Department of Biological Sciences

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Date and time: 9/9/24; 11.00 a.m- 12.00 pm Venue: AB3 building , Room no: 403

Understanding Collective cell migration in Colorectal adenocarcinoma

Colorectal cancer (CRC) is the fourth leading cause of cancer-related fatalities. 9.2% of global deaths are attributed to CRC, and India has the eighth-highest rate of male CRC mortality (https://gco.iarc.fr/). Although India's absolute rates are modest, rising rates present a concern in terms of elevated cancer mortality. CRC stroma infiltration is often caused by collective movement of tumors cell clusters as evident from histopathological studies [1]. Collective cell migration (CCM) is the process that permits groups of cells to move together in a coordinated manner while remaining connected to each other by cell-cell contacts. Various multicellular organisms rely on collective cell migration, which serves as the basis for a plethora of processes ranging from organ development to cancer metastasis [2]. How CCM takes place at the cellular and molecular levels is still elusive.

The Hippo pathway is a highly conserved signalling pathway that extends from drosophila to higher order vertebrates. The mechanotransducers of this pathway, YAP and TAZ acts as co-transcriptional activators and influences cell growth, organ size, survival to stress and dedifferentiation.

Aberrant activation of nuclear YAP/TAZ promotes oncogenic transformation in several tissue types. In several types of cancer, including CRC, YAP/TAZ facilitates multiple stages of metastatic progression, such as migration, invasion, and epithelial to mesenchymal transition [3].

Based on the oncogenic role of YAP/TAZ, we propose that the differently regulated YAP/TAZ target genes may assist collective invasion of CRC tumour clusters during distinct stages of metastatic progression. By utilizing a high throughput differential gene expression analysis, reverse genetics, along with quantitative proteomics in 2D and 3D model systems, we intend to uncover novel sets of differentially expressed YAP target genes and design the underlying mechanisms that regulate collective movement of CRC tumour cells.

References:

1. Pavlič A, Boštjančič E, Kavalar R, Ilijevec B, Bonin S, Zanconati F, Zidar N. Tumour budding and poorly differentiated clusters in colon cancer - different manifestations of partial epithelial-mesenchymal transition. J Pathol. 2022 Nov;258(3):278-288. doi: 10.1002/path.5998. Epub 2022 Sep 5. PMID: 36062412; PMCID: PMC9825925.
2. Qin L, Yang D, Yi W, Cao H, Xiao G. Roles of leader and follower cells in collective cell migration. Mol Biol Cell. 2021 Jul 1;32(14):1267-1272. doi: 10.1091/mbc.E20-10-0681. PMID: 34184941; PMCID: PMC8351552.
3. Cunningham, Richard, and Carsten Gram Hansen. “The Hippo pathway in cancer: YAP/TAZ and TEAD as therapeutic targets in cancer.” Clinical science (London, England :1979) vol. 136,3 (2022): 197-222. doi:10.1042/CS20201474