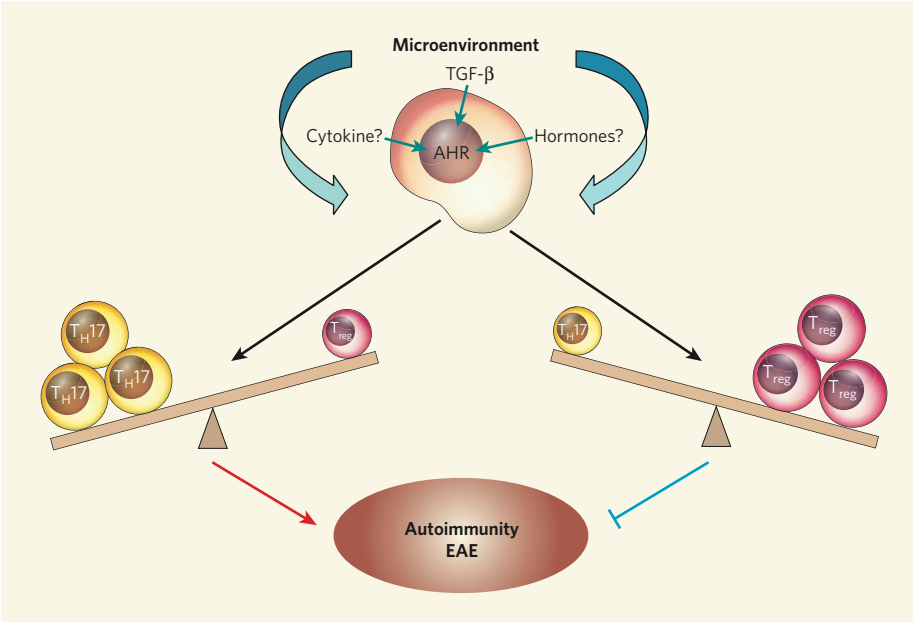

Figure 1 | One cell's poison is another cell's antidote. Regulatory T cells (T_{reg}) suppress the immune system, whereas T_H17 cells promote inflammation. Veldhoen *et al.*[2] demonstrate that activation of the transcription factor AHR in T_H17 cells increases expression of pro-inflammatory cytokines 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 sensors[7]. 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 contexts[8]. Furthermore, Quintana and colleagues' results[1] 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 activity[1]. 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 microenvironmental 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 networks[1]. 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 Newman[2] (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

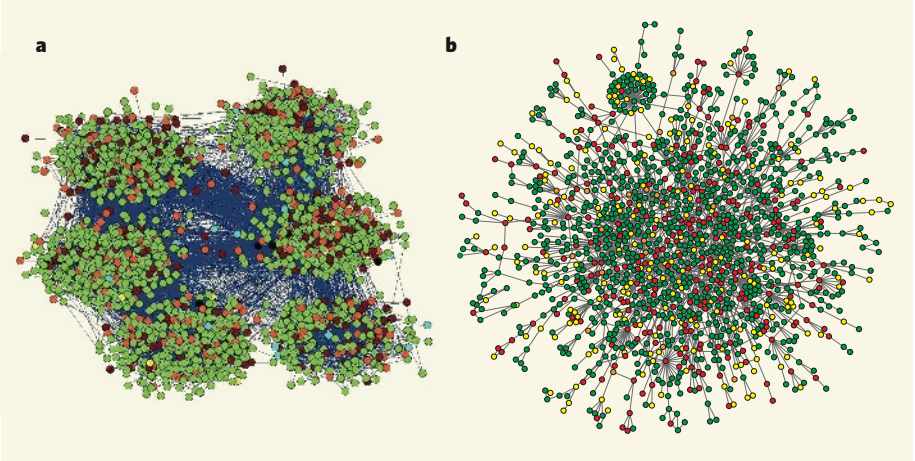

Figure 1 | Assortative, disassortative. **a**, In assortative networks, well-connected nodes tend to join to other well-connected nodes, as in many social networks — here illustrated by friendship links in a school in the United States[6]. **b**, In disassortative networks, by contrast, well-connected nodes join to a much larger number of less-well-connected nodes. This is typical of biological networks; depicted here is the web of interactions between proteins in brewer's yeast, *Saccharomyces cerevisiae*[7]. Clauset and colleagues' hierarchical random graphs[2] provide an easy way to categorize such networks. (Part **a** reproduced with permission from ref. 6.)

our cousins of the nth degree? In most cases, it is obvious that this probability decreases as the degree of separation in the hierarchy increases: we are more likely to know close family members than distant relatives.

This basic family tree describes a highly unrealistic, insular population: only children and parents know each other directly (are directly connected in the tree), and no other social connections exist. Clauset *et al.*[2] incorporate a more social and random aspect into their model by adding lateral connections between nodes in the tree that share a common ancestor. The probabilities of these connections depend in a general way on the closeness of the nodes in the tree, and can be adjusted to describe a diverse range of networks in the social and biological worlds. The flexibility afforded by their model provides a simple way to interpolate between the signature network behaviours of assortativity and disassortativity[3,4] (Fig. 1).

The model can thus account for the myriad ways in which social participants can mix. One can, in fact, identify reversed patterns of sociability in which connection increases with degree of separation: that is, where distant relatives are more likely to know each other than be acquainted with members of their own nuclear family. This apparently bizarre situation seems to arise in food webs[5], in which two predator species may prey on the same species without preying on (being acquainted with) each other, and species that are many feeding levels apart, and thus only distantly related, routinely eat or are eaten by each other.

Perhaps the most intriguing application of the hierarchical random graph construction is the possibility of efficiently predicting missing links in networks in which the available information is incomplete. Naively, one should query every pair of ostensibly unconnected nodes to uncover all the missing links. But such an exhaustive search is grossly inefficient, because the computational effort grows as the square of the number of nodes. By first taking all known network connections and statistically fitting them to a hierarchical random graph, one can infer the dependence of the lateral-connection probabilities on the depth of the nodes in the hierarchy. One then restricts queries to node pairs for which the probability exceeds a specified threshold, a computationally much more efficient process.

The authors tested the effectiveness of their method by removing connections at random from three sets of network data: a bacterial metabolic network; a food-web among grassland species; and, most piquantly, the network of associations among terrorist cells. Next, they determine the lateral-connection probabilities of the underlying hierarchical random graph that best represents the incomplete network. Finally, they test for missing links by looking for unconnected node pairs with a high lateral-connection probability. In a related vein, the method can also ferret out false-positive links: links that appear in the data, but exist between nodes with a low lateral-connection probability.

In many cases, the new method was more reliable in reconstructing the true network structure than were other commonly used algorithms. In our ever-more-interconnected world, there is an increasing need for such theoretical tools that