Oncogenes

Major finding: CRAF has a direct role in mitosis that does not require the RAF effector MEK.

Mechanism: CRAF interacts with PLK1 and promotes its activity and accumulation at kinetochores.

Impact: Allosteric RAF inhibitors that block phospho-Ser338 CRAF may be effective cancer therapies.

CRAF HAS MEK-INDEPENDENT FUNCTIONS IN MITOSIS AND TUMOR PROGRESSION

ATP mimetic-type RAF kinase inhibitors have been shown to induce CRAF Ser338 phosphorylation and promote progression of *RAS*-mutant cancers, but the role of phospho-Ser338 CRAF in tumor progression remains unclear. Mielgo and colleagues observed that phospho-Ser338 CRAF levels strongly increased during M phase and that loss of phospho-Ser338 CRAF led to an accumulation of cells at pro-metaphase and a delay in mitotic progression. Mechanistically, phosphorylation was required for CRAF γ-tubulin binding and centrosome and mitotic spindle localization, suggesting that phospho-Ser338 CRAF directly functions in mitotic cell division. Indeed, phospho-Ser338 CRAF specifically coprecipitated and colocalized with the mitotic regulators polo-like kinase 1 (PLK1) and Aurora kinase A (AURKA) at the centrosomes and spindle poles and was required for PLK1 activity and accumulation at kinetochores. Phospho-Ser338 was readily detected in biopsies of human tumors, and the requirement of phospho-Ser338 CRAF for proper orchestration of the mitotic machinery was relevant to tumor progression, as expression of a phosphomimetic Ser338Asp CRAF mutant led to a significant increase in tumor size compared with the size of tumors expressing wild-type CRAF. Surprisingly, the Ser338Asp tumors exhibited increased phospho-PLK1, but not phospho-MEK, and their accelerated growth was unaffected by a second mutation ablating CRAF kinase activity. Together with the observation that the mitotic defects of phospho-Ser338–deficient cells could be rescued by a kinase-dead CRAF mutant, these results indicate that CRAF plays a critical kinase-independent role in mitosis and tumor progression outside of the canonical RAF–MEK–ERK signaling pathway. Allosteric RAF inhibitors that prevent CRAF Ser338 phosphorylation may represent a useful therapeutic approach for a wide range of malignancies and might show activity in tumors that develop resistance to ATP mimetics.

Mielgo A, Seguin L, Huang M, Camargo MF, Anand S, Franovic A, et al. A MEK-independent role for CRAF in mitosis and tumor progression. Nat Med. 2011 Nov 13. [Epub ahead of print].

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