May 20th, 12:30 PM

Establishment of Rab-11 Induced Inflammatory Regulation as Therapeutic Targets in Colon Cancer Progression

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Et al.

Establishment of Rab-11 induced inflammatory regulation as therapeutic targets in colon cancer progression

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Colon cancer is the third-deadliest cancer in the United States. Better understanding the cancer microenvironment/niches is crucial to the development of successful therapeutic targets.

An RNAi screening using enterocyte specific driver was performed in *Drosophila melanogaster* intestine to search for niches regulating the intestine stem cell homeostasis. A small GTPase, Rab11 caused strong intestine stem cell (ISC) proliferation and tissue hyperplasia upon knockdown, due to increased production of inflammatory cytokines and growth factors. Increased inflammatory cytokines and proliferation were also observed in mouse Rab11a knockout (KO) intestine, indicating Rab11 regulatory role in the inflammation-induced hyperplasia is evolutionarily conserved and may also apply to human.

We hypothesized that Rab11 is required to maintain cytokines in an appropriate state and its expression is down regulated in cancers. We investigated dextran sulfate sodium and chemical induced mouse colon cancer. Rab11 was largely reduced/absent in cancer tissues whereas well present in the normal tissue. We also investigated the correlation of Rab11 level and human cancer progression by immunofluorescence staining, and found that close to 50% and 40% of the cases studied had reduced Rab11 level by 20% and 30%, respectively. The greater the reduction is, the higher chance it is associated with more progressed cancer. Rab11, therefore, functions to suppress cancer progression and can be potentially developed towards a better diagnosis and treatment target for colon cancer. We will screen FDA approved drugs for ISC proliferation regulation, using a fly intestine tumor model established by expressing a human activated RAF^{GOF}gene and a luciferase gene in the fly gut precursor cells. Selected drugs will be applied to test the Rab11 induced hyperplasia in fly, and further validated by mouse and human organoids derived from Rab11 KO mouse or human colon cancer tissues.