Natural mechanism causes 50-fold increase in T-cell activation sensitivity

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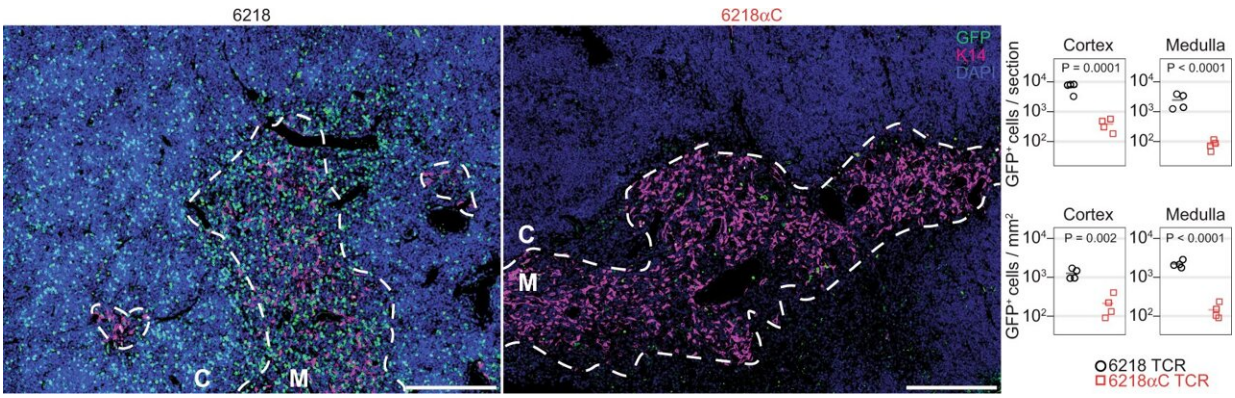

Thymic cortical T cell deletion induced by a CDR3 cysteine. TCR-retrogenic mice expressing the 6218 or 6218αC TCR were made as described in Fig. 1, except that all recipients were male B6 mice (n = 4 for 6218; n = 4 for 6218αC). TCR-retrogenic mice were analyzed 5 weeks after BM transfer at 99-138 days of age. Thymus sections were stained for GFP (green), with medullary areas identified by staining for cytokeratin-14 (K14, magenta). Dashed lines demarcate cortex (C) from medulla (M); scale bars: 200 μm. Graphs shows the number of GFP+ cells per section (top) or per mm2 (bottom) in cortical and medullary areas. Each symbol in a graph represents one mouse. P values were determined using unpaired two-tailed t tests. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-32692-4

While immunotherapy has been a huge step forward in the treatment of some cancers and autoimmune diseases, there are many patients for

whom this type of therapy does not work.

Researchers from La Trobe University, Monash University and QUT have discovered a way to "rev up" T cells, potentially increasing the scope and success of T cell-based immunotherapy.

The research, published in *Nature Communications* was co-led by Professor Stephanie Gras with Dr. Chris Szeto from La Trobe University, Dr. Pirooz Zareie and Professor Nicole La Gruta from Monash University, and Dr. Stephen Daley from QUT, identifies a new mechanism by which T cells can react to lower doses of antigens.

The research group discovered a previously unobserved immune interaction "which had remained invisible because the level of T cell activation was above a threshold that generally results in those T cells being 'deleted' from the immune system," Dr. Zareie said.

The researchers found a novel biochemical mechanism by which T cells are "deleted" before they can fully mature.

"We performed comprehensive biochemical affinity-based measurements and observed the formation of a covalent bond between antigens and T cell antigen receptors" said Dr. Szeto.

In collaboration with the Australian Synchrotron, "we confirmed the presence of a disulfide bond using X-ray crystallography," Professor Gras said.

"We provide functional evidence that this covalent interaction results in a 50-fold increase in T cell activation sensitivity," Dr. Zareie said.

"This discovery came from basic research on the thymus, which is an organ that tailors the immune system to fit its host."

"Immunotherapy was not on our radar when we started this work, but now we can see how this natural mechanism might be co-opted in future treatments for cancer and autoimmune disease," Dr. Daley said.

More information: Christopher Szeto et al, Covalent TCR-peptide-MHC interactions induce T cell activation and redirect T cell fate in the thymus, *Nature Communications* (2022). DOI: 10.1038/s41467-022-32692-4

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