

cAMP-response element binding protein (CREB) is an essential survival factor for normal respiratory epithelium, however, its role in lung cancer development has not been investigated. Our aim was to define the impact of CREB on *KRAS*-driven lung adenocarcinoma. Wild-type (W), conditional mutant *KRAS*-expressing (*LSL.KRAS^{G12D}*; K), and *Creb1*-deleted (*Creb1^{ff}*; C) mice were intercrossed in all possible combinations, followed by intraperitoneal urethane or single intratracheal adenovirus (Ad)-Cre delivery. Conditional *Creb1*-deleted lung cancer cell lines (CCLC) were derived from the lungs of urethane- but not Ad-Cre-treated C mice. (Ad)-Cre-treated C mice were markedly protected from urethane-triggered lung tumorigenesis compared with W controls [lung tumor mass, median(95%CI), respectively: 1(5-11) and 24(19-45) μ L; $P < 0.001$] and (Ad)-Cre-treated KC mice developed significantly smaller lung tumors compared with K controls [lung tumor fraction, median(95%CI), respectively: 15(9-23) and 33(26-39) % of lung volume; $P < 0.001$]. *In vitro* Cre-mediated *Creb1* deletion or treatment of CCLC with CREB-inhibitor ICG-001 diminished cellular proliferation, *in vivo* tumor growth, and spontaneous lung metastasis. *KRAS* silencing in CCLC lead to decreased CREB activation, whereas microarray analysis of *Creb-1* deleted CCLC revealed marked reductions in C-X-C chemokine expression. CREB signaling is essential for *KRAS*-driven lung adenocarcinoma by augmenting tumor-associated inflammation.

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