SUPPRESSION OF DENDRITIC CELLS BY IL10 LIMITS CHEMOTHERAPY RESPONSES

Reducing macrophage infiltration through blockade of colony-stimulating factor 1 (CSF1) suppresses tumor growth when combined with chemotherapy in mouse models of mammary carcinoma via activation of CD8\(^+\) T cells. However, the mechanisms by which macrophages impair antitumor immune responses to chemotherapy are poorly understood. Ruffell and colleagues found that treatment of mice bearing mammary tumors with \(\alpha\)-CSF1 antibody and paclitaxel reduced the expression of myeloid-associated genes in the tumor microenvironment, in particular the immunosuppressive cytokine IL10, which was primarily expressed by macrophages. In addition, IL10 expression in human breast cancers was correlated with genes associated with immunosuppressive \(\gamma\delta\)2-type macrophage subsets. Accordingly, IL10 receptor (IL10R) blockade enhanced the tumor response to paclitaxel in a CD8\(^+\) T-cell–dependent manner, similar to the antitumor effects of \(\alpha\)-CSF1 antibody. However, in contrast to \(\alpha\)-CSF1 treatment, IL10R blockade did not inhibit macrophage recruitment to tumors or the ability of macrophages to suppress CD8\(^+\) T-cell proliferation, suggesting that IL10 indirectly inhibits CD8\(^+\) T-cell activity.

Consistent with this idea, assessment of IL10R levels on tumor-infiltrating leukocytes revealed elevated expression on dendritic cells (DC) including CD103\(^+\) DCs, which exhibited increased recruitment into tumors in response to combined therapy with \(\alpha\)-IL10R or \(\alpha\)-CSF1 and paclitaxel. Mechanistically, administration of \(\alpha\)-IL10R or \(\alpha\)-CSF1 with paclitaxel resulted in the upregulation of IL12, a potent T-cell activator, in tumor-infiltrating CD103\(^+\) DCs, suggesting that IL10 regulates the DC phenotype and their expression of IL12. Indeed, macrophage-derived IL10 repressed IL12 mRNA expression in DCs, whereas IL12 blockade eliminated the improved response to chemotherapy associated with \(\alpha\)-CSF1 or \(\alpha\)-IL10R treatment.

These findings elucidate the role of macrophage-produced IL10 in limiting cytotoxic T-cell responses and indicate that IL10 inhibition may enhance the efficacy of chemotherapy by increasing the maturation and functionality of IL12-expressing DCs in human breast cancer.


RAB1A PROMOTES ONCOGENESIS IN COLORECTAL CANCER VIA mTORC1 ACTIVATION

The mTOR complex 1 (mTORC1) controls cell growth in eukaryotes in response to nutrient signals such as amino acids and is commonly hyperactivated in cancer. Although upstream regulators of mTORC1, such as the PI3K and MEK pathways, are commonly mutated in cancer, these mutations do not correlate with response to mTOR-targeted therapy. Thomas, Zhang, and colleagues identified the small GTPase RAB1A, a regulator of ER-to-Golgi vesicular trafficking, as a mediator of mTORC1 signaling in response to amino acid stimulation. Loss of RAB1A in yeast and human cells decreased mTORC1 activity and conferred rapamycin sensitivity in a GTP- and amino acid–dependent manner, indicating that this regulatory mechanism is evolutionarily conserved. Amino acid stimulation promoted the interaction of RAB1A–GTP with mTORC1, and disruption of either RAB1A GTP binding or RAB1A localization to the ER/Golgi attenuated this interaction. Loss of RAB1A inhibited formation of the Ras homolog enriched in brain (RHEB)–mTORC1 complex in the Golgi, but not RAG–mTORC1 interaction in the lysosome, indicating that RAB1A regulates amino acid–induced mTORC1 activity independent of RAG proteins. Intriguingly, RAB1A expression was increased in primary colorectal cancer samples compared with adjacent normal tissues and was correlated with markers of increased mTORC1 signaling, increased tumor invasion and progression, and decreased overall survival, suggesting that RAB1A promotes oncogenic growth in colorectal cancer via activation of mTORC1. Indeed, RAB1A knockdown in colorectal cancer cells with high RAB1A expression suppressed mTORC1 signaling and inhibited colony formation and the growth of xenograft tumors. In addition, ectopic RAB1A expression was sufficient to induce oncogenic transformation and to enhance the malignant growth of established tumors. Furthermore, RAB1A overexpression in colorectal cancer cells conferred increased sensitivity to rapamycin. These data identify RAB1A as a common mechanism of activation of amino acid–mTORC1 signaling in cancer and suggest that RAB1A may represent a determinant of rapamycin sensitivity.

RAB1A Promotes Oncogenesis in Colorectal Cancer via mTORC1 Activation

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