Track (AM/SM/AF/AI/BD/DM/HR/ID/MT/PR/SD/SE/EG/TD/TL/RD): Track no.6 **HR**

Mechanotransduction in colon cancer metastasis

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Colon cancer accounts for the third most common cancer worldwide, with the second-highest death rate among all cancers. Most colon cancer deaths occur at the metastasis stage and decrease the five-year progression survival rate to 14 percent. Metastasis is egression followed by migration of cancer cells from the primary site to a distant site and colonize to form a secondary tumor. Metastasis is initiated by various biochemical and biophysical cues from the tumor microenvironment. Standard treatment regimes in colon cancer aim to target cancer's proliferative nature but do not reduce the migration and cancer stem cell population. Novel therapeutic targets that inhibit metastasis are required for colon cancer treatment.

Cancer cells sense biochemical and biophysical cues through various receptors. One of the vital receptors is Piezo1. Piezo1 is a mechanosensitive ion channel activated by mechanical stimuli such as external pressure, lipid bilayer stretching, osmotic pressure, and shear stress. Its activation leads to calcium ion influx in cancer cells and stem cells, which activates calcium-dependent pathways responsible for the proliferation and migration of cells. In this study, we investigate the functional role of Piezo1 as a therapeutic target for inhibition of colon cancer metastasis. Effect of Piezo1 ion channel activation on proliferation, self-renewal, and signaling pathways were investigated in Piezo1 silenced colon cancer cells in the presence of Piezo1 agonist Yoda1, shear stress, and external pressure.

Activation of Piezo1 with Yoda1 has not affected the self-renewal and clonogenic properties of DLD1 and HCT116 cell lines in adherent cultures. Whereas in suspension culture where Piezo1 is activated using shear stress, Piezo1 silenced DLD1 cells were found to have increased the clonogenic potential compared to the Piezo1 wildtype cells indicating the essential role of Piezo1 in sensing the shear stress. The phospho-ERK level increased in the DLD1 cell line and decreased in the HCT116 cell line when Piezo1 was silenced, indicating the propagation of the Piezo1 signal through MAPK/ERK pathway. To further understand the MAPK/ERK signaling regulation upon Piezo1 silencing, DLD1 cells were treated with ERK inhibitor (BVD523) under shear stress conditions. The observed results indicate that the ERK inhibition has shown a diminutive effect on the self-renewal ability of cells but affects the proliferation of cells drastically, indicating the hyperactivation of MAPK/ERK pathway with Piezo1 silenced in DLD1 cell lines.

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The results indicate that the Piezo1 ion channel is essential for sensing the physical cues from the tumor microenvironment. Also, activation of MAPK/ERK pathway with Piezo1 silencing varies across the different stages of colon cancer, which need to be further investigated to identify the differential regulation by Piezo1 across the colon cancer stages for therapeutic significance.

References:

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