Opportunity 2018107

Improved Type 1 diabetes diagnosis using insulin neoepitopes

The identification of oxidative post-translational modifications (oxPTM) of insulin (oxPTM-INS) peptide neoepitopes can allow for the implementation of antibody and T cell assays as disease biomarkers and the development of oxPTM-INS targeted immunotherapies.

Background

(T1D) is an autoimmune disease resulting from the chronic autoimmune-mediated destruction of insulin-producing pancreatic beta cells. Oxidative post-translational modifications (oxPTM), due to high levels of reactive oxygen species (ROS), generate neoantigenic epitopes that are recognised by circulating autoantibodies and pathogenic T Cells in T1D. Autoantibodies to insulin post-translationally modified by reactive oxidants (oxPTM-INS) have been detected in newly diagnosed Type 1 diabetics and in children at risk of T1D.

The Problem

There is a pressing need for user-friendly, highly sensitive tests to predict and diagnose T1D early, especially for patients whose immune responses to pancreas proteins remain undetectable by current gold standard blood tests, making disease progression prediction challenging.

Invention: Benefits & Application

The present invention focuses on the identification of epitopes within the insulin sequence recognised by autoantibodies in T1D. This breakthrough involved pinpointing and characterising the exact oxidised insulin fragments resulting from oxPTM, a critical contribution to the field due to the unpredictability of the ROS modification process.

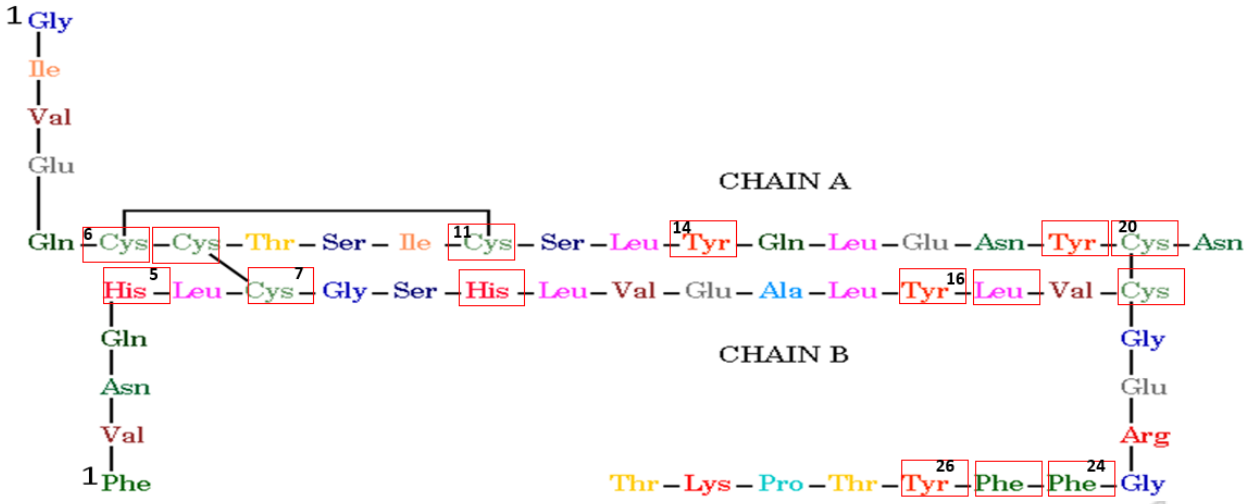

Fig.1. Mapping the oxidised amino acid hotspots in oxPTM-INS. Red boxes indicate the amino acid hotspots.

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Mapping the neoepitopes facilitated the production of native insulin peptides and oxidative post-translationally modified insulin peptides (oxPTM-INSP), which could be tested for their ability to stimulate humoral and cellular immune responses in T1D patients. Antibody and T cell responses were identified in 3 out of 6 peptides. 44.4% of T1D patients showed a concordant autoimmune response to the oxPTM-INSP involving simultaneously CD4+ and CD8+ T cells and autoantibodies.

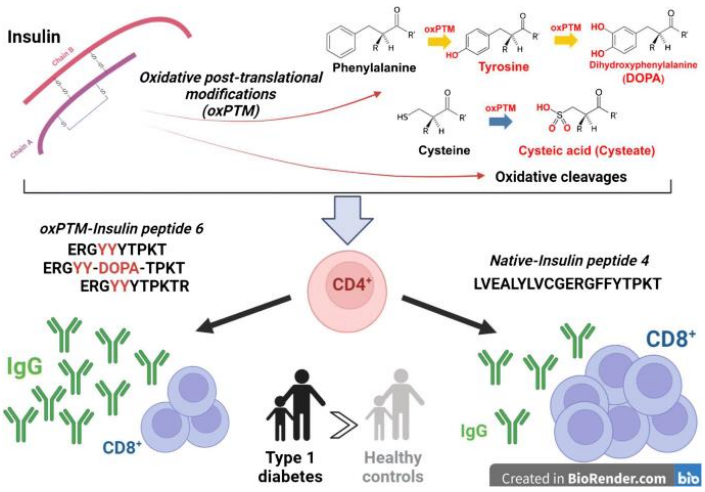

Fig.2. Schematic representation of the production and characterisation of oxPTM-INSP. Identification of oxPTM and insulin fragments produced aided the design of oxPTM and native insulin peptide which were tested for their humoral and cellular immune responses in T1D and healthy control patient sera.

The oxPTM-INSP can therefore provide a method for diagnosing T1D by testing a subject's sample for antibodies against these specific oxidised peptides, offering a robust approach to identifying the disease, especially in patients with new-onset T1D. The use of multiple oxidised peptides can also improve diagnostic coverage. Various immunoassays, including ELISA, can be employed to determine the presence or absence of antibodies against the peptides, making this invention practical for clinical applications.

Additionally, this innovative approach extends its utility to the detection of T cells specific to oxidised insulin forms, offering potential diagnostic applications for T1D, Type 2 diabetes (T2D), and latent autoimmune diabetes of adulthood (LADA). Furthermore, it introduces a novel method for treating T1D by identifying and administering therapeutic agents based on the presence of T cells specific to these peptides. These methods can be employed independently or in combination to enable comprehensive diagnosis and treatment strategies.

Patents

A PCT patent application has been filed WO/2016/146979

Publication

Autoantibody and T cell responses to oxidative post-translationally modified insulin neoantigenic peptides in type 1 diabetes. Diabetologia 66, 132–146 (2023).

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