00481 Elucidating the Role GNA13 in Colorectal Peritoneal Carcinomatosis (CrPC)

Lalitha Vaishnavi Subramanyan[1], *Josephine Hendrickson*[2], *Suhail Ahmed Kabeer Rasheed*[1], *Ong Chin-Ann Johnny*[2], *Patrick J. Casey*[1]

[1]Duke-NUS Medical School, [2]National Cancer Centre Singapore

Aims: Colorectal cancer (CRC) commonly metastasizes to liver and lungs. However, up to 20% of cases metastasize to peritoneal cavity and lead to Colorectal Peritoneal Carcinomatosis (CrPC), which is associated with grave prognosis. Proteomic analysis of ascites, the fluid accumulated in peritoneum of patients, shows a marked elevation of ligands for G-protein coupled receptor (GPCR) signaling mediated by the G12 family of heterotrimeric G proteins in PC. Interestingly, GNA13, a member of the G12 family, is upregulated in many solid tumors and its expression correlates with increased metastatic potential, drug resistance and poor prognosis. This project aims to elucidate the role of GNA13 in CRC, particularly in the context of peritoneal metastasis.

Methodology: GNA13 protein expression was assessed in a panel of eight CRC cell lines using immunoblotting. Cell lines with high (HCT-116, HCT-15 and Colo-205) and low (SNUC-1) GNA13 expression were used as models. GNA13 expression was knocked down using shRNAs or eliminated by CRISPR/CAS9 mediated genome editing. Migration and invasion experiments were performed using Boyden chamber assay. Soft-agar colony formation assays were performed to assess anchorage-independent growth.

Result: Colo-205 cells grown in 5% ascites showed a significant increase in colony formation compared to cells grown in 10% FBS. Depletion of GNA13 in HCT- 116 cells resulted in an increased growth in soft agar in the presence 5% ascites. Migration experiments on HCT-116 and Colo-205 revealed an increase in migration towards 5% ascites upon GNA13 depletion.

Conclusion: Our preliminary results from two CRC cells indicate that GNA13 depletion favours an increased migratory response towards ascites. This, taken together with the increased anchorage-independent growth in ascites upon GNA13 knockdown in HCT-116, indicate that GNA13 may play a tumor suppressive role in the context of CrPC. This contrasts with its oncogenic role in other solid tumors, and suggests a tissue/niche-dependent function of GNA13 in CrPC development.