Genetic evidence for efficacy of targeting IL-2 and IL-6 signaling in prevention of type 1 diabetes

Background:

Type 1 diabetes is a prevalent autoimmune disease, which leads to impaired glucose metabolism, necessitating daily insulin administration and glucose monitoring to prevent complications. Although the risk of type 1 diabetes can be accurately predicted, no widely available disease-modifying therapy exists. To improve this situation, we investigated genetic evidence to support the repurposing of 12 drugs for prevent of type 1 diabetes.

Methods

We collected genome-wide study (GWAS) summary statistics for the risk of type 1 diabetes as well as for blood gene expression and serum protein levels for genetic polymorphisms near 12 potential drug target genes. Using colocalization, we examined whether the same genetic variants increased the risk of type 1 diabetes also affected the relevant drug target levels (serum protein level or blood gene expression).

Findings

Colocalization analysis revealed that lead variants affecting blood IL2RA or IL6R expression also increased the risk of type 1 diabetes (posterior probabilities of the shared variant 100% and 96.3%, respectively). We observed no colocalisation between drug target levels and the risk of type 1 diabetes near the other target genes (IFNAR2, IL12B, IL23A, IL2RB, IL2RG, IL6ST, JAK1, JAK2, JAK3, TYK2).

Interpretation

Our findings offer robust genetic evidence supporting interventions such as tocilizumab and low-dose aldesleukin for prevention of type 1 diabetes. Furthermore, these findings encourage the development of drugs targeting the trimeric IL-2 receptor, which includes IL-2-receptor alpha subunit and is predominantly localized in regulatory T-cells.

Funding

Introduction

Despite advances in continuous glucose monitoring and insulin administration, managing type 1 diabetes remains a significant burden. Several drugs have shown potential in delaying the loss in beta cell function in those at risk of or newly diagnosed with type 1 diabetes. However, no current therapy can completely halt the disease progression. Challenges in progress towards this goal include the pathogenic heterogeneity of type 1 diabetes and a limited pool of autoantibody-positive individuals available for prevention trials. Thus, it is crucial to prioritize the access to this pool for the most promising drugs.

The pharmaceutical industry increasingly uses genetic evidence increasingly to select of drug candidates for clinical development, as candidates backed by such evidence tend to have higher success rates. High-resolution genome-wide association studies (GWAS) enable the examination of variability near drug target genes and its impact on both the drug target levels and disease risk. If a single variant influences both aspects (i.e. the traits colocalize), this provides robust genetic evidence that drug target levels influence the disease risk. Cis-Mendelian randomization can further estimate how manipulating the drug target levels would likely alter the disease risk.

To inform the design of prevention trials of type 1 diabetes, we assessed the genetic evidence for efficacy of 12 promising market approved drugs in prevention of type 1 diabetes. Our analysis revealed genetic evidence supporting IL6 and IL2 signaling in preventing type 1 diabetes. Our results encourage the prevention trials of type 1 diabetes involving drugs such as tocilizumab and low-dose aldesleukin, and support the role of the regulatory T-cells in prevention of human type 1 diabetes.