Sushil Tripathi, J Proteomics Bioinform 2018, Volume 11
DOI: 10.4172/0974-276X-C3-118

Systematic transcriptomic profiling defines critical LKB1 substrates in gastrointestinal tumorigenesis

Sushil Tripathi
University of Helsinki, Finland

The mechanism by which loss-of-function mutations of the LKB1 kinase lead to Peutz- Jeghers Syndrome (PJS) polyposis is unknown. Based on PJS models the characteristic hamartomatous polyps are driven by clonally expanding stromal myofibroblasts providing a starting point for molecular studies. LKB1 phosphorylates and thereby activates at least 14 related family kinases including AMPKa1, AMPKa2, NUAK1, NUAK2, SIK1, SIK2, SIK3, SNRK, BRSK1, BRSK2, MARK1, MARK2, MARK3 and MARK4. Genetically, LKB1 has been implicated as a regulator of metabolism, polarity, cell growth and migration and the LKB1 substrate kinases are partly linked to these cellular events. However, it is unknown, which of the LKB1 substrates are critical for LKB1-mediated tumor suppression. To investigate this, we established an in vitro system to study molecular changes following shRNA-mediated depletion of Lkb1 substrate kinases in cultured fibroblasts with myofibroblast characteristics. In this system, loss of Lkb1 leads to transcriptomic changes (Lkb1-signature) with a highly significant overlap with changes observed in Lkb1-deficient tumors in vivo, thus allowing for further defining a 134 gene Lkb1-myofibroblast signature possibly involved in driving tumorigenesis. Gene Set Enrichment Analysis (GSEA) of Lkb1- myofibroblast signature genes indicates that the Lkb1-deficiency is associated with signatures of Cancer-Associated Fibroblasts (CAFs) and extracellular matrix organization. Depletion of 14 Lkb1 substrate kinases lead to variable overlaps with Lkb1-signature genes and cumulatively the overlap is 75% supporting their importance in mediating Lkb1 functions. We have validated some these substrates and their commonly regulated genes for their involvement as potential mediators of tumorigenesis.

Biography

Sushil Tripathi is a postdoctoral researcher in University of Helsinki. He had completed his PhD from Norwegian University of Science and Technology, Norway.

sushilth@gmail.com

Notes: