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Gerard F. Hoyne
University of Notre Dame Australia, gerard.hoyne@nd.edu.au

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T cell homeostasis is regulated by a program of mRNA alternative splicing mediated by heterogeneous nuclear ribonuclear protein L-like (hnRNPLL)

G. F. Hoyne [1,2], Z. Wu [1], M. Yabas [1], D. Zac [3], A. Aderem [3], C. C. Goodnow [1]

[1] *Immunology Program, JCSMR, The Australian National University, Canberra, ACT, Australia*
[2] *School of Health Sciences, University of Notre Dame Australia, Fremantle, WA, Australia*
[3] *Institute for Systems Biology, Seattle, United States*

It is essential that the immune system maintains stable numbers of a diverse range of lymphocytes since they play important roles in both innate and adaptive immune responses. T lymphocytes are critical for generating cellular immunity and memory following infections (e.g. CD4+ and CD8+ TCR ab + cells), they are also involved in immune regulation (e.g. CD4+ foxp3+ regulatory T cells), as well as immune surveillance at mucosal surfaces and controlling responses to tumors (e.g. TCR gd + cells, NKT cells). Each cell lineage must be contained within a defined cellular compartment and the size of each compartment is physically constrained due to limitations of nutrients and space. Growth factors that belong to the common gamma chain family of cytokines (e.g. IL-7, IL-15 and IL-2) are particularly important for T cell survival but the molecular regulation of lymphocyte survival remains poorly understood. However our understanding of the molecular mechanisms that control T cell homeostasis remains poorly defined.

We have recently identified a novel role for the nuclear protein heterogeneous nuclear ribonuclear protein L-like (hnRNPLL) for the homeostasis of CD4+ and CD8+ T cells in the peripheral immune system through the characterization of a mouse strain derived from an ENU mutagenesis screen (1). The *thunder* mouse strain was identified on the basis of reduced numbers of peripheral T cells and we have gone onto to show that the cellular phenotype is caused by a hypomorphic mutation in the *Hrnpll* gene which controls mRNA alternative splicing. We have used a genomic approach to study the target genes in naïve and memory T cells whose splicing is dependent on hnRNPLL. This revealed that the transition from the naïve to memory phenotype involves a program of mRNA alternative splicing that involves hundreds of genes. The *thunder* mutation does not affect T cell development but it has a non redundant role in regulating the persistence of T cells in the peripheral immune system. These studies have uncovered that temporal changes in mRNA alternative splicing underpins the control T cell homeostasis in vivo that occurs in response to growth factor and antigen receptor signalling.

(1) 1. Wu, Z et al 2008. Memory T cell RNA rearrangement programmed by heterogeneous nuclear ribonucleoprotein hnRNPLL. Immunity 29: 863-875