Scientists discover novel oncogenic driver gene in human lung cancer

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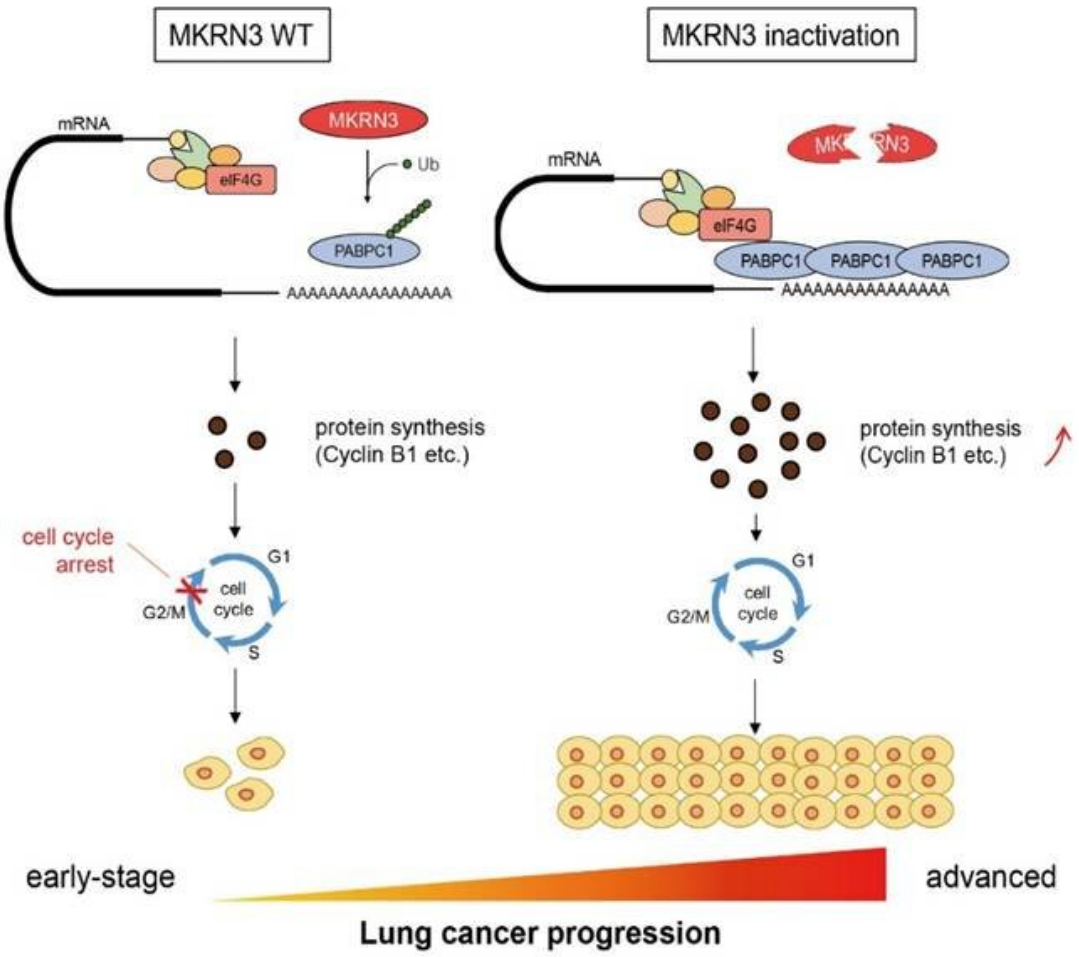

A model depicting how the MKRN3-PABPC1 axis controls cell proliferation and progression in lung cancer. Credit: WANG Yuexiang's group

A research team led by Prof. Wang Yuexiang from the Shanghai Institute of Nutrition and Health (SINH) of the Chinese Academy of Sciences discovered a novel oncogenic driver gene in human lung cancer, the leading cause of cancer-related mortality worldwide.

Their findings were published in *Journal of Experimental Medicine* on June 18.

Approximately 85% of all lung cancer cases are non-small cell lung cancers (NSCLCs). Although tyrosine kinase inhibitors and immunotherapy have contributed to survival benefits in some patients, the overall survival rates for NSCLCs remain low.

Patients with NSCLC that are driven by KRAS mutations are often unresponsive to tyrosine kinase inhibitors and have a poor prognosis. Although inhibitors for the $KRAS^{G12C}$ mutant have been approved to treat NSCLC patients, a general strategy that targets all KRAS mutants remains elusive.

Central precocious puberty (CPP) is largely caused by germline mutations in the MKRN3 gene. Interestingly, CPP has been epidemiologically linked to various diseases in adulthood, including cancers. Cohorts of individuals with CPP show an increased risk of malignancies such as lung cancers.

To investigate whether central precocious puberty-associated MKRN3 gene is mutated in human cancers, the research team led by Prof. Wang Yuexiang queried The Cancer Genome Atlas (TCGA) Pan-Cancer genomic data sets. Strikingly, MKRN3 is frequently mutated in NSCLCs. MKRN3 aberrations are significantly enriched in human NSCLC samples harboring oncogenic KRAS mutations.

The researchers further presented genetic, functional, mouse models and

mechanistic data that identify the central precocious puberty-associated gene MKRN3 gene as a bona fide tumor suppressor in NSCLC. They uncovered its tumor suppressing mechanism and highlighted MKRN3-PABPC1 axis deregulation as a key pathway in lung cancer oncogenesis.

MKRN3 inactivation led to lung cancer proliferation and progression through PABPC1 ubiquitination mediated global protein synthesis. MKRN3 restoration in MKRN3-inactivated NSCLC suppressed tumor growth in nude mice. Therefore, molecular interventions targeting MKRN3 deficiency may have therapeutic potential for KRAS-mutant NSCLC treatment.

These findings showed that biological mechanisms of central precocious puberty are relevant in tumorigenesis, which may help in developing anticancer drugs.

More information: Ke Li et al, E3 ligase MKRN3 is a tumor suppressor regulating PABPC1 ubiquitination in non–small cell lung cancer, *Journal of Experimental Medicine* (2021). DOI: 10.1084/jem.20210151

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