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T-cell receptor repertoire of insulin-reactive lymphocytes in type 1 diabetes

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Background: Type 1 diabetes (T1D) is due to the autoimmune destruction of the pancreatic β-cells. Autoantigen specificity is determined by the T-cell receptors (TCRs) of autoreactive lymphocytes but their characteristics are poorly understood. Next-generation sequencing now offers methodological possibilities for exploring the vast diversity of the somatically rearranged TCRs for possibilities of personalized diagnosis and intervention.

Objective: To define the TCRs reactive to whole proinsulin, the most important T1D autoantigen.

Methods: We examined T-cells from the peripheral blood of nine children with T1D and two normal controls, by proliferated *in vitro* after 12 days of activation with proinsulin and isolated by CFSE dye-dilution flow-sorting. TCRs were amplified from whole RNA by 5'RACE and amplicons sequenced on the Illumina miSeq with a 250 x 2 protocol. Beta-chain reads were analysed by a paired-end modification of the standard algorithm.

Results: Response to proinsulin was highly polyclonal in the T1D patients but much fewer clones were seen in the two controls, where 29% and 80% of all proliferating clones had the same TCR (p=0.018, rank test). Interestingly, 562 out of the 5,446 clones that showed at least 20-fold expansion were "public", i.e. exactly the same in different subjects. These clones tended to have a higher ratio of expansion (mean 123 vs. 103, p=0.04.

Conclusion: TCR clonality of proinsulin specificities appears to distinguish cases from controls and, if confirmed, may be an important predictor of diabetes, and immune-progress biomarker. Definition of the main TCR clones in early pre-diabetes may provide opportunities for antigen-specific immunosuppression.

Biography

Constantin Polychronakos specialized in Pediatric Endocrinology in Canada after medical studies at Aristotelian University in Greece, and finished his Post-doctoral research training at McGill University in Montreal, where he is now Full Professor in the Department of Paediatrics with cross-appointment in Human Genetics. He is credited with the discovery of the effect of the INS locus in the thymus in type 1 diabetes, with two of the first GWAS for type 1 and type 2 diabetes and one of the first uses of exon capture combined with NGS to elucidate the cause of a rare monogenic form of diabetes.

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