

KRAS mutation subtypes and their association with other driver mutations in oncogenic pathways

Koushik Mondal ^{1,2,*}, Mahesh Kumar Posa ³, Revathi P. Shenoy ⁴ and Susanta Roychoudhury ^{1,5,*}

¹ Division of Basic & Translational Research, Saroj Gupta Cancer Centre & Research Institute, MG Road, Kolkata-700063, West Bengal, India; mkoushik9@gmail.com

² Department of Cancer Immunology, SwasthyaNiketan Integrated Healthcare & Research Foundation, Koramangala, Bengaluru-560034, Karnataka, India; mkoushik9@gmail.com

³ School of Pharmaceutical Sciences, Jaipur National University, Jagatpura, Jaipur, Rajasthan-302017, India; posa.mahesh@gmail.com

⁴ Department of Biochemistry, Kasturba Medical College, Manipal Academy of Higher Education, Manipal-576104, Karnataka, India; revathi.shenoy@manipal.edu

⁵ CSIR-Indian Institute of Chemical Biology, 4 Raja S.C.Mullick Road, Jadavpur, Kolkata-700032, West Bengal, India; susantarc@gmail.com

* Correspondence: KM (mkoushik9@gmail.com); SR (susantarc@gmail.com)

Supplementary Figures:
Supplementary Figure S1:

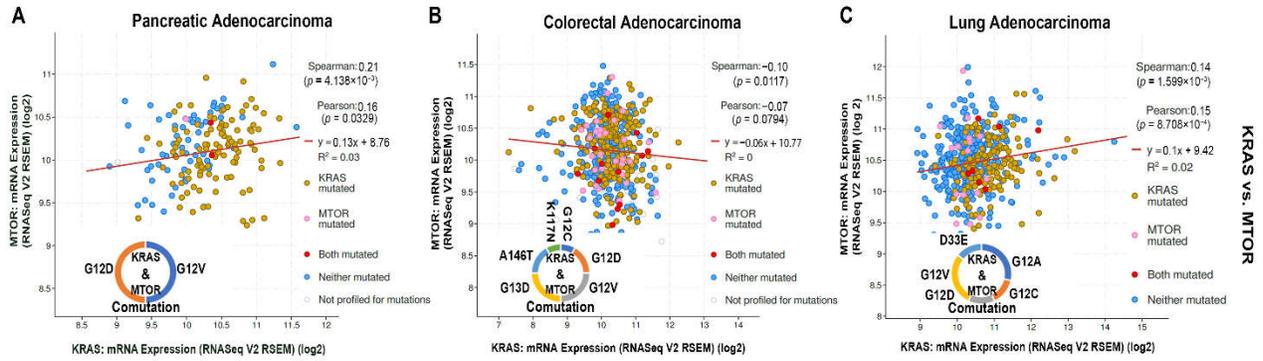


Figure S1: Mutant variants of KRAS with the coexisting mutations of MTOR in Pancreatic adenocarcinoma (PAAD), Colorectal adenocarcinoma (CRAD), and Lung adenocarcinoma (LUAD). In the Dot plots (A-C), mutated KRAS is represented as orange, mutated MTOR as pink, coexisting mutation of KRAS and MTOR as red, no mutation as blue, and not profiled for modification as white. The doughnut diagram (A-C) in each plot represents the KRAS mutation associated with the MTOR co-mutation. According to cBioPortal, G12D and G12V are the most prevalent mutations associated with MTOR co-mutation in PAAD (A). In the case of CRAD, G12C, G12D, G12V, G13D, A146T, and K117N KRAS mutations are associated with MTOR co-mutation. The prevalent KRAS mutations are G12V and G13D KRAS mutations (B). In contrast, G12A and G12V KRAS mutations are mainly associated with MTOR co-mutation in LUAD (C). Dot plots show no correlation between KRAS and MTOR in PAAD (A), CRAD (B), and LUAD (C). Data collected from cBioPortal.

Supplementary Figure

Supplementary Figure S2:

