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Homeostatic chemokines, such as CC-chemokine ligand 21 (CCL21) and CXC-chemokine ligand 13 (CXCL13), control homing and migration of immune cells in lymphoid tissues. However, how these immune factors are regulated and how they direct cell mobility and immune responses is not fully understood. Here, Mueller *et al.* show that, by a process that requires interferon- γ (IFN γ), the expression of CCL21 and CXCL13 in lymphoid tissues is transiently reduced during immune responses, resulting in altered lymphocyte and dendritic cell (DC) migration.

Analysis of CCL21 and CXCL13 expression revealed temporary downregulation of these chemokines in the spleen and peripheral lymph nodes after infection of mice with lymphocytic choriomeningitis virus. This modulation correlated with the generation of virus-specific B- and T-cell responses and was specific for homeostatic chemokines, as the expression of the inflammatory chemokines CCL2 and CCL5 was upregulated in both lymphoid and

non-lymphoid tissues. A similar transient downregulation of CCL21 and CXCL13 was detectable in the spleen after infection of mice with vaccinia virus or *Listeria monocytogenes*, and in the draining mediastinal lymph nodes after intranasal infection with influenza virus. Moreover, immunization of mice with non-replicating antigens, such as virus-like particles or lipopolysaccharide, also induced downregulation, indicating that chemokine modulation might be a generalized programmed response rather than a result of pathogen-induced pathology.

Minimal transient downregulation of CCL21 and CXCL13 could be detected after infection in IFN γ -deficient mice, MHC-class-II-deficient mice or mice depleted of CD4⁺ T cells. In addition, infection with the nematode *Nippostrongylus brasiliensis* or the protozoan *Leishmania major* — both of which induce strong T_H2 (T helper 2)-type immune responses — did not result in the transient downregulation of CCL21

or CXCL13. These observations strongly suggest that the described modulation of homeostatic chemokines is a feature of T_H1-type immune responses.

But what are the functional consequences of this downregulation? The authors transferred fluorescently labelled naive CD8⁺ T cells, CD4⁺ T cells, DCs or B cells into uninfected and infected mice and determined their localization in the spleen. In uninfected mice the transferred naive T cells or DCs predominantly migrated to the T-cell zones of the white pulp, whereas in infected mice this migration was abrogated and instead the transferred cells accumulated in the red pulp. Importantly, this modified migration directly correlated with the amount of CCL21 downregulation. Reduced migration of transferred naive B cells to B-cell zones was also observed. The authors also found that the altered localization of lymphocytes owing to the transient chemokine downregulation had a negative effect on the priming of T-cell responses to a second unrelated antigen during an ongoing immune response. This might contribute to the transient immune suppression seen during acute viral infections.

So, by preventing the accumulation of lymphocytes and DCs in certain areas of the lymphoid tissues, the downregulation of homeostatic chemokines might provide the adaptive immune response with a beneficial mechanism to avoid resource and space competition during an ongoing immune response and thereby promote the generation of memory cells. However, this seems to happen at the cost of briefly compromising the immune system in the event of a second infection.

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ORIGINAL RESEARCH PAPER Mueller S. N. *et al.* Regulation of homeostatic chemokine expression and cell trafficking during immune responses. *Science* 317, 670–674 (2007)