Title: JAK Kinases in the Pathogenesis and Treatment of Type 1 Diabetes

Authors:
Vivian Kettunen, Anniina Virtanen, Heikki Hyöty, Olli Silvennoinen

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Abstract

Type 1 diabetes (T1D) is a prevalent autoimmune disease in which genetic predisposition and environmental factors drive autoreactive T-cell responses against insulin-producing pancreatic β-cells. Enterovirus (EV) infections have been identified as key environmental triggers capable of establishing persistent pancreatic infection, thereby contributing to islet autoimmunity through a distinct proinflammatory cytokine milieu. Within this inflammatory signature, type I and II interferons are major players, and they employ a specific combination of Janus kinases (JAKs) – JAK1-3, and TYK2 – to regulate innate immune responses (type I, IFN-α: JAK1/TYK2), as well as cytotoxic T-cell-mediated β-cell attack (type II, IFN-γ: JAK1/JAK2).

T1D still lacks disease-modifying therapies and the central role of JAKs positions them as promising therapeutic targets to attenuate deleterious cytokine signaling. Recent preclinical and early clinical evidence supports the potential of JAK-inhibitors (JAKinibs) in preserving β-cells. However, a systematic evaluation of clinically approved and highly selective JAK inhibitors in the context of T1D pathogenesis has not been conducted and the precise roles of JAKs remain incompletely understood. Here, by applying cytokine- and EV-induced pancreatic cell models alongside immune cell systems, and employing a comprehensive JAKinib evaluation platform supplemented with transcriptomic and immunoassay-based analyses of key T1D biomarkers, we aim to pinpoint critical JAK-dependent immune circuits in T1D pathogenesis and assess the therapeutic potential of JAKinibs in preclinical settings. Ultimately, this project aims to identify the most effective JAKinib candidates for clinical repurposing in T1D.