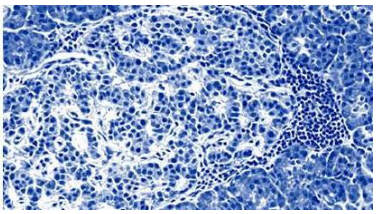
nPOD
Network for Pancreatic Organ Donors with Diabetes



CD8+ T-cell recognition of post-translationally modified antigens: a case study with citrullinated GRP78

AUTHORS

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PURPOSE

The CD8$^+$ T-cell-mediated beta-cell destruction of T1D may be favored by the recognition of neo-epitopes, e.g. citrullinated glucose-regulated protein 78 (GRP78) peptides described in the NOD mouse and human insulitis.

METHODS

We therefore studied the recognition of HLA-A2-restricted native and citrullinated GRP78 peptides by CD8$^+$ T cells in the blood, using combinatorial HLA-A2 multimer (MMr) assays, and in the pancreas, by in situ MMr staining. The expression of peptidyl-arginine deiminase (PADI) citrullinating enzymes in human islets and thymic medullary epithelial cells (mTECs) was analyzed by RNAseq.

SUMMARY OF RESULTS

Citrullination modulated CD8$^+$ T-cell responses to GRP78 by altering TCR recognition rather than HLA-A2 binding. CD8$^+$ T cells reactive to native and citrullinated GRP78 peptides circulated at similar frequencies in T1D and healthy donors. Either the native or citrullinated GRP78 isoform was preferentially recognized depending on the peptide, by distinct CD8$^+$ T-cell pools, with no cross-reactivity between the native and citrullinated isoforms. The CD8$^+$ T-cell preference for native GRP78 isoforms may at least in part be shaped by cross-reactivity with homologous peptide sequences from gut commensal bacteria. Contrary to what observed in the blood, the citrullinated isoform of a dominant GRP78 peptide was

preferentially recognized in the pancreas, but with no specificity for T1D. Citrullinating PADI enzymes were however not expressed in human islets, suggesting that citrullination may rather be triggered by immune cells infiltrating the islets. PADI enzymes were instead expressed in mTECs, suggesting that negative selection may impact both native and citrullinated peptides.

CONCLUSIONS

Post-translationally modified peptides may not always favor loss of tolerance toward beta cells. Their $CD8^+$ T-cell recognition may be shaped by cross-reactivity with microbial homologues and by thymic expression of post-translationally modifying enzymes.