RB1 REGULATES MYELOID-DERIVED SUPPRESSOR CELL DIFFERENTIATION

Aberrant myelopoiesis promotes the expansion of myeloid-derived suppressor cells (MDSC) that lack markers of mature macrophages and dendritic cells (DC) and stimulate tumor growth by inhibiting antitumor immune responses. MDSCs consist of 2 subgroups, monocytic MDSCs (M-MDSC) and polymorphonuclear MDSCs (PMN-MDSC), which differ in their morphology and expression profiles. These cells have been proposed to develop from monocyte and granulocyte progenitors, respectively, but the mechanisms underlying MDSC differentiation in tumors are unclear. Youn and colleagues detected an accumulation of PMN-MDSCs but not M-MDSCs in murine tumor models and in patients with various types of cancer. This expansion did not occur via increased proliferation of PMN-MDSCs or neutrophil precursors but required the differentiation of M-MDSCs from tumor-bearing mice into PMN-MDSCs. Unlike monocytes, most M-MDSCs did not generate macrophages or DCs but instead acquired morphologic and functional properties of PMN-MDSCs, including cell surface expression of lymphocyte antigen 6 complex, locus G (Ly6G), production of reactive oxygen species, and immunosuppressive activity. Intriguingly, retinoblastoma 1 (Rb1) expression was decreased in PMN-MDSCs of tumor-bearing mice and in a subset of weakly proliferative M-MDSCs capable of generating Ly6G-positive cells, as well as in PMN-MDSCs from patients with cancer, suggesting that RB1 may modulate myeloid differentiation. Indeed, deletion of Rb1 in mice stimulated the differentiation of monocytes into PMN-MDSCs, whereas Rb1 overexpression in murine M-MDSCs diminished PMN-MDSC accumulation in favor of increased macrophage and DC differentiation. This reduction in Rb1 expression was mediated by histone deacetylase-2 (HDAC2)–driven epigenetic silencing of the Rb1 promoter, and treatment with HDAC inhibitors triggered differentiation of M-MDSCs into macrophages and DCs. These results implicate RB1 as a critical regulator of myeloid differentiation and suggest that targeted blockade of HDAC 2 may redirect this process to limit the expansion of tumor-promoting MDSCs.


Gastrointestinal Cancer

Major finding: GP130-driven mTORC1 activation promotes inflammation-associated gastrointestinal tumorigenesis.

Mechanism: PI3K/JAK-induced mTORC1 stimulates proliferation and tumor vascularization independent of STAT3.

Impact: Targeted inhibition of mTORC1 reduces the growth of cytokine-dependent tumors in mice.

mTORC1 SIGNALING DRIVES INFLAMMATION-ASSOCIATED TUMOR GROWTH

Chronic inflammation enhances the growth and progression of gastrointestinal tumors in large part through activation of the STAT3 transcription factor, which is driven by signaling of the cytokines interleukin (IL)-6 and IL-11 through their receptor, IL-6 signal transducer (IL-6ST, also known as GP130), which stimulates Janus-activated kinases (JAK). Activation of mTORC1 (mTORC1), a critical regulator of cell growth, has also been linked to protumorigenic inflammatory cytokine expression, but its role in gastrointestinal tumor progression is unclear. Thiem and colleagues found frequent coactivation of mTORC1 and STAT3 within tumor epithelial cells and adjacent stroma in both human intestinal-type gastric cancer (IGC) samples and a mouse model of gastric cancer driven by an activating mutation in the Rb1 promoter, which recapitulates human IGC. mTORC1 activation was induced by IL-11 ligand stimulation of GP130 and subsequent JAK-dependent activation of phosphoinositide 3-kinase (PI3K)/AKT signaling but occurred independently of GP130 tyrosine phosphorylation and STAT3 activity. Strikingly, treatment of gp130mutant mice with RAD001 (everolimus), a clinically approved mTORC1-specific inhibitor, significantly reduced tumor burden; continuous prophylactic RAD001 administration was also sufficient to suppress tumor formation. In addition, RAD001 similarly diminished tumor growth in a mouse model of colitis-associated colon cancer, suggesting that GP130-stimulated mTORC1 activity is broadly required for the initiation and progression of inflammation-associated gastrointestinal tumors in mice. This antitumor effect was not associated with suppression of inflammation or impaired STAT3 activation but rather was mediated by decreased cyclin expression, reduced cancer cell proliferation, and ineffective tumor vascularization. These findings implicate mTORC1 signaling as a driver of inflammation-associated tumor growth and suggest that PI3K/mTORC1 inhibitors may provide therapeutic benefit to patients with these types of tumors.

mTORC1 Signaling Drives Inflammation-Associated Tumor Growth


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