Title: Effectiveness of JAK Inhibitors in Modulating IFN Regulated Pathways in Celiac Disease

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Abstract

Celiac disease (CeD) is an autoimmune disorder triggered by dietary gluten. A central event in its pathogenesis is the activation of transglutaminase 2 (TG2), which deamidates gluten peptides leading to amplified immune responses. The pro-inflammatory cytokine IFNγ induces TG2 expression and activity through the JAK/STAT signaling pathway. Another key enzyme, HMGCS2, regulates ketone body production in intestinal epithelial cells, and its dysregulation has been linked to intestinal tissue damage. Targeting JAK signaling therefore provides a promising therapeutic strategy to modulate multiple pathogenic mechanisms in CeD.

This study aimed to investigate how JAK inhibitors affect IFN mediated signaling and downstream gene expression using human intestinal organoids. STAT1 phosphorylation was analyzed by western blot after IFNγ stimulation in samples treated individually with 15 JAK inhibitors. Gene expression changes were examined by qPCR, and TG2 enzymatic activity was assessed by immunofluorescence imaging.

Eight inhibitors significantly reduced STAT1 phosphorylation. Analysis by qPCR showed that IFNγ upregulated TG2 while downregulating HMGCS2. Treatment with JAK inhibitors reduced TG2 expression and restored HMGCS2 levels close to baseline. Immunofluorescence imaging confirmed IFNγ induced TG2 enzymatic activity, which was abolished by tofacitinib. Comparable effects on STAT1 signaling and TG2 gene expression were observed with type I IFNs (IFNα and IFNβ) using a subset of inhibitors.

The demonstrated actions of JAK inhibitors highlighted their potential to both reduce aberrant TG2 activity and restore metabolic balance in the intestinal epithelium. These findings provide mechanistic insights into how JAK inhibitors could be optimized for the precision treatment of celiac disease.