Bala et al. (2017) Can J Biotech, Volume 1, Special Issue, Page 58
https://doi.org/10.24870/cjb.2017-a45

Canadian Journal of Biotechnology

ISSN 2560-8304

Poster Presentation OPEN ACCESS

Category: Cancer Genomics **Poster Prize Winner**

Exome sequencing reveals novel oncogenic mutations in early-onset sporadic rectal cancer

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Abstract

Colorectal cancer (CRC) is an aging related disease with 72% of newly diagnosed cases aged 65 years or older (Cancer Registration Statistics, 2012). Past few decades of research from the West have identified aberrantly activated canonical Wnt/β-catenin signaling and microsatellite instability (MSI) as the major pathways driving CRC tumorigenesis. In India however majority of cases appear to belong to a younger age group with preponderance of rectal cancer. Molecular genetic screening of early-onset sporadic rectal cancer (EOSRC) performed earlier from our laboratory identified a significant proportion of EOSRC to be driven neither by aberrant Wnt signaling nor MSI. We performed whole exome sequencing of 27 tumor/normal pairs obtained from surgically resected rectal adenocarcinomas (microsatellite stable with no aberrant Wnt signaling) using the Illumina HiSeq 2500 platform. We identified recurrently mutated genes in EOSRC including known tumor suppressors (TSG) and oncogenes such as TP53, APC, KRAS, SMAD4 and PIK3CA. More importantly, we discovered mutations in uncharacterized TSGs and oncogenes such as ARID2, FAT3, FAT4, ZEB2 and TRPC7. These included putative oncogenic mutations in the zinc finger domains of ZEB2, a DNA-binding transcriptional repressor that promotes epithelial to mesenchymal transition in tumors. Functional work is underway to characterize the effect of these mutations on CRC tumor progression. APC mutations detected in this study were present in major population of cells, yet were not driving β-catenin to the nucleus. This observation suggests β-catenin degradation independent tumor suppressor function of APC, which is being validated.

Citation: Bala, P., Gupta, R. and Bashyam, M.D. Exome sequencing reveals novel oncogenic mutations in early-onset sporadic rectal cancer [Abstract]. In: Abstracts of the NGBT conference; Oct 02-04, 2017; Bhubaneswar, Odisha, India: Can J biotech, Volume 1, Special Issue, Page 58. https://doi.org/10.24870/cjb.2017-a45