

quantum optics through their promise of accuracy improved beyond the standard quantum limit in interferometry⁶, measurements of atomic processes⁷ and other sensing techniques.

Squeezed light was first generated in rubidium vapour⁸ just over 20 years ago by exploiting correlations created by the interference of light of different frequencies, a technique known as four-wave mixing. That success was replicated shortly after in a nonlinear crystal⁹ using parametric downconversion, which involves generating correlated photons by splitting a high-energy photon into two lower-energy ones. These first experiments achieved a reduction in the amplitude variance to 93% and 50% of the shot-noise values, respectively.

Spectacular as these experiments were as a proof of principle, the gain in signal-to-noise ratio fell some way short of that required for the technique to become useful in applications. Indeed, in most applications one can simply double the observation time and obtain the same improvement of sensitivity as produced with 50% squeezing. The tables are turned, however, as soon as light is squeezed down to around 10% of shot-noise variance. This is particularly true in applications such as gravitational-wave detection or the probing of sensitive atoms and molecules, where the exposure time for a measurement is limited.

Consequently, efforts towards this kind of extreme squeezing have been going on ever since the pioneering days. Now come some undeniable breakthroughs. In particular, Vahlbruch *et al.*¹ have used parametric downconversion, coupled with state-of-the-art materials and optical elements, to achieve 10 decibels of squeezing — equivalent to fluctuations at 10% of shot-noise variance. That squeezing increases to 5%, or 13 decibels, when corrected for detector inefficiency. Similarly, Takeno *et al.*² have achieved 9 decibels of squeezing. And in parallel, McCormick *et al.*³ optimize the four-wave mixing method to squeeze the intensity difference between two optical beams by 8 decibels, corrected for detector inefficiency.

There is no reason to think that this is the end of the road. The degree of observed squeezing possible with parametric downconversion is limited primarily by optical losses and the limited quantum efficiency of photodetectors (that is, the probability that a photon will spark a measurable electrical signal); both will certainly be bettered in time.

Besides their use in ultra-precise measurements, squeezed states are also gaining relevance in quantum information science. They have been successfully employed for quantum teleportation¹⁰, and uses have also been proposed for them in global schemes for quantum computation and quantum communication¹¹. In this context, it is particularly significant that the notion of squeezed states has of late propagated to atomic systems, where spin-squeezed states¹² have already been generated¹³. The uncertainties in the spin components of

an atomic ensemble in different directions are connected through a variant of Heisenberg's uncertainty principle, just as the uncertainties in light's phase and amplitude are. An ensemble is considered to be spin-squeezed if it has a mean spin J_x in a particular direction, but an uncertainty in the spin projection at right angles to that direction of less than $\sqrt{1/2 J_x}$. Spin-squeezed states would allow standard quantum noise limits in atomic clocks and magnetometers to be overcome, and could also have their uses for the teleportation of atomic systems and for memory stores in quantum communication and quantum computing¹³.

Squeezed states were among the first non-classical states generated in the laboratory. As the number of applications hitting the limit to their sensitivity set by quantum noise grows, and as more squeezing becomes possible, the breadth of potential of squeezed states can only continue to expand. ■

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IMMUNOLOGY

T cells hang in the balance

Emily A. Stevens and Christopher A. Bradfield

Equally important as the immune system's function in fighting invaders is its ability to tolerate self. But environmental toxins could shift the equilibrium between these activities one way or the other.

To ensure the efficient execution of its various activities, the immune system has distributed responsibility between different sets of its cells. But disease, pathogens and pollutants might disrupt the levels and functions of these cells. Take two subsets of T cells for instance: T_{reg} cells are involved in recognizing and 'tolerating' the body's own cells and molecules as harmless; T_H17 cells, by contrast, promote inflammation. In this issue, Quintana *et al.*¹ (page 65) and Veldhoen *et al.*² (page 106) demonstrate that environmental toxins tilt the balance in the levels of these two cell types, altering the severity of experimental autoimmune encephalitis (EAE), a condition in mice that mimics multiple sclerosis.

