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► **COVER:** 'Flexible functionality' by Simon Bradbrook, inspired by the review on p811.


LUCY BIRD


KIRSTY MINTON


OLIVE LEAVY

Immunologists have become more adept at distinguishing different types of B and T cell, leading to new questions about the functions and differentiation pathways of these cells. Understanding how these phenotypes arise and interact holds the promise of more effective immunotherapies and vaccines with fewer side effects.

Jeffrey Bluestone, Charles Mackay, John O'Shea and Brigitta Stockinger discuss some of the controversies regarding the degree of flexibility between different types of T cell in a Viewpoint article on page 811. The consensus view seems to be that the answer very much depends on your definition of flexibility. Many T cell subsets are not terminally differentiated lineages — which is by definition an irreversible state — and can alter their cytokine production in response to environmental stimuli. We now need to determine when a T cell becomes committed to a particular fate, versus assuming a temporary phenotype to suit the environment, and the factors that regulate stability versus plasticity.

One example of a T cell subset with great flexibility of origin is T follicular helper (T_{FH}) cells, which can develop independently of other T cell subsets or be derived from other T helper (T_H) cells. On page 757, Cecile King discusses recent studies that have looked at the relationship between T_{FH} and T_H cells. Are T_{FH} cells a distinct lineage or can T_{FH} cells differentiate into other T_H cell subsets outside the germinal centre microenvironment?

For B cells, an important dichotomy exists between circulating follicular B cells, which interact with T_{FH} cells to produce high-affinity antibodies specific for T cell-dependent antigens, and splenic marginal zone B cells, which produce lipid-specific antibodies. Shiv Pillai and Annaiah Cariappa (page 767) discuss how the differentiation of these two subsets is regulated by the integration of signalling through several pathways.

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