

The cyclic AMP response element binding protein (CREB) pathway is essential for respiratory epithelial development and is mutated in some patients with lung adenocarcinoma (LA), but its role in the disease is unknown. Our aim is to define the importance of CREB signaling in KRAS-driven LA. Mutant KRAS expression in LA cells was manipulated using shRNA or dedicated vectors. KRAS-mutant LA was induced in conditional Creb1-deleted (Creb1^f) mice via 1 g/Kg intraperitoneal urethane or intercross with conditional KRAS^{G12D}-expressing mice. Creb1 was deleted across the respiratory epithelium or selectively in KRAS^{G12D}-expressing cells via intratracheal adenovirus encoding Cre (Ad-Cre). Conditional Creb1-deleted LA cells were derived from urethane-treated Ad-Cre-naïve Creb1^f mice. Active CREB was overexpressed in LA, a phenomenon that was found to be dependent on mutant KRAS signaling. Creb1^f mice were markedly protected from urethane- and KRAS^{G12D}-triggered LA compared with controls [LA volume/lung, median (95% CI), respectively, urethane model: 1(5-11) and 24(19-45) μ L, $P < 0.001$; KRAS^{G12D} model: 15(9-23) and 33(26-39) μ L, $P < 0.001$]. In vitro Creb1-deletion in LA cells or treatment with CREB-inhibitor ICG-001 inhibited cell proliferation, in vivo tumor growth, and spontaneous pulmonary metastasis from ectopic sites. CREB signaling functioned to upregulate a large conductance calcium-activated channel in LA cells that facilitates cell motility and metastasis. CREB is addicted to mutant KRAS signaling and drives KRAS-mutant LA.

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