

High-throughput discovery of T cell epitopes in type 1 diabetes using DNA barcode labelledpeptide-MHC multimers

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934**Autoantigen microarray profiling identified IgA antibody clusters associated with autoimmune clinical manifestations in Systemic lupus erythematosus, systemic sclerosis and idiopathic inflammatory myositis**Li, Q.-Z.¹, Yan, M.¹, Zhao, H.², Zuo, X.²¹University of Texas Southwestern Medical Center, Immunology, Dallas, United States, ²Central-South University of China, Rheumatology, Changsha, China

Systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and idiopathic inflammatory myositis (IIM) are systemic autoimmune diseases characterized by autoantibodies (AutoAbs) against various self-antigens. In this study, we measured the serum IgA AutoAbs against 124 self-antigens in a cohort of 128 SLE, 73 SSc, 75 IIM and 140 healthy controls (HC) using autoantigen microarrays. Our result indicated that IgA AutoAbs were highly prevalent in SLE and SSc compared with IIM and NC. 58.4% SLE and 41.7% SSc have 5 or more IgA AutoAbs compared with 16% in IIM and 14.1% in NC. 9 IgA AutoAbs most significantly elevated in SLE were anti-DNA antigens including dsDNA (54.7%), ssDNA (51.1%), and chromatin (46%). 32 IgA AutoAbs were significantly increased in SSc with highest reactivity to Scl-70 (55.6%). IIM showed lower prevalence of IgA AutoAbs with highest in anti-Jo-1 (20%), anti-muscarinic receptor (8%) and anti-B2-microglobulin (6.7%). Significant correlation was observed between IgA and IgG isotypes on most AutoAbs. 3 IgA autoAbs (anti-gDNA, anti-C1q and anti-dsDNA) positively correlated with SLEDAI Score, but only anti-C1q IgA was significantly elevated in lupus nephritis. 14 anti-nuclear IgA AutoAbs negatively correlated with serum complement C3 and/or C4 levels. Our study indicated that autoreactive IgA AutoAbs against nuclear components, in parallel with IgG AutoAbs, are highly prevalent in SLE and SSc patients. IgA AutoAbs could be used as biomarkers for diagnosis and prognosis of systemic autoimmune diseases, and the molecular mechanisms underlining IgA AutoAbs production in systemic autoimmune diseases warrant further study.

935**High-throughput discovery of T cell epitopes in type 1 diabetes using DNA barcode labelled peptide-MHC multimers**Lyngaa, R.¹, Kai Bentzen, A.¹, Julie Overgaard, A.², Piciot, F.², Størling, J.², Reker Hadrup, S.¹¹Veterinary Institute, DTU, Section of Immunology and Vaccinology, Fredriksberg C, Denmark,²Copenhagen Diabetes Research Center, University Hospital Herlev, Department of Pediatrics E, Herlev, Denmark

Type 1 diabetes (T1D) is characterized by a CD8⁺ lymphocyte-mediated selective destruction of the insulin-producing β -cells causing clinical diabetes. Several autoantigens including glutamic acid decarboxylase 65kDa (GAD65), insulin, protein tyrosine phosphatase (IA-2) and zinc transporter 8 (ZnT8) have been identified based on reactivity in sera from T1D individuals. Here we investigate if post-translational deamination of arginine in the form of citrullination plays a role in T cell recognition of T1D autoantigens. Citrullination may lead to generation of neo-epitopes, which has been described as T cell targets in other autoimmune diseases. We used netMHC prediction algorithm to identify 764 epitopes from Insulin, GAD65, IA-2 and ZnT8 restricted to HLA-A2, A24, B8 and B15. Among these 91 peptide sequences were susceptible for citrullination. We evaluate the MHC-affinity of both the citrullinated and non-citrullinated library, to identify potential neo-epitopes and to understand the impact of citrullination on MHC affinity. In parallel we will analyse peripheral blood lymphocytes from 50 T1D patients for immune reactivity against the full library. The large library screen will be conducted applying a novel technology where the selection of MHC-multimer binding T cells is followed by amplification and sequencing of MHC multimer-associated DNA barcodes revealing their recognition. This technique enables simultaneous detection of >1000 specificities. Identifying post translational modifications capable of eliciting autoreactive T cell responses in T1D patients is highly relevant for understanding the underlying mechanisms leading to T1D.