# Dendritic Cells: Tissue-specific

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## Dendritic cell heterogeneity

Dendritic cells (DCs) can be divided into subsets based on properties that include cell-surface phenotype, developmental origins and tissue location. These subsets play distinct roles in immune responses. **Secondary lymphoid tissue** (lymph nodes, spleen) contains both **lymphoid-resident DC**, that are directly derived from blood-borne precursors, and **migratory DC**, which traffic from peripheral tissues (skin, mucosae etc.; **Figure 1**). Under non-inflammatory 'steady-state' conditions migratory DC have a superior ability to induce **regulatory T cells** (**Tregs**) and play an important role in maintaining tolerance to tissue specific self-antigens.

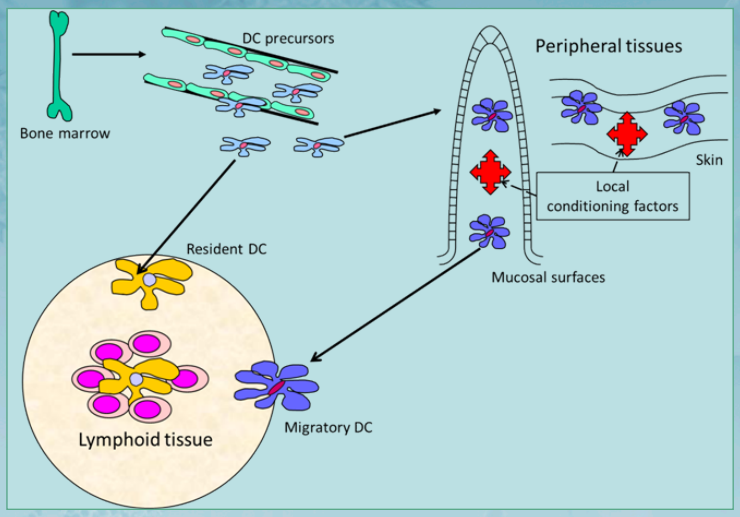


**Figure 1.** The different developmental paths for lymphoid-resident- vs migratory dendritic cells

## Tissue-specific properties of mucosal DC

Mucosal surfaces pose particular challenges to the immune system because they are major sites of exposure to both harmful and innocuous foreign antigens. In the healthy intestinal mucosa, migratory DC identified by expression of the **integrin CD103**, are specialised for the generation of Treg which limit responses to commensal bacteria and food antigens. CD103+ DC produce **all-trans retinoic acid** (**ATRA**) and **TGFb** which act in combination to enhance Treg generation (**Figure 2**). The ability to produce ATRA is restricted to intestinal DC because only these cells express the retinaldehyde dehydrogenase enzymes required for ATRA generation. DC generate active TGFb by integrin-mediated cleavage of its inactive precursor. ATRA also imprints gut tropism on **T cells** activated by intestinal DC by inducing expression of a4b7 integrin and the chemokine receptor CCR9 (**Figure 2**). These interact with MAdCAM-1 and CCL25 respectively to facilitate entry into the intestinal mucosa. Thus, the tissue specific production of ATRA by intestinal DC enhances Treg generation and targets these cells to the gut. In addition, enhanced production of **IL-10** by DC in Peyer's patches contributes regulatory responses in the healthy intestine. DC in the lung also have tissue specific properties and some DC may be biased towards the generation of Th2 responses.

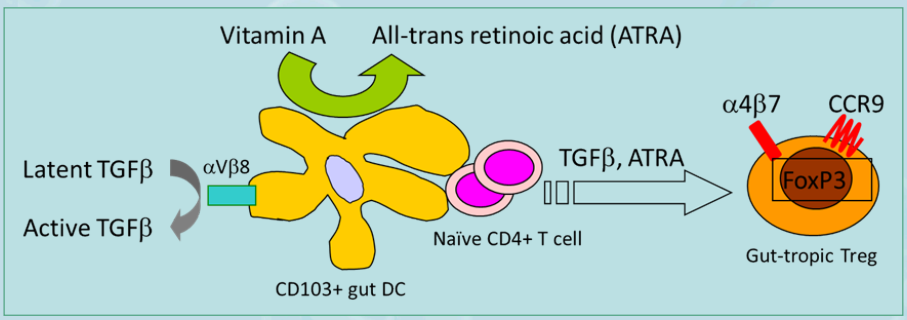


**Figure 2.** CD103+ DC-mediated induction of Treg

## Signals from epithelial cells influence the function of tissue DC

The properties of DC in mucosal tissue are not hardwired but are influenced by conditioning signals produced by **epithelial cells**, constitutively or in response to microbial signals. The tolerogenic properties that characterise gut DC can be induced by factors released from intestinal epithelial cells including ATRA and TGFb. **Thymic stromal lymphopoietin** (**TSLP**) produced by intestinal epithelial cells inhibits the production of pro-inflammatory **IL-12** by DC and facilitates the generation by DC of Th2 responses in parasite infections. Loss of appropriate conditioning signals from DC can lead to a failure of DC to adopt tolerogenic properties and the emergence of inflammatory responses. In the lung, activation of epithelial T cells by TLR ligands leads to the release of TSLP, **IL-25** and **IL-33** which in turn drive DC to stimulate **allergen-specific Th2 responses**. Thus, DC within tissues are functionally plastic cells with properties shaped by local host–microbe interactions.