OFFICIAL ABSTRACT and CERTIFICATION

Arachidonic Acid Enhances Intestinal Epithelial Cell Stemness Through Canonical Wnt Signaling

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Cancer stem cells promote resistance to current chemotherapeutics through the promotion of a tumor microenvironment and cellular heterogeneity. Dietary factors could propagate cancer stem cells through stemness. As the mechanisms linking dietary factors and stemness remains elusive, this study investigated the role of arachidonic acid (AA) in the perpetuation of intestinal cell stemness. Annotated-cluster, differentiation lineage, gene-level and differential expression analysis of single-cell RNA sequencing data elucidated AA' s impact. AA decreased crypt domain frequency ($p<.001$) and enlarged organoids ($p<.001$) suggesting decreased differentiation and increased inflammation, proliferation, and cell growth, indicating stemness was promoted. 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 β-catenin ($p<0.001$) and β-catenin target gene ($p<0.001$) expression. As expression was greater in PGE2 than AA($p<0.001$), this suggests 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 AA metabolite, PGE2, recruits S100A6 to promote β catenin. The correlation between S100A6 and canonical Wnt signaling presents a potential therapeutic target for cancer stem cells in colorectal cancer. CUT&RUN analysis identified AA increases promoter length of S100A6 suggesting epigenetic upregulation. Future investigations involve identification of the specific molecular interaction between AA induced S100A6 and Canonical Wnt signaling.

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