Immune Evasion

Major finding: CD8$^+$ T cells are required for induction of IDO and PD-L1 and recruitment of Treg cells to tumors.

Mechanism: IDO and PD-L1 are induced by IFNγ secretion, whereas CCL22–CCR4 signaling recruits Treg cells.

Impact: Inhibition of these immune checkpoints may be effective only in tumors with T-cell inflammation.

IMMUNOSUPPRESSIVE PATHWAYS ARE ACTIVATED BY THE IMMUNE SYSTEM

Immunosuppressive pathways, including inhibition of antitumor CD8$^+$ T cells by FOXP3$^+$ regulatory T (Treg) cells, induction of the metabolic enzyme indoleamine-2,3-dioxygenase (IDO), and interaction of the negative regulatory receptor programmed cell death 1 (PD-1) with its ligand PD-L1, have been shown to promote tumor immune escape. Although it has been suggested that cancer cells may stimulate these inhibitory immune checkpoints, the mechanisms that regulate activation of these pathways remain unclear. Recent studies have shown that although a subset of melanoma metastases exhibit an antigen-specific CD8$^+$ T-cell inflammatory response, these tumors are not eliminated, suggesting that immunosuppressive signaling is activated in these tumors. Consistent with this idea, Spranger and colleagues found that metastatic melanomas with a T-cell inflamed microenvironment exhibited elevated expression of IDO, PD-L1, and FOXP3 and increased numbers of Treg cells compared with tumors lacking infiltrating CD8$^+$ T cells. Induction of IDO and PD-L1 was dependent on the presence of CD8$^+$ T cells and secretion of the proinflammatory cytokine IFNγ by these cells *in vivo*. Accumulation of Treg cells in the tumor microenvironment was also mediated by CD8$^+$ T cells, which modestly increased Treg-cell proliferation in the tumor site. In addition, CD8$^+$ T cells enhanced Treg-cell recruitment via secretion of chemokine (C-C motif) ligand 22 (CCL22) and signaling through the chemokine receptor CCR4 on Treg cells. Importantly, human CD8$^+$ T cells also promoted the recruitment of human Treg cells via CCL22–CCR4 chemokine signaling in a melanoma xenograft model. These results indicate that these immunosuppressive pathways are intrinsically activated by the intratumoral immune response via negative feedback signaling, rather than by cancer cells. Furthermore, these findings suggest that cancer immunotherapies targeting Treg cells, IDO, and PD-L1 may be most effective in patients whose tumors exhibit a T-cell inflammatory response. ■

Spranger S, Spaapen RM, Zha Y, Williams J, Meng Y, Ha TT, et al. Up-regulation of PD-L1, IDO, and T_{regs} in the melanoma tumor microenvironment is driven by CD8$^+$ T cells. Sci Transl Med 2013;5:200ra116.

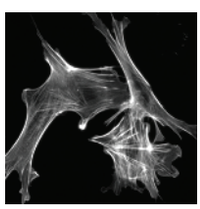
Cell Biology

Major finding: Mechanical regulation of YAP and TAZ stimulates local cell proliferation within epithelial monolayers.

Mechanism: F-actin capping and severing proteins inhibit YAP and TAZ at sites of low mechanical stress.

Impact: A mechanical stress checkpoint can spatially restrict cell proliferation within tissues.

MECHANICAL STRESS DICTATES MULTICELLULAR PROLIFERATIVE CAPACITY



Spatial restriction of proliferation is required for tissue homeostasis, but little is known about how the microenvironment locally regulates proliferation. Each tissue is structurally maintained by a distinct pattern of mechanical forces that follow the tissue architecture and are elevated at points of tissue curvatures, borders, or extracellular matrix (ECM) anchoring sites. Aragona and colleagues report that mechanical stress–induced activation of the transcription factors YAP and TAZ, which sense cytoskeletal tension and transduce mechanical signals to the nucleus, underlies spatial regulation of proliferation in multicellular contexts. High epithelial cell density leads to formation of a monolayer, which inhibits YAP/TAZ nuclear localization and suppresses growth through contact inhibition of proliferation (CIP). Such densely packed cells also are smaller and experience less mechanical stress. The authors showed that decreasing mechanical stress on individual cells by plating them on small ECM islands or soft substrates similarly led to YAP/TAZ nuclear exclusion and inhibited proliferation, suggesting that reduced mechanical stress is the main determinant of CIP. Conversely, applying mechanical stress to growth-arrested, densely packed epithelial monolayers by stretching or increasing the stiffness of the surrounding ECM promoted YAP/TAZ nuclear localization and cell proliferation. The authors found that spatial variations in tensional forces within a multicellular layer translated into differentials in YAP/TAZ activity and, in turn, in localized sources of cell proliferation. Mechanical regulation of YAP and TAZ required F-actin capping and severing proteins to inhibit YAP/TAZ under conditions of low mechanical stress and was independent of and dominant over Hippo pathway signaling. However, loss of YAP/TAZ regulation by Hippo kinases cooperated with mechanical activation to promote proliferation and invasiveness of cells within epithelial sheets. The identification of a YAP/TAZ-dependent mechanical checkpoint provides insight into how local growth patterns can be controlled by the microenvironment and how loss of mechanical regulation might contribute to tumor growth. ■

Aragona M, Panciera T, Manfrin A, Giulitti S, Michielin F, Elvassore N, et al. A mechanical checkpoint controls multicellular growth through YAP/TAZ regulation by actin-processing factors. Cell 2013;154:1047–59.

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