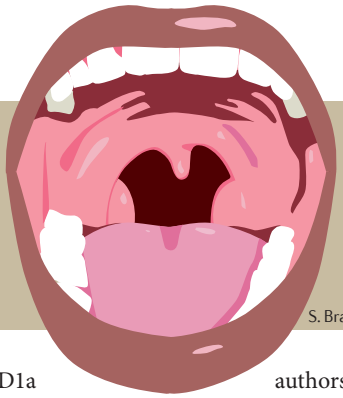
Nature Reviews Immunology | AOP, published online 9 March 2012; doi:10.1038/nri3196

T CELL DEVELOPMENT

Tonsils turn out T cells too



S. Bradbrook

The thymus has long been known to be the site of T cell development and is required for the generation of a healthy T cell repertoire. Now, McClory *et al.* describe a stepwise programme of T cell development in human tonsils.

The authors carried out extensive flow cytometry analyses of cells isolated from human paediatric tonsils and compared them with known subsets of developing thymocytes. Five T cell populations, which were similar to various thymic developmental intermediates, were identified in the tonsils. Population one consisted of $CD34^+CD38^{low}$ cells that lacked expression of a range of lineage (LIN) markers, and population two were $CD34^+CD38^{hi}LIN^-$ cells. Low expression of CD38 by $CD34^+$ cells identifies multipotent haematopoietic progenitors, and upregulation of CD38 expression is associated with their maturation. This suggests that these two populations represent the earliest stages of T cell development. Indeed, these cells resembled, but were not identical to, early double-negative thymocytes.

Upregulation of CD1a expression by $CD34^+$ cells is associated with commitment to the T cell or dendritic cell ($CD11c^+$) lineages. The third population identified in tonsils consisted of $CD34^+CD1a^+CD11c^-$ cells. This population was remarkably similar to thymic $CD34^+CD1a^+$ double-negative thymocytes and expressed several other early T cell markers, including the lymphocyte-specific DNA polymerase terminal deoxynucleotidyl transferase (TdT; also known as DNTT).

$CD34^-CD1a^+CD11c^-CD3^-$ cells made up population four, and these cells also expressed CD4 and CD8, similarly to double-positive thymocytes. Population five expressed CD3 ($CD34^-CD1a^+CD11c^-CD3^+$ cells) and resembled $CD3^+$ near-mature T cells in the thymus.

Furthermore, the expression pattern of various genes that are used to track thymocyte development (such as *RAG1, PTCRA, BCL2L1* and *ZBTB7B* (encoding THPOK)) was similar in the corresponding tonsil populations. And, importantly, the authors showed that all five tonsil populations were capable of differentiating into T cells *ex vivo*.

Finally, TdT^+ cells expressing CD34 and/or CD1a were shown to reside in regions near the fibrous scaffold of the tonsil. Furthermore, these regions expressed the Notch ligands Delta-like ligand 1 (DLL1) and DLL4, which are essential for T cell development. This suggests that these regions have a unique anatomical function that supports extrathymic T cell development.

So, these five subsets identified in human tonsils would appear to represent intermediates in a programme of extrathymic T cell development. Although, the contribution of this extrathymic T cell development pathway to the healthy T cell repertoire remains to be determined, it may augment the T cell pool in settings of poor thymic function.

Olive Leavy

ORIGINAL RESEARCH PAPER McClory, S. *et al.* Evidence for a stepwise program of extrathymic T cell development within the human tonsil. *J. Clin. Invest.* 1 Mar 2012 (doi:10.1172/JCI46125)