Research Watch

Melanoma

Major finding: A mutation in the CYSLTR2 G-protein–coupled receptor promotes tumorigenesis in uveal melanomas.

Concept: CYSLTR2 mutations constitutively activate Gαq in tumors lacking GNAQ, GNA11, and PLCB4 mutations.

Impact: CYSLTR2 is an uveal melanoma oncogene, and CYSLTR2 mutations may be actionable targets.

UVEAL MELANOMAS HARBOUR RECURRENT ACTIVATING MUTATIONS IN CYSLTR2

Uveal melanomas are eye tumors arising from melanocytes in the uveal tract. These tumors harbor frequent activating mutations in two subunits of Gαq heterotrimeric G proteins (GNAQ and GNA11), and in PLCB4, a downstream effector of Gαq signaling. To identify additional mutations driving uveal melanoma, Moore and colleagues analyzed whole-genome and whole-exome sequencing data from 136 patients with uveal melanoma from multiple cohorts. Using a mutation analysis algorithm to detect hotspot mutations in oncogenes, a previously undescribed mutation in cysteinyl leukotriene receptor 2 (CYSLTR2) was identified only in samples lacking mutations in GNAQ, GNA11, and PLCB4 (4 of 9 samples), suggesting that these mutations activate the same pathway. CYSLTR2 encodes a G-protein–coupled receptor, CysLT1R, involved in leukotriene-mediated signaling in inflammation and fibrosis. The identified mutation results in a Leu129Gln substitution in transmembrane helix 3, which associates with the extracellular ligand, intracellular Gq subunit, and other transmembrane helices. Leu129Gln CysLT1R was coupled to Gαq and was constitutively active, as evidenced by increased calcium mobilization and insensitivity to the CysLT1R agonist leukotriene D4. Leu129Gln CysLT1R had melanocyte lineage–specific effects, as it allowed melan-a melanocytes to grow in the absence of 12-O-tetradecanoylphorbol-13-acetate (TPA), which is usually required for melanosome growth and pigmentation. Moreover, Leu129Gln CysLT1R rescued pigmentation of Melan-a cells withdrawn from TPA, and enhanced expression of melanocyte lineage–specific genes. Subcutaneously engrafted melan-a cells expressing Leu129Gln CysLT1R were able to form tumors more rapidly than wild-type cells, indicating that the mutation enhances melanoma tumorigenesis in vivo. Further, CYSLTR2 knockdown suppressed the growth of Leu129Gln CysLT1R cells, and reduced expression of melanocyte-lineage genes. Taken together, these findings reveal an oncogenic role for CYSLTR2 in uveal melanoma through activation of Gαq signaling, and further suggest that Leu129Gln CysLT1R may be a potential therapeutic target in uveal melanoma.


Targeted Therapy

Major finding: Rigosertib acts as a RAS mimic, binding to the RAS-binding domain of multiple RAS effector proteins.

Concept: Rigosertib inhibits RAS-mediated activation of MEK–ERK and PI3K pathway signaling.

Impact: RAS signaling can be effectively targeted by disruption of RAS binding to downstream effectors.

BLOCKADE OF RAS-BINDING DOMAIN INTERACTIONS INHIBITS RAS SIGNALLING

Aberrant RAS signalling is present in the majority of human tumors and promotes proliferation and survival, but development of RAS inhibitors has been largely unsuccessful due to the lack of well-defined druggable pockets on the surface of RAS. Rigosertib is a non-ATP competitive inhibitor that suppresses the growth of various types of cancer cells and is currently in clinical development, but its mechanism of action is not well understood. In a mass spectrometry–based approach to identify direct targets of Rigosertib, Athuluri-Divakar and colleagues identified three proteins that contain a RAS binding domain (RBD) as the primary Rigosertib-binding partners: ARAF, BRAF, and CRAF. Determination of the BRAF RBD–Rigosertib complex structure with nuclear magnetic resonance (NMR) revealed that rigosertib bound to the same region of the RBD as RAS, suggesting that rigosertib would prevent RAS and RAF from interacting. These findings were supported by RAF mutagenesis studies, which indicated that mutations in the RAF RBD that disrupted RAS binding also disrupted rigosertib binding. As predicted by NMR, rigosertib blocked the association between RAS and the RAF RBD. Rigosertib inhibited RAF heterodimerization and activation, and suppressed phosphorylation of the downstream effectors MEK and ERK, indicating that blocking the RAS–RAF interaction inhibits MEK–ERK pathway signaling. Rigosertib also bound to the RBD of PI3Ks and reduced AKT phosphorylation, suggesting that it also inhibited PI3K/AKT signaling by disrupting the RAS–PI3K interaction. In mouse models of mutant KRAS–driven colorectal, lung, and pancreatic cancers, rigosertib reduced tumor growth and reduced the phosphorylation of MEK, ERK, and AKT, indicating that rigosertib can inhibit RAS-driven MAPK and PI3K signaling in vivo. Taken together, these results suggest that rigosertib suppresses tumors by acting as a RAS mimic, and illustrate that RAS can be effectively targeted by preventing its interaction with downstream effectors.

Uveal Melanomas Harbor Recurrent Activating Mutations in CYSLTR2


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