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T cell development in the thymus: From periodic seeding to constant output

Anna Q. Cai[a], Kerry A. Landman[a,*], Barry D. Hughes[a], Colleen M. Witt[b]

[a]*Department of Mathematics and Statistics, The University of Melbourne, Vic. 3010 Australia*
[b]*RCMI Advanced Imaging Center, Department of Biology, University of Texas at San Antonio, TX 78249, USA*

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Abstract

T cell development occurs in the thymus throughout life. Recent experimental findings show that the seeding of the thymus by multipotent stem cells from the bone marrow is periodic rather than continuous, as previously assumed. However it is well known that the output rate of cells from the thymus is relatively constant. A quantitative model is used to verify the current hypotheses regarding T cell development in the steady state mouse thymus. The results show that the thymus could be at a periodic steady state with out-of-phase thymocyte populations. Experiments to examine possible periodic fluctuations in the thymus are proposed and methods for further analysis are outlined.

Keywords: Thymocytes; Thymus; Proliferation; Differentiation; Periodic oscillations

1. Introduction

T cell development begins with multipotent precursor stem cells being periodically released from the bone marrow and migrating into the thymus, where they undergo proliferation and differentiation before migrating out of the thymus as mature T cells. The murine thymus is made up of two lobes, each of which is compartmentalised into an outer cortex and inner medulla region. Development of T cells coincides with the tightly regulated movement of defined intermediate populations between these two major compartments (Witt and Robey, 2005). Fig. 1 is a photograph of an adult murine thymus with one such cortex and medulla region labelled.

The developmental program of T cells is summarised schematically in Fig. 2. Precursors to the T cell lineage are released periodically from the bone marrow, enter the bloodstream, and find their way to the thymus. Precursors enter at the cortico-medullary junction (CMJ) and fill up the finite number of niches available. The niches are found to be receptive to precursor cell seeding at periodic intervals, with the seeding cycle remaining relatively constant throughout life (Donskoy et al., 2003; Foss et al., 2001; Goldschneider, 2006). Cells at this developmental stage are not yet committed to becoming cells of the T lineage, but retain multi-potentiality. As they lack expression of either the CD4 or CD8 surface molecule, they are referred to as double negative (DN) cells. The DN population consists of four early T cell sub-sets, DN1–DN4.

Following their arrival at the CMJ, DN1 cells undergo numerous rounds of cell division (Penit et al., 1995; Vasseur et al., 2001). As cell division ceases, this population migrates away from the CMJ and into the mid-cortex where they progress to the DN2 stage and become developmentally committed to the T cell lineage. Cells continue to migrate outwards until they arrive at the outer region of the cortex known as the sub-capsular zone (SCZ) (Lind et al., 2001). Approximately one third of these cells successfully pass through a critical developmental checkpoint (DN3 stage) leading to robust cell division (DN4 stage) (Penit et al., 1995). As this second burst of proliferative activity subsides, the cells begin to express

*Corresponding author. Tel.: +613 83446762; fax: +613 83444599.
E-mail address: k.landman@ms.unimelb.edu.au (K.A. Landman).

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both the CD4 and CD8 co-receptors and are now known as double positive (DP) cells. DP cells withdraw from the cell division cycle and lose their proliferative ability (Petrie and Zúñiga-Pflücker, 2007). The cortex is dominated in number by DP cells. Through contact with the stromal cells in the cortex, a small percentage of DP cells pass successfully through a second critical checkpoint known as *positive selection*. These cells receive survival signals through the selection process that allow them to mature further to the final stage of development, the single positive (SP) stage. In addition, the nature of the signal determines the lineage fate of the developing thymocyte; depending on the interactions, expression of either the CD4 or the CD8 surface molecule shuts off leaving the cell fated to mature into one of two T cell sub-populations, cytotoxic CD8+ or helper CD4+ cells. The vast majority of DP cells do not become selected, and therefore, receive no such survival signals. These cells eventually die in the cortex in 3–5 days time.

