ALK phosphorylates SMAD4 on tyrosine to disable TGF-β tumor suppressor functions

A multi-laboratory research team led by Prof. Feng XinHua (冯新华) in the Life Sciences Institute, Zhejiang University has recently reported a novel mechanism underlying TGF-β resistance in ALK-positive tumors (*Nature Cell Biology*, 2019, 21: 179—189). The study was conducted with support from the National Natural Science Foundation of China and other supports.

TGF-β signaling plays critical roles in tumorigenesis by regulating cell proliferation, apoptosis, angiogenesis, immune surveillance and metastasis. Loss of TGF-β tumor suppressive response is a hallmark of human cancers. Tumor cells have developed a number of strategies to escape from negative growth control of TGF-β signaling. One major mechanism to resist the cytostatic effect of TGF-β is through inactivating mutations/deletions in the TGF-β signaling pathway, which frequently occur in gastrointestinal and pancreatic cancer. As a central player in TGF-β signal transduction, SMAD4/DPC4 is frequently mutated or deleted in these cancers. However, such genetic alterations are rare in most cancer types and the underlying mechanisms for TGF-β resistance remain largely unclear.

In the current study, Feng and colleagues have elucidated a molecular mechanism for TGF-β resistance in ALK-positive tumors. Abnormal activation of ALK occurs in numerous cancers, including lymphoma, lung cancer, neuroblastoma, glioblastoma multiform and inflammatory breast cancer. Feng and colleagues demonstrate that in ALK-positive tumors, SMAD4 is highly phosphorylated at Tyr95. Phosphorylated SMAD4 is unable to bind to DNA and fails to elicit TGF-β gene responses and tumor suppressing responses. Chemical or genetic interference of the oncogenic ALK restores TGF-β responses in ALK-positive tumor cells.

These findings reveal, for the first time, that SMAD4 is tyrosine-phosphorylated by an oncogenic tyrosine kinase during tumorigenesis. This suggests a novel mechanism by which SMAD4 is inactivated through oncoproteins in cancers and provides guidance to logical therapeutic designs in cancer prevention, diagnostics and treatment.

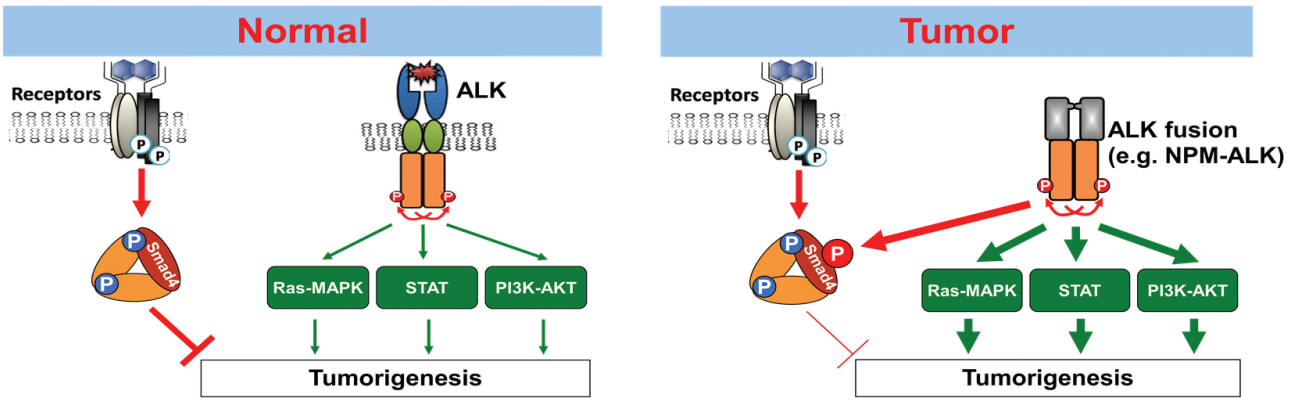

Figure A working model for the role of tyrosine phosphorylation of SMAD4 on TGF-β tumor suppressive signaling. In normal tissues, SMAD proteins transduce TGF-β tumor suppressing signals. In ALK-positive tumors, SMAD4 is phosphorylated on tyrosine-95 in the DNA-binding domian. Phosphorylated SMAD4 fails to bind to chromatin and to elicit genomic responses necessary for tumor suppression.