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T CELLS

Steroids improve T cell fitness

> the polyclonal $GR^{lck\text{-}Cre}$ T cell repertoire has a lower avidity for self

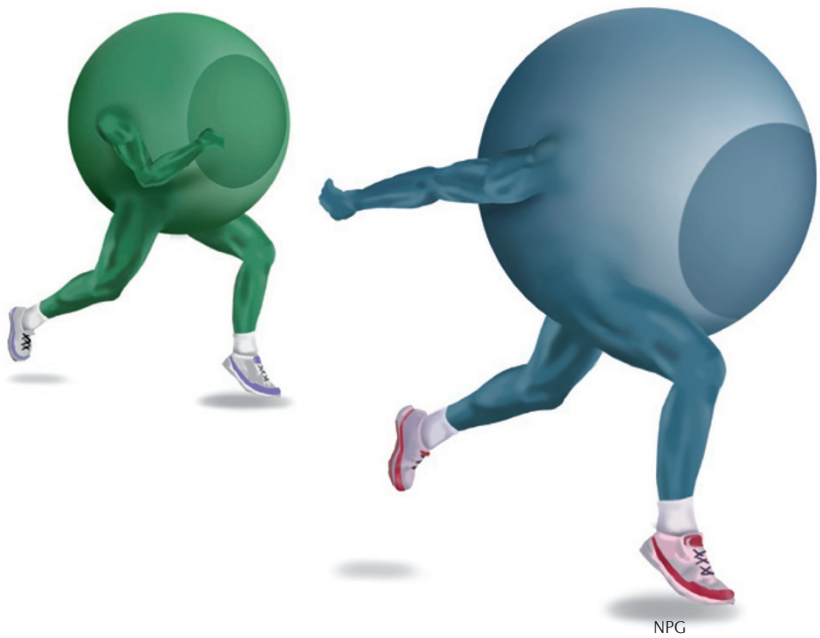
During their development in the thymus, T cells are selected on the basis of the avidity of their T cell receptor (TCR) for self peptide–MHC complexes, to generate a self-tolerant but antigen-responsive T cell repertoire. A new study shows that the endogenous steroid hormones glucocorticoids influence the selection of T cells with an appropriate avidity for self and are required for the development of a fully responsive T cell repertoire.

Although glucocorticoids are best known for their immunosuppressive effects, previous studies had suggested they could have a positive role in thymocyte selection. To test this further, the authors generated mice in which the gene encoding the glucocorticoid receptor (GR) is deleted in thymocytes prior to thymocyte selection ($GR^{lck\text{-}Cre}$ mice). Unresponsiveness to glucocorticoids did not affect signalling following TCR crosslinking by an antibody and did not cause obvious changes to the overall T cell pool. However, T cells from immunized $GR^{lck\text{-}Cre}$ mice responded poorly to antigen re-stimulation *in vitro*, and primary T cell responses to alloantigens or viral infection were markedly compromised in $GR^{lck\text{-}Cre}$ mice. This impairment of the T cell response was not due to an intrinsic defect in responsiveness but rather to an altered TCR repertoire, because when $GR^{lck\text{-}Cre}$ T cells expressed a transgenic TCR they had normal primary and secondary responses to their cognate antigen.

Next, the authors noted that constitutive tyrosine phosphorylation of the TCR ζ-chain (a measure of tonic TCR signalling) was reduced in $GR^{lck\text{-}Cre}$ peripheral T cells compared with wild-type T cells and TCR-transgenic $GR^{lck\text{-}Cre}$ T cells. This suggests that the polyclonal $GR^{lck\text{-}Cre}$ T cell repertoire has a lower avidity for self. Using a model in which the affinity of the TCR for self could be varied experimentally, it was shown that, in the absence of GR, TCR affinities for peptide–MHC that would normally lead to positive selection instead caused negative selection. This finding was consistent with the observations of reduced thymus cellularity and differential use of TCR Vβ CDR3 regions in $GR^{lck\text{-}Cre}$ mice compared with wild-type mice.

So, this study suggests that endogenous glucocorticoids increase the avidity threshold for thymocyte selection to support the generation of a T cell repertoire that has sufficient affinity for self and immunological fitness in the periphery.

Lucy Bird



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ORIGINAL RESEARCH PAPER Mittelstadt, P. R., Monteiro, J. P. & Ashwell, J. D. Thymocyte responsiveness to endogenous glucocorticoids is required for immunological fitness. *J. Clin. Invest.* 1 Jun 2012 (doi:10.1172/JCI63067)

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