Investigating enhancer reprogramming and 3D organisation in p53 deficient/mutant colorectal cancer cells

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Abstract

Alterations in epigenetic modifications and chromatin structure are known to drive tumor initiation and progression. Though genetic regulation and mutations in several oncogenes have been extensively reported in colorectal cancer; epigenetic events that drive oncogenic functions are not clearly understood. Colorectal cancer (CRC) shows 40-50% mutations in tumor suppressor p53 that lead to early onset of tumour, aggression, higher metastatic potential and development of resistance to conventional therapies. The clinical importance of p53 mutations in colorectal cancer emphasizes the need to understand the interplay between p53 signaling and epigenetic regulation in colon cancer. Previous studies in the lab through high throughput and high resolution based imaging studies revealed a global increase in the level of trimethylation marks (both active and repressive) with the loss of p53 in colorectal cancer cells. Genome wide investigation of histone modifications with the loss of p53 reveals a differential occupancy around the promoters and intergenic regions. Enhancers and Super enhancers associated with the loss of p53 hint at enhancer driven reprogramming of cell cycle regulation, spliceosome and MyC active pathways. Loss of p53 shows enhancer mediated upregulation of various epigenetic factors like SRSF3,SRSF1, UHRF1 and SETMAR. Loss of p53 also contributes to stemness and mesenchymal state which might be mediated by SALL4, ASCL1, KLF8 upon enhancer binding. ATAC-seq analysis through TCGA-COAD in p53 null mutation patient cohort reveals gained accessibility around these enhancer driven genes. These pathways will be validated on CRC patient tissues towards identifying epigenetic biomarkers for devising targetted therapy for p53 lost/mutant colorectal tumours.