Fall 2024

Biochemistry and Molecular Biology Brown Bag Series

Seth Murdock
Graduate Student

"1FBXL16 Stabilizes Tumor Driver, ERK3"

Tuesday, November 12, 2024

11:00 AM

Location 105 Biological Sciences Building

Lab: Weiwen Long, Ph.D.

Boonshoft School of Medicine
WRIGHT STATE UNIVERSITY

WRIGHT STATE UNIVERSITY

https://science-math.wright.edu/biochemistry-and-molecular-biology

Abstract

Extracellular signal-regulated kinase 3 (ERK3) is an atypical member of the Mitogenactivated protein kinase family. While ERK3 has shown to promote lung cancer progression and metastasis, its regulation and activation remain elusive. FBOX proteins are a family of proteins responsible for the ubiquitination and subsequent degradation of numerous proteins in the cell. However, FBXL16, an understudied member of the FBOX family of proteins, is shown to stabilize ERK3, rather than contribute to its degradation. This research seeks to elucidate the ambiguous relationship between FBXL16 and ERK3.

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Abdulghafar Alagili
Graduate Student

"FBXL16 downregulates ERK1/2 signaling by suppressing FBXO31-mediated DUSP6 protein degradation in lung adenocarcinoma harboring KRASG12C mutation"

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Abstract

Lung adenocarcinoma (LUAD) remains a significant health challenge globally, with molecular heterogeneity posing a hurdle in therapeutic interventions. The KRAS G12C mutation is prevalent among the various oncogenic alterations and contributes substantially to tumor progression. Although novel covalent inhibitors that target KRAS G12C have shown promise in clinical trials, some patients have either intrinsic or acquired resistance to these treatments. There is a significant need to identify new therapeutic targets for lung adenocarcinoma patients with activating KRAS mutations, particularly those who are resistant to KRAS G12C inhibitors. Our lab has recently found that the F-Box protein FBXL16 is selectively upregulated in LUAD with KRAS mutations. It promotes LUAD cell growth and transforms lung epithelial cells. Intriguingly, while FBXL16 knockdown greatly decreased cell growth, it led to a remarkable increase in ERK1/2 phosphorylations. It has been shown that hyperactivity of ERK1/2 is cytotoxic for LUADs with activating KRAS mutations, and it needs to kept at an optimal level via dual-specificity phosphatases (DUSP6), which is critical for growth of LUAD cells with activating KRAS mutations. We thus tested whether FBXL16 upregulates DUSP6 to downregulate ERK1/2 phosphorylations in LUADs with activating KRAS mutations. Indeed, FBXL16 increases DUSP6 protein stability and expression level. Further, we have revealed FBXL16 increases DUSP6 protein stability via suppressing FBXO31, which is E3 known for promoting DUSP6 polyubiqutination and proteasomal degradation.