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► **COVER:** 'Holding back the tide' by Neil Smith, inspired by this month's Focus on Immune Tolerance.


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Our immune system has developed an inbuilt mechanism, known as immune tolerance, that protects us from the system's potential destructive effects. However, when this process goes awry, the immune system can attack self tissues, resulting in autoimmune diseases. Understanding the mechanisms involved in the induction and maintenance of immune tolerance, as well as anergy (a state of unresponsiveness to antigen), is essential to fully elucidate the causes of autoimmune disease.

This month, therefore, we present a special Focus issue on the latest advances in our understanding of tolerance and anergy. Garrison Fathman and Neil Lineberry describe the molecular mechanisms of T-cell anergy (page 599), John Cambier and colleagues discuss the salient features of anergic B cells (page 633) and, on page 645, Diane Mathis and Christophe Benoist describe how our understanding of the role of autoimmune regulator (AIRE) in central tolerance has developed over the past 10 years.

Peripheral immune tolerance is regulated by a relatively small number of immune cells that have the task of keeping the rest of the immune system under control. Recent studies have hinted that the suppressive powers of these cells could be harnessed to treat people with autoimmune diseases and to help prevent transplant rejection. So, in this issue we also have three Review articles that discuss the therapeutic potential of regulatory T cells (by Maria-Grazia Roncarolo and Manuela Battaglia, page 585), tolerogenic dendritic cells (by Adrian Morelli and Angus Thomson, page 610) and CD3-specific antibodies (by Lucienne Chatenoud and Jeffrey Bluestone, page 622) to induce long-term tolerance.

Finally, four leading researchers provide us with their personal views on the future of cell-based tolerogenic therapy in a Viewpoint article on page 650.

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