Homologous Histone Acetyltransferases KAT2A (GCN5) and KAT2B (PCAF) Roles in the Intestinal Epithelium

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Cellular proliferation and differentiation are fundamentally regulated by the physical landscape of the chromatin. In the intestine, a highly regulated molecular process maintains homeostasis and the proliferation-differentiation balance. Previous investigations established that KAT2A and KAT2B are homologous lysine acetyltransferases that transfer acetyl groups to lysines on histone proteins, opening up the compact chromatin. Such epigenetic modifications result in downstream changes, including interferon pathways activation in intestinal epithelial cells, impacting cancer progression and development. In this study, the phenotypic effects of KAT2A and KAT2B in the intestinal epithelium were examined and distinguished through a gain-of-function methodology. Ex-vivo organoids derived from intestinal stem cells isolated from tamoxifen-inducible intestine-specific Villin-CreERT2; Kat2afl/fl; Kat2b-/- double knockout (KAT2DKO) mice were plated. KAT2DKO organoids were treated with polyinosinic:polycytidylic acid (poly I:C) and the resulting interferon-mediated immune response was exacerbated. As a consequence, necroptosis markers, which were observed in KAT2DKOs intestinal epithelium, were induced to a greater degree while levels of intestinal stem cell markers were downregulated, all measured by qRT-PCR assay. Collectively, this data indicates that genetic ablation of KAT2A and KAT2B enhances the interferon response and necroptosis in intestinal epithelium while decreasing stemness. Because of their important biological functions in the intestine, the proposed research facilitates the molecular understanding of KAT2A and KAT2B in intestinal homeostasis and tumorigenesis.