*Nature Reviews Immunology* | AOP, published online 14 September 2012; doi:10.1038/nri3308

IMAGE 100

AUTOIMMUNITY

# The lung takes over CNS traffic control

The pathogenesis of multiple sclerosis involves numerous steps, including the activation of autoreactive T cells, their migration through the blood–brain barrier and the development of inflammatory lesions in the central nervous system (CNS). Now, Odoardi *et al.* report that early homing of activated autoreactive T cells in the lungs enables T cell migration to the CNS.

The authors used an animal model of experimental autoimmune encephalomyelitis (EAE) that involved intravenous transfer to Lewis rats of activated myelin basic protein (MBP)-specific T cells expressing green fluorescent protein (GFP). Imaging of the transferred autoreactive T cells revealed that only a few cells migrate into the CNS during the first 60 hours. Moreover, the intravenously transferred cells rapidly disappeared from the circulation and remained virtually undetectable in the blood and spleen during the first 48 hours. Reappearance of the autoreactive T cells in the circulation (48 hours after transfer) was followed by their rapid migration to the CNS.

> “the pathogenesis of multiple sclerosis may involve … inflammation of the respiratory tract”

So, the authors hypothesized that some early events endow activated autoreactive T cells with the capacity to migrate to the CNS. Indeed, GFP$^+$ T cells that were re-isolated 60 hours after the initial transfer could cross the meningeal vessels and move into the CNS parenchyma only minutes after their transfer to secondary naive recipients. Notably, the recipients of such pre-conditioned autoreactive T cells developed clinical EAE symptoms 48 hours earlier than the recipients of unconditioned autoreactive T cells.

Intriguingly, the authors observed that the activated autoreactive T cells appear in the lung parenchyma within the first 12 hours after transfer and then move along bronchial structures to the bronchus-associated lymphoid tissue (BALT). Later, GFP$^+$ T cells accumulate in the lung-draining mediastinal lymph nodes, through which they re-enter the circulation. Interestingly, the early homing of activated autoreactive T cells in the BALT depended on CC-chemokine ligand 19 (CCL19) and CCL21 signalling.

Moreover, lung-derived GFP$^+$ T cells induced CNS inflammation following their transfer to secondary recipients, indicating that homing in the lungs enables migration to the CNS. This is of particular importance as MBP-specific memory T cells were found to persist in the lungs. Notably, intratracheal injection with the MBP antigen was as effective as subcutaneous injection in triggering autoimmune inflammation in the CNS of rats bearing autoreactive memory T cells.

Finally, the gene expression profile of activated autoreactive T cells was found to change during their migration through the lungs to the CNS. The reprogramming of effector T cells in the lungs entailed downregulation of proliferation- and activation-associated gene expression, and upregulation of migration-associated molecules, including sphingosine-1-phosphate receptors (which allowed the exit of activated T cells from the lungs) and the adhesion molecules ninjurin 1 and integrin α4 (which enabled transendothelial migration to the CNS parenchyma).

The authors suggest that the pathogenesis of multiple sclerosis may involve environmental factors that trigger inflammation of the respiratory tract, thereby licensing lung-resident autoreactive T cells to migrate to the CNS.

*Maria Papatriantafyllou*

**ORIGINAL RESEARCH PAPER** Odoardi, F. *et al.* T cells become licensed in the lung to enter the central nervous system. *Nature* **488**, 675–679 (2012)
**FURTHER READING** Ransonhoff, R. M. & Engelhardt, B. The anatomical and cellular basis of immune surveillance in the central nervous system. *Nature Rev. Immunol.* **12**, 623–635 (2012)