Linking Diet and Cancer: Arachidonic Acid Augments Canonical Wnt Signaling to Enhance Stemness

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Despite studies linking a high fat diet to colorectal cancer incidence, little is known regarding intestinal adaptation to a high fat diet. As intestinal regeneration is regulated by Canonical Wnt, the role of Arachidonic acid (AA) in the variable expression of Wnt targets and intestinal stemness was investigated. Annotated-cluster, differentiation lineage, gene-level and differential expression analysis of single-cell RNA sequencing data and CUT&RUN analysis elucidated AA's impact. AA decreased crypt domain frequency ($p<.001$) and enlarged organoids ($p<.001$) suggesting decreased differentiation and enhanced stemness. Annotated cluster analysis revealed AA increased stem cell frequencies ($p<.001$). A lack of cluster relapse in differentiation lineages reveals AA promotes stemness exclusively through symmetric division, not dedifferentiation. Gene-level analysis revealed AA and metabolite, PGE2, increased B-catenin ($p<0.001$) and B-catenin target gene ($p<0.001$) expression. As expression was greater in PGE2 than AA ($p<0.001$), suggesting AA promotes stemness through PGE2 induced canonical Wnt signaling. Differential expression and gene-level analysis revealed S100A6 expression was upregulated two-fold with AA ($p<0.0001$) and six-fold with PGE2 ($p<0.0001$) suggesting PGE2 recruits S100A6 to promote B catenin. CUT&RUN analysis identified AA elongates S100A6 promoter regions through histone acetylation. The mechanism linking AA and canonical Wnt presents a potential therapeutic target for stemness in colorectal cancer. Future investigations involve the identification of PGE2 mediated histone acetylation.

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