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Blockade of STAT3 Causes Severe In Vitro and In Vivo Maturation Defects in Intestinal Organoids Derived from Human Embryonic Stem Cells

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Human intestinal organoids (hIOs), which resemble the human intestine structurally and physiologically, have emerged as a new modality for the study of the molecular and cellular biology of the intestine in vitro. We recently developed an in vitro maturation technique for generating functional hIOs from human pluripotent stem cells (hPSCs). Here, we investigated the function of STAT3 for inducing in vitro maturation of hIOs. This was accompanied by the tyrosine phosphorylation of STAT3, whereas treatment with pharmacological inhibitors of STAT3 suppressed the phosphorylation of STAT3 and the expression of intestinal maturation markers. We generated and characterized STAT3 knockout (KO) human embryonic stem cell (hESC) lines using CRISPR/Cas9-mediated gene editing. We found that STAT3 KO does not affect the differentiation of hESCs into hIOs but rather affects the in vitro maturation of hIOs. STAT3 KO hIOs displayed immature morphologies with decreased size and reduced budding in hIOs even after in vitro maturation. STAT3 KO hIOs showed markedly different profiles from hIOs matured in vitro and human small intestine. Additionally, STAT3 KO hIOs failed to maintain upon in vivo transplantation. This study reveals a core signaling pathway consisting of STAT3 controlling the in vitro maturation of hIOs derived from hPSCs. View Full-Text