**Immunotherapy**

**Major finding:** CBL-B-dependent ubiquitination of TYRO3, AXL, and MER (TAM) receptors inhibits NK cell activation.

**Concept:** CBL-B deficiency or TAM inhibition enables NK cells to restrain metastatic tumor growth.

**Impact:** Downmodulating CBL-B or TAM signaling may be an effective approach to enhance NK cell antitumor activity.

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**TAM RECEPTOR OR CBL-B INHIBITION ENABLES TUMOR REJECTION BY NK CELLS**

Loss of the E3 ubiquitin ligase CBL-B improves tumor surveillance by the immune system, but the underlying mechanisms are not completely understood. Paolini and colleagues investigated the contribution of the innate immune system, particularly natural killer (NK) cells, toward tumor rejection in CBL-B-deficient mice and found that loss of CBL-B in NK cells improved NK cell proliferative and cytotoxic responses toward target cells in vitro, indicating that CBL-B negatively regulates NK cell activity and raising the possibility that CBL-B-deficient NK cells may promote tumor rejection. Indeed, the growth and metastasis of melanoma cells implanted into CBL-B-deficient mice or into mice expressing an E3 ligase-defective CBL-B were suppressed in an NK cell–dependent manner. In addition, transfer of CBL-B-deficient or CBL-B-disabled NK cells into syngeneic hosts reduced metastasis in multiple tumor models. To determine how CBL-B regulates NK cell activity, the authors performed in vitro ubiquitilation reactions on 9,000 proteins and identified the TYRO3, AXL, and MER (TAM) receptor tyrosine kinases as targets of CBL-B. Exposure to the TAM ligand GAS6 impaired activation of wild-type NK cells, whereas loss of CBL-B reduced TAM receptor ubiquitylation, decreased GAS6-induced TAM receptor internalization, and rendered NK cells resistant to GAS6-mediated inactivation. Administration of a small-molecule TAM receptor kinase inhibitor blocked GAS6 inhibition of wild-type NK cell activity in vitro and reduced metastases in several tumor models when administered intraperitoneally or orally. Interestingly, low doses of warfarin, which blocks stimulation of TAM receptors without affecting coagulation, also enhanced NK cell cytotoxicity and reduced metastases in wild-type mice injected with melanoma cells. Together, these data implicate CBL-B and TAM as negative regulators of NK cell activity and suggest that interfering with this pathway may improve NK cell–mediated tumor surveillance.

**Drug Resistance**

**Major finding:** Co-inhibition of EGFR and MEK kills colorectal cancer cells with acquired EGFR antibody resistance.

**Concept:** Heterogeneous mutations drive EGFR antibody resistance and converge on the MEK—ERK pathway.

**Impact:** Adding MEK inhibitors to anti-EGFR therapy may overcome acquired resistance in colorectal cancer.

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**COMBINED INHIBITION OF EGFR AND MEK REVERSES EGFR ANTIBODY RESISTANCE**

EGF receptor (EGFR)-blocking antibodies such as cetuximab and panitumumab have been used to treat a subset of RAS–wild-type colorectal cancers, yet responsiveness is transient, as tumors become resistant and progress within months. Acquired resistance to targeted therapies is difficult to overcome because relapsed tumors are highly heterogeneous. To model acquired resistance in vitro, Misale and colleagues treated a panel of RAS–wild-type colorectal cancer cell lines with cetuximab or panitumumab and found that the resistant populations that emerged harbored polyclonal activating mutations in KRAS, NRAS, or BRAF. Sustained MEK and/or ERK activation occurred in all resistant clones independently of their mutational status, and acquired anti-EGFR therapy resistance mechanisms in colorectal cancer cells converged upon the MEK–ERK pathway. However, the MEK inhibitor pimasertib did not significantly affect the growth of resistant cells, as it induced only a transient suppression of ERK activation and subsequently stimulated EGFR phosphorylation. In contrast, combined treatment with pimasertib plus cetuximab blocked EGFR phosphorylation and caused a sustained inhibition of ERK activation. Concomitant MEK and EGFR blockade also induced a long-term growth suppression of resistant cell lines in vitro and triggered a significant regression of established tumors derived from resistant cell lines in nude mice. Notably, heterogeneous KRAS, NRAS, and BRAF mutations could be detected in the blood of patients with colorectal cancer who had developed resistance to anti-EGFR antibodies, and combined pimasertib–cetuximab treatment markedly impaired tumor growth in a colorectal cancer patient–derived xenograft model. Together, these findings highlight the MEK–ERK pathway as a critical point of convergence for multiple genetic alterations that drive anti-EGFR drug resistance in colorectal cancer and provide a rationale for clinical evaluation of concomitant EGFR and MEK inhibition in patients with refractory colorectal cancer.

**Research Watch**


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