 10.1126/science.adr3026