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► **COVER:** 'Fine-tuning' by Simon Bradbrook, inspired by the Reviews on pages 163 and 201.



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Excessive inflammatory responses can be horribly destructive. Unsurprisingly, therefore, immune responses are dampened down and fine-tuned in a multitude of ways to minimize their damaging effects. Four articles in this issue provide examples of such immune regulation on four different levels.

Wolfgang Junger (page 201) explains that cells take it upon themselves to control their behaviour to extracellular cues through autocrine feedback loops involving purinergic receptors. ATP or adenosine released by immune cells following stimulation feeds back on the cells through activating or suppressive purinergic receptors that fine-tune cell functions and activation.

Luke O'Neill and colleagues (page 163) suggest that microRNAs acting on mRNAs may be as important as transcription factors in controlling the protein content of a cell and therefore in regulating cell responses. They focus on the roles of microRNAs in the regulation of Toll-like receptor signalling and during the switch from a pro-inflammatory response to the resolution of inflammation.

A fine balance between protective immunity and inflammatory pathology is also achieved through synergistic and antagonistic signalling crosstalk between innate immune receptors. The Review on page 187 illustrates how pathogens can undermine this fine-tuning for their benefit through various mechanisms; for example, by co-opting inhibitory receptors, inducing immunosuppressive mediators, promoting safe pathogen uptake and disrupting cooperative receptor interactions involved in host protection.

Finally, in an Essay on page 221, Polly Matzinger and Tirumalai Kamala propose that immune responses are regulated at the level of the tissues in which an insult occurs. They suggest that tissue cells are responsible for tailoring the effector class of an immune response to suit the tissue, thereby protecting it from the destructive consequences of inflammatory responses.

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