Control of immune responses is essential to health. T_{reg} cells suppress both the proliferation of effector cells and the secretion of immune mediator proteins called cytokines. The outcome can be positive (a reduction in autoimmune disease and allergy) or negative (limited immune response to infections or inhibition of anti-tumour responses)³. Similarly, by promoting inflammation, T_H17 cells can either participate in the clearance of external pathogens or cause autoimmunity⁴. The cytokine microenvironment of activated T cells seems to influence whether they differentiate into T_{reg} or T_H17 cells. For example, adding the cytokine

TGF- β to T cells in culture induces their differentiation into T_{reg} , whereas in the presence of another cytokine, IL-6, TGF- β promotes production of T_H17 cells^{3,4}.

Both T_{reg} and T_H17 cells express the aryl hydrocarbon receptor (AHR) — a ligand-activated gene transcription factor that has pathological as well as physiological activity. In mammals, the AHR is well known as a mediator of the toxicity of environmental pollutants, including its prototype ligand, dioxin. The toxic effects of dioxin include thymic atrophy, chloracne, tumour promotion and wasting, and can even lead to death. In addition, studies of AHR-deficient mice have uncovered numerous physiological roles for this receptor, although the ligands that mediate these roles are yet to be discovered. Considerable experimental evidence indicates^{5,6} that the AHR mediates its physiological roles, as well as most, if not all, of the toxic effects of dioxin through alterations in gene expression.

Quintana *et al.*¹ and Veldhoen *et al.*² now establish a link between the AHR and T_{reg}/T_H17 differentiation. T_H17 cells secrete the pro-inflammatory cytokines IL-17 and IL-22, which are required for effective clearance of some pathogens⁴. Veldhoen *et al.* show that activation of the AHR increases the expression of these cytokines in cultured T_H17 cells,

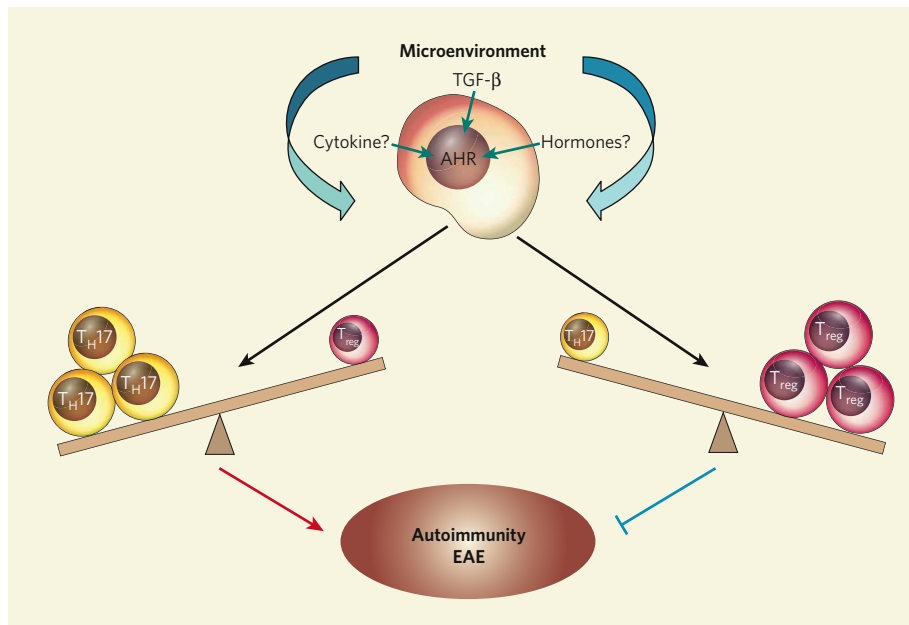


Figure 1 | One cell's poison is another cell's antidote. Regulatory T cells (T_{reg}) suppress the immune system, whereas T_H17 cells promote inflammation. Veldhoen *et al.*² demonstrate that activation of the transcription factor AHR in T_H17 cells increases expression of pro-inflammatory cytokines and worsens experimental autoimmune encephalitis (EAE). Quintana *et al.*¹ show that AHR signalling in T_{reg} cells increases their activity and dampens EAE. TGF- β is involved in both T_{reg} and T_H17 cell differentiation. Through its role as an environmental sensor, AHR might ensure an equilibrium between these two T-cell subpopulations during an immune response via its interactions with the TGF- β -mediated signalling pathway.

which would be consistent with increased T_H17 -mediated inflammation *in vivo*. They also find that, on induction of EAE in AHR-deficient mice, the absolute number of T_H17 cells is reduced, whereas the number of T_{reg} cells remains unchanged.

