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A Braf kinase-inactive mutant induces lung adenocarcinoma

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The initiating oncogenic event in almost half of human lung adenocarcinomas is still unknown, complicating the development of selective targeted therapies. Yet these tumours harbour a number of alterations without obvious oncogenic function, including BRAF-inactivating mutations. Researchers at the Spanish National Cancer Research Centre (CNIO) have demonstrated that the expression of an endogenous Braf (D631A) kinase-inactive isoform in mice, corresponding to the human BRAF(D594A) mutation, triggers lung adenocarcinoma in vivo, indicating that BRAF-inactivating mutations are initiating events in lung oncogenesis.

The paper, published in *Nature*, indicates that the signal intensity of the MAPK pathway is a critical determinant not only in tumour development, but also in dictating the nature of the cancer-initiating cell and ultimately the resulting tumour phenotype.

The RAS-MAPK signalling cascade serves as a central node in transducing signals from membrane receptors to the nucleus. This pathway is aberrantly activated in a substantial fraction of human cancers. There is also abundant evidence that elevated RAS-MAPK signaling results in cellular toxicity that may serve as a natural barrier to cancer progression early in tumorigenesis. These findings suggest that defined thresholds of RAS-MAPK activity are required for homeostasis as well as for malignant transformation, but compelling genetic evidence is missing.

Mutational analysis of different human cancers has recently uncovered that among the BRAF hot spots in lung adenocarcinoma, which comprise a component of the RAS-MAP kinase pathway, those resulting in inactivating mutations predominate over the V600E activating substitution, the main oncogenic form in other tumours such as melanoma. However, the contribution of BRAF-inactive mutants to lung cancer progression is unclear.

Using public databases, researchers have identified inactivating BRAF mutations in a subset of KRAS-driven human lung tumours. Subsequently, using mouse models, researchers have replicated these observations showing that the co-expression of oncogenic Kras and inactive Braf markedly enhances the onset of lung adenocarcinoma. Also, this combination accelerates tumour progression when the inactivating Braf mutation is genetically induced in advanced tumors. Surprisingly, in this same study, the researchers showed that individually, the inactivating mutations of Braf are also oncogenic events that induce the appearance of lung adenocarcinoma.

The paper provides the first genetic evidence demonstrating that a kinase-inactivating Braf mutation induces lung adenocarcinoma development. Moreover, results suggest that lung adenocarcinoma patients with hypoactive BRAF could benefit from therapies based on selective CRAF inhibitors.

More information: Patricia Nieto et al, A Braf kinase-inactive mutant induces lung adenocarcinoma, *Nature* (2017). DOI: 10.1038/nature23297

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