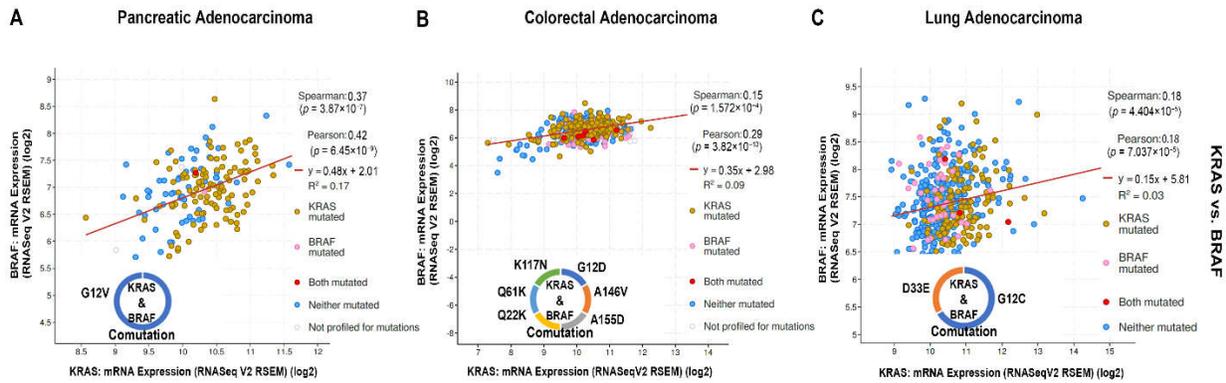


Figure S2: Mutant variants of KRAS with the coexisting mutations of BRAF in Pancreatic adenocarcinoma (PAAD), Colorectal adenocarcinoma (CRAD), and Lung adenocarcinoma (LUAD). In the Dot plots (A-C), mutated *KRAS* is represented as orange, mutated *MTOR* as pink, coexisting mutation of *KRAS* and *BRAF* as red, no mutation as blue, and not profiled for modification as white. The doughnut diagram (A-C) in each plot represents the *KRAS* mutation associated with the *BRAF* co-mutation. According to cBioPortal, co-mutation of *KRAS* and *BRAF* is mainly associated with CRAD. Though co-mutation exists in the CRAD, however, no significant correlation was observed between *KRAS* and *BRAF* in CRAD (B). Data collected from cBioPortal.

Supplementary Figure

Supplementary Figure S3:

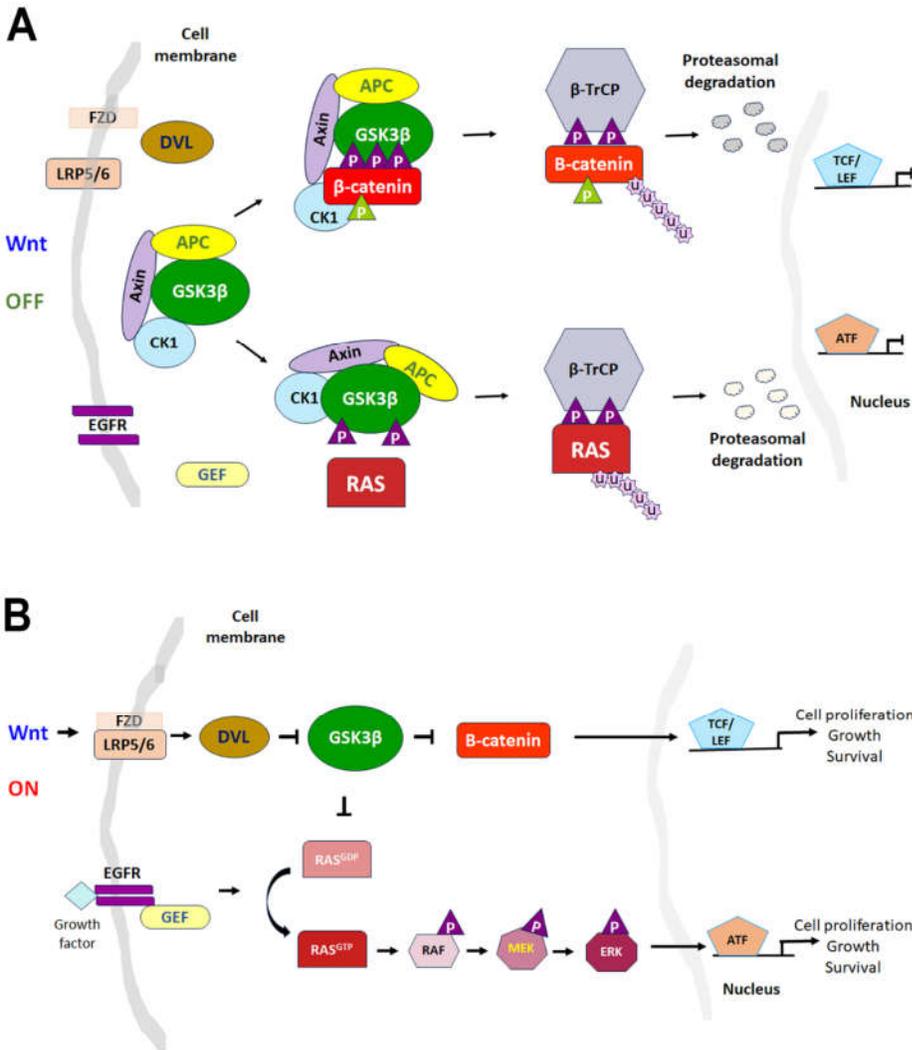


Figure S3: Diagrammatic presentation of crosstalk between Wnt and RAS signaling pathway. (A) The beta-catenin destruction complex (β CdC) consisting of APC, axin, GSK3 β , and CK1 phosphorylates β -catenin with the help of GSK3 β . This same protein complex (β CdC) also phosphorylates RAS protein by GSK3 β . Next, phosphorylated β -catenin and RAS protein eventually leads to proteasomal degradation associated with the E3 ubiquitin ligase protein, β -TrCP. (B) In the presence of Wnt ligands, this β CdC dissociates itself from the degradation mechanism of β -catenin and RAS proteins and is associated with the plasma membrane-bound complex LRP5/6, FZD, and DVL. Freed β -catenin eventually enters the nucleus and influences various neoplastic factors. When the β -TrCP does not degrade RAS, it is activated by the EGFR-associated GEF complex and shifts to RAS-GTP form. This eventually phosphorylates the ERK. Activated ERK enters the nucleus and is responsible for the cell's proliferation, growth, and survival.