Targeted Therapy

Major finding: The Bruton tyrosine kinase inhibitor ibrutinib targets interleukin-2 inducible kinase (ITK) in T cells.

Concept: Irreversible inhibition of ITK by ibrutinib prevents Th2 cell activation and promotes Th1 cell expansion.

Impact: Ibrutinib may be useful in cancers that are driven by ITK or supported by Th2-based immune responses.

IBRUTINIB ALSO INHIBITS ITK

Ibrutinib is a small-molecule inhibitor of Bruton tyrosine kinase (BTK) that has shown significant clinical activity in B-cell malignancies. BTK shares significant homology with interleukin-2 inducible kinase (ITK), which acts downstream of the T-cell receptor (TCR). ITK is active in T-cell malignancies and has been linked to tumor immune invasion and survival through its critical role in T helper type 2 (Th2) cell differentiation, making it an attractive therapeutic target. Given the structural homology between BTK and ITK and *in silico* docking studies suggesting similarities in active site occupancy and covalent binding by ibrutinib, Dubovsky and colleagues hypothesized that ITK might also be an ibrutinib target. Indeed, ibrutinib irreversibly bound ITK both *in vitro* and in the peripheral blood mononuclear cells of ibrutinib-treated patients. Ibrutinib also inhibited ITK kinase activity in a dose-dependent manner and blocked activation of signaling pathways downstream of ITK upon TCR stimulation. To determine the effect of ibrutinib-mediated ITK inhibition on Th2 cells, naïve CD4 T cells were polarized into Th1 and Th2 cells *in vitro* and treated with ibrutinib. Ibrutinib inhibited ITK-dependent signaling and cytokine production in Th2 cells, whereas Th1 cells, which express a kinase that can compensate for loss of ITK, were unaffected. Consistent with these findings, prolonged ibrutinib treatment specifically blocked Th2 cell activation and provided selective pressure for expansion of Th1 cells and Th1 cytokine skewing in patients with chronic lymphocytic leukemia (CLL). Ibrutinib-dependent Th1 skewing also reversed $CD8^+$ T cell–mediated immunosuppression and promoted clearance of *Listeria monocytogenes* infections in leukemic mice, a notable finding given that infections are the primary cause of death in immunosuppressed patients with CLL. The identification of ibrutinib as an inhibitor of ITK in T cells suggests that this drug could be used more broadly as an immunomodulator or in combination with cancer immunotherapies. ■

Dubovsky JA, Beckwith KA, Natarajan G, Woyach JA, Jaglowski S, Zhong Y, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1 selective pressure in T-lymphocytes. Blood 2013 Jul 25 [Epub ahead of print].

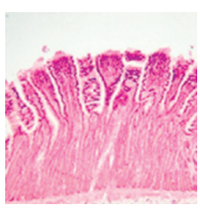
Stem Cells

Major finding: R-spondin 1 and SLIT2 cooperate to induce ISCs and enhance survival after chemoradiotherapy.

Mechanism: SLIT2 and its receptor, ROBO1, are required for intestinal homeostasis and repair after injury.

Impact: Adjuvant R-spondin 1 and SLIT2 treatment may promote tolerance to aggressive chemoradiation.

SLIT2 AND RSPO1 PROTECT AGAINST CHEMORADIATION-INDUCED TISSUE INJURY



Intensive chemoradiation regimens used to treat advanced, metastatic cancers can induce significant and often lethal injury in tissues such as the gastrointestinal tract, emphasizing the importance of identifying strategies to repair tissue injury and increase therapeutic tolerance. Zhou and colleagues found that the receptor roundabout 1 (ROBO1) and its ligand SLIT2, which regulate axon guidance, were highly expressed in transient amplifying cells and $LGR5^+$ (leucine-rich repeat containing G protein-coupled receptor 5-positive) intestinal stem cells (ISC) within crypts of the mouse small intestine compared with differentiated cells in villi. Heterozygous deletion of *Robo1* or inhibition of the SLIT2–ROBO1 interaction resulted in the formation of aberrantly small villi characterized by reduction in the number of $LGR5^+$ ISCs and proliferating intestinal cells and decreased expression of ISC marker genes, and impaired the formation of intestinal organoids, suggesting that SLIT2–ROBO1 signaling is necessary for intestinal homeostasis. In support of this idea, ectopic expression of *Slit2* promoted hypertrophic growth of intestinal villi, accumulation of $LGR5^+$ ISCs, increased expression of ISC markers, and intestinal organoid formation. In addition, SLIT2 cooperated with R-spondin 1 (RSPO1), a secreted protein that activates WNT signaling and has been shown to enhance intestinal repair following chemotherapy- or radiation-mediated tissue damage, to stimulate intestinal organoid growth *in vitro* and decrease chemotherapy-induced intestinal injury *in vivo*. Combined SLIT2 and RSPO1 treatment synergistically protected $LGR5^+$ ISCs from chemotherapy-induced depletion, potentiated intestinal regeneration, and prolonged the survival of mice receiving lethal chemotherapy or irradiation. This protective effect required ROBO1 expression and did not enhance intestinal tumor formation or diminish the sensitivity of tumor cells to chemotherapy. These results suggest that adjuvant RSPO1 and SLIT2 may promote intestinal tissue repair following aggressive chemoradiation by inducing adult stem cells. ■

Zhou WJ, Geng ZH, Spence JR, Geng JG. Induction of intestinal stem cells by R-spondin 1 and Slit2 augments chemoradioprotection. Nature 2013 Jul 31 [Epub ahead of print].

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