The hallmark of T_{reg} cells is expression of the transcription factor Foxp3, which is required for the suppressive activity of these cells. Quintana *et al.*¹ show that the AHR directly regulates Foxp3 expression. Moreover, they demonstrate that whether the AHR shifts the balance in favour of T_{reg} cells or T_H17 cells depends on the ligand that activates it. Dioxin increases T_{reg} activity and proliferation, decreases the number and function of T_H17 cells, and suppresses EAE. Another potent activator of the AHR, 6-formylindolo[3,2-b]carbazole (FICZ), has the opposite effect^{1,2}: it increases T_H17 -cell activity and exacerbates EAE.

The AHR is a member of the PAS family of transcription factors, which are known as environmental sensors⁷. Being a transcription factor, the AHR is poised to fine-tune signalling at the level of gene expression. It can therefore probably sense and integrate environmental cues, such as cytokines, hormones and chemicals, as well as modulate the immune response by affecting T_H17/T_{reg} cell differentiation.

The TGF- β -mediated signalling pathway is also involved in both T_H17 and T_{reg} cell differentiation^{1,2}, and interactions between the AHR and TGF- β signalling pathways have been characterized in many contexts⁵. Furthermore, Quintana and colleagues' results¹

indicate that dioxin influences T_{reg} differentiation through TGF- β . They show that TGF- β mimics dioxin's effects on T_{reg} cells and that inhibiting TGF- β signalling suppresses dioxin-induced T_{reg} activity. FICZ also seems to modulate TGF- β activity¹. So it is by modulating TGF- β signalling within the nucleus that the AHR is likely to shift the balance between

the two T-cell populations with opposing effects (Fig. 1).

Although a physiological role for the AHR in regulating the levels of T_{reg}/T_H17 cells would be intriguing, the pharmacology of this system is far from clear. A reason for the conflicting effects of dioxin and FICZ on EAE could be the pharmacology or pharmacokinetics of these chemicals. The AHR solely mediates the effects of dioxin, whereas FICZ might affect additional signalling pathways. Also, whereas FICZ is rapidly metabolized, dioxin is not. Nonetheless, the degree or timing of AHR stimulation with these chemicals could mimic various micro-environmental cues that a developing T cell might receive from its natural environment. Understanding how specific AHR ligands lead to different outcomes *in vivo* will not only provide information about AHR biology, but will also shed light on how the levels of T_{reg} and T_H17 cells regulate the immune response. This knowledge is crucial for any potential therapeutic approach directed at the AHR. ■

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NETWORKS

Teasing out the missing links

Sid Redner

Focusing on the hierarchical structure inherent in social and biological networks might provide a smart way to find missing connections that are not revealed in the raw data — which could be useful in a range of contexts.

As human beings, we are all participants in complex, interlocking social networks¹. As the information revolution gathers pace, the scope and reach of those networks is rapidly expanding. The World Wide Web provides easy connections to informational, commercial and recreational websites. Many people, especially the young, are hooked up to social-networking websites. Social bookmarking, in which participants share links to their favoured websites, is the latest craze.

In this increasingly tangled web, is it possible to make sense of the patterns of connections

between people, and so perhaps learn something useful? In this issue, Clauset, Moore and Newman² (page 98) introduce an appealing, simple and flexible model to do just that: the 'hierarchical random graph'.

Their starting point is the well-known hierarchical structure of a family tree, or dendrogram. We are genetically connected to our siblings (our 'zeroth cousins') through our parents, to our first cousins by our grandparents, to our second cousins through our great-grandparents, and so on, onwards and upwards. What is the probability that we actually know