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Can tumor cells proliferate without ERK5?

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The extracellular-regulated protein kinase (ERK) 1/2 signaling pathway has been at the forefront of cancer research aimed at developing effective molecular targeted therapies. This is supported by a large body of work over the last 30 y which have rigorously established the requirement of ERK1/2 in supporting the proliferation of tumor cells harbouring clinically relevant oncogenic drivers of the RAS-RAF pathway. Nevertheless, the therapeutic success of BRAF (vemurafenib) and MEK1/2 (trametinib or selumetinib) inhibitors has been greatly limited by the emergence of tumor resistance. These disappointing results have highlighted the importance of finding novel combinatorial therapies.

One potentially important strategy which is gaining translational momentum for cancer treatment is the use of anti-ERK5 therapy. ERK5, also known as Big MAP Kinase 1 (BMK1), displays several distinct structural and functional properties that set it apart from ERK1/2 and the other members of the MAPK family.[1] In particular, its unique extended C-terminal tail comprises a bipartite nuclear localization sequence important for targeting ERK5 to the nucleus and a transcriptional activation domain that enables ERK5 to directly regulate gene expression. These features clearly indicate distinct mechanisms implicated in upstream regulation of ERK5 and downstream regulation of targets.

The specific role of ERK5 in signal transduction is further supported by genetic evidence that the pathway exerts non-redundant function *in vivo*. Notably, consistent with the requirement of ERK5 for the maintenance of vascular integrity during development, genetic inactivation of ERK5 suppressed tumor growth through reduced neovascularisation of melanoma and carcinoma xenografts.[2] Accordingly, pharmacological inhibition of ERK5 impaired tumor development, not only by preventing tumor angiogenesis, but also by blocking tumor cell proliferation.[3] These observations are clinically highly relevant considering that aberrant ERK5 signaling in human epithelial tumors correlates with shorter disease-free intervals and increased risk of metastasis.[4]

Nevertheless, the development of anti-ERK5 based therapies has lagged behind that of anti-ERK1/2, mostly because of our lack of molecular understanding of the MEK5-ERK5 pathway in oncogenic signaling. In particular, the requirement of RAS for mediating ERK5 activation downstream of growth factor stimulation remains controversial. Moreover, the ability of a constitutive active mutant of MEK5 to synergise with CRAF-induced cellular transformation has never been validated.[5] To investigate the protumourigenic function of ERK5, Lochhead et al. performed careful pharmacokinetics analyses of BIX02189, a specific MEK5 inhibitor, in a panel of colorectal carcinoma (CRC) cell lines harbouring $KRAS^{G12C/G13D}$ or $BRAF^{V600E}$ mutations and which display some resistance to selumetinib.[6] After finding no evidence that the KRAS-BRAF pathway directly activated ERK5, the authors showed that at a concentration where ERK5 activity was almost completely inhibited, BIX02189 had no effect on cancer cell proliferation, in presence or in absence of selumetinib. Likewise, cancer cells displaying elevated ERK5 expression due to *MAPK7* (*ERK5* gene) amplification, were insensitive to MEK5 inhibition or ERK5 downregulation by siRNA. Altogether, these results convincingly showed that, unlike ERK1/2, ERK5 was dispensable for the proliferation of cancer cells displaying KRAS or BRAF mutations, or *MAPK7* amplification.

Clearly, this work adds to the understanding of pro-oncogenic signaling mechanisms. Future direction may be to analyze primary CRCs from human biopsies at different stages of tumor progression and in response to anti-BRAF and anti-MEK1/2 therapies, in order to confirm that the MEK5-ERK5 pathway does not contribute to tumor cell proliferation downstream of oncogenic RAS and BRAF mutations. Similar detailed pharmacokinetics analyses in tumors where inhibition of ERK5 was shown to have a strong anti-proliferative effect should also be performed.[3,4] Ultimately, it will be critical to underpin the oncogenic potential of the ERK5 pathway in various types of cancers to firmly establish the clinical application of ERK5 inhibitors predicted from the analyses of genetically modified mouse models and human tumor biopsies. The study from Lochhead et al.[6] suggests focusing these investigations beyond tumor cell-autonomous proliferation. Accordingly, more attention may have to be paid in the putative role of ERK5 in reciprocal interactions between cells in the tumor

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to devise blood supply and a supportive immune environment.[2,7]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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