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The activation of RAF/MEK/ERK kinase cascade by variable β3-αC loop deletions triggers oncogenesis

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RAF/MEK/ERK kinase cascade has well-defined role in cancer development. Aberrant activation of this kinase by genetic alterations exists in >40% human cancers, which functions as a driver to trigger cancer pathogenesis. In current study, we identified a new catalogue of mutations in RAF and MEK with variable deletions of β3-αC loop. These mutants are constitutively active and highly oncogenic *in vitro* and *in vivo*. To develop strategies for targeting these mutants-driven cancers, we tested whether they were sensitive to RAF/MEK inhibitors that used for clinic treatment of BRAF (V600E)-harboring cancers or undergoing clinic trials, and found that all of them exhibit a strong drug resistance at cellular level and in tumor-xenograft mouse model. To explore molecular mechanism that underlies this phenomenia, we next carried out a serial of biochemistry and structral analysis and demonstrated that β3-αC loop deletions stimulate the homo-oligomerization of both RAF and MEK, which not only triggers their kinase activity but also dramatically decreases their drug affinity. Together, our study provides a solid evidence that RAF and MEK mutants with β3-αC loop deletions function as a cancer driver and a clear molecular basis that β3-αC loop deletions activate RAF and MEK and lead to strong inhbitor resistance, and appeals a development of new inhibitors.

Biography

Hu Jiancheng received his PhD from University of Colorado Denver in 2007 and then Post-doctoral training at Washington University in St. Louis and Howard Hughes Medical Institute. Since 2014, he has joined National Cancer Centre Singapore where he has served as the Principal Investigator at the Laboratory of Cancer Signaling. He has published more than 15 papers in international renowned journals. His research interests include: (1) the regulatory mechanism of RAF kinase and other oncogenic protein kinases under normal/pathological conditions; (2) molecular basis that underlie intrinsic and acquired resistance of kinase inhibitors in clinic treatment of cancers; (3) the development of novel kinase inhibitors.

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