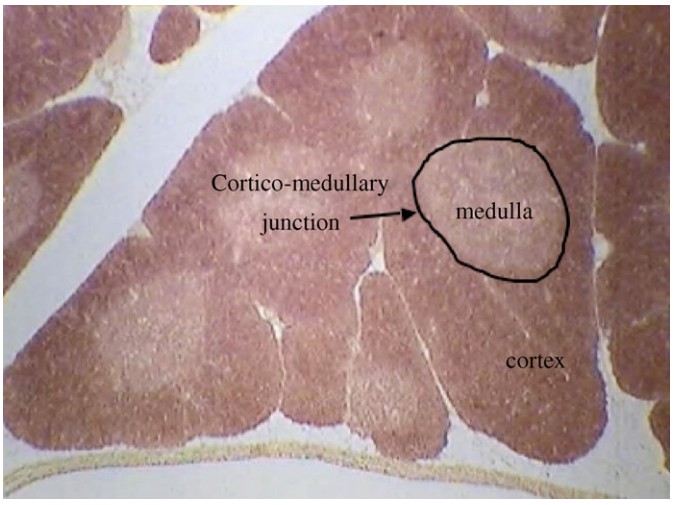

Fig. 1. A photograph of an adult mouse thymus with a cortex and medulla region labelled.

In contrast to all other sub-populations of developing T cells, positively selected DP thymocytes have access to the medulla. Experimental evidence shows that post-selected cells exhibit biased movement away from the thymic capsule and may be chemotactically attracted to the medulla (Witt et al., 2005a). Upon arrival in the medulla, SP cells interact with antigen presenting cells (APC) for their final test. APC present fragments of proteins

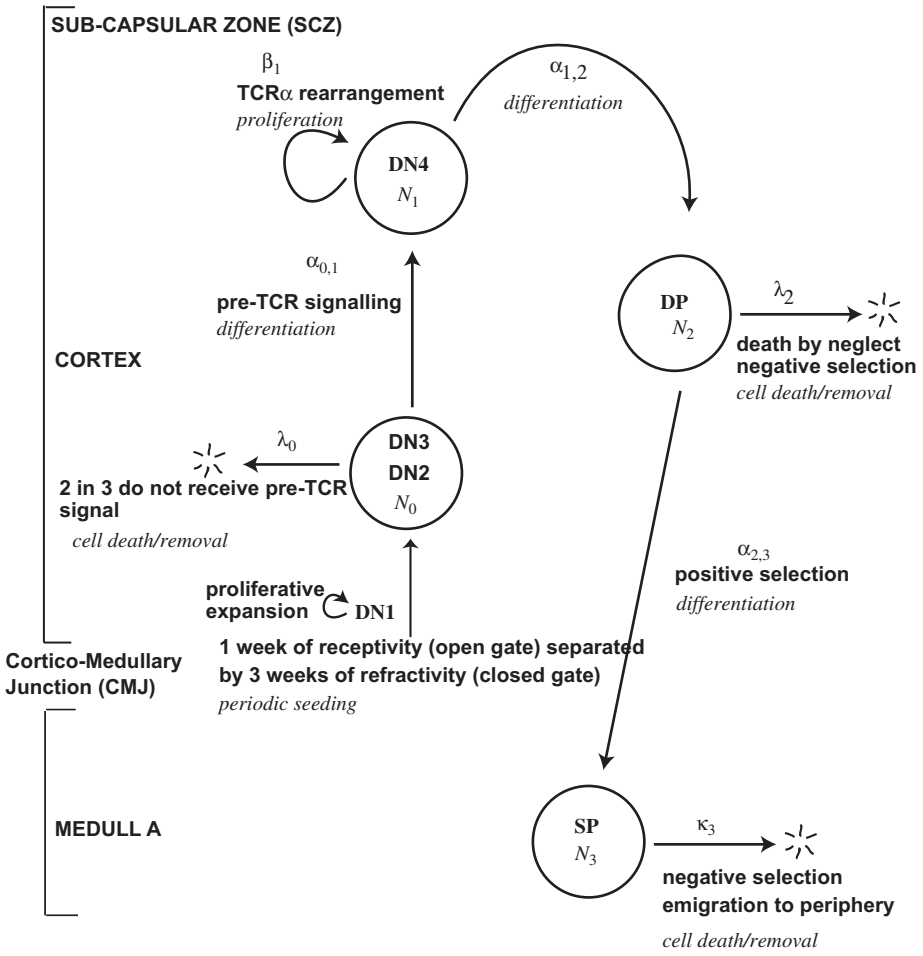

Fig. 2. A schematic diagram of T cell development in the thymus. In bold font are thymocyte populations and major developmental events. The modelled thymocyte populations and developmental events described by Eqs. (1)–(4) are in italic font.