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B CELLS

KLF2 keeps B cells in their place

In this study, Hoek *et al.* describe a role for the transcription factor Kruppel-like factor 2 (KLF2) in the regulation of migratory receptor expression by marginal zone and follicular B cells. The authors show that the loss of KLF2 expression in B cells results in the disrupted positioning of these cells in the spleen and allows follicular B cells to respond to marginal zone-associated antigens.

Marginal zone B cells are non-circulating cells that reside in the white pulp of the spleen and mount responses to antigens without the need for T cell help. By contrast, follicular B cells are circulating cells and need to be localized near T cell areas to mount antigen-specific responses. KLF2 is involved in naive T cell trafficking, so the authors generated mice that specifically lacked *Klf2* expression in B cells (*Klf2*$^{fl/fl}$*Cd19*-Cre$^{+/-}$ mice) to determine whether this transcription factor also has a role in B cell migration. B cells in these mice prematurely exited the bone marrow, and there were higher numbers of both marginal zone and follicular B cells in the spleen compared with control mice. Of note, the marginal zone, but not the follicular area, was increased in size.

KLF2-deficient marginal zone B cells expressed lower levels of the migratory receptors CXC-chemokine receptor 5 (CXCR5) and sphingosine 1-phosphate receptor 1 (S1P1). By contrast, KLF2-deficient follicular B cells expressed higher levels of these receptors and had enhanced migration in response to CXCR5 and S1P1 ligands compared with wild-type follicular B cells. Further analysis showed that follicular B cells were present in the marginal zone of *Klf2*$^{fl/fl}$*Cd19*-Cre$^{+/-}$ mice, which indicates that disrupted B cell trafficking occurs in the absence of KLF2.

Humoral immune responses to the T cell-independent type 2 antigen trinitrophenol (TNP)-coupled Ficoll were enhanced in *Klf2*$^{fl/fl}$*Cd19*-Cre$^{+/-}$ mice. This antigen preferentially activates marginal zone B cells in wild-type mice; however, the enhanced response seen in *Klf2*$^{fl/fl}$*Cd19*-Cre$^{+/-}$ mice was due to the defective homing of follicular B cells into the marginal zone, as it was T cell dependent, required S1P1, was associated with germinal centre formation and occurred in the absence of marginal zone B cells.

Finally, infection of *Klf2*$^{fl/fl}$*Cd19*-Cre$^{+/-}$ mice with *Borrelia burgdorferi* (the initial humoral response to which is dependent on marginal zone B cells) resulted in enhanced bacterial clearance and higher levels of IgG1 than in control mice. KLF2-deficient follicular B cells were shown to mediate this enhanced humoral response, which indicates that in the absence of KLF2, follicular B cells can respond to marginal zone-associated antigens.

So, KLF2 controls B cell localization in the spleen and prevents follicular B cells from gaining access to the marginal zone, thereby preventing follicular B cell responses to marginal zone antigens. This study raises a key question: why has the immune system evolved KLF2-dependent homing mechanisms that seem to be counterproductive to the clearance of blood-borne pathogens?

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ORIGINAL RESEARCH PAPER Hoek, K. L. *et al.* Follicular B cell trafficking within the spleen actively restricts humoral immune responses. *Immunity* 5 Aug 2010 (doi:10.1016/j.immuni.2010.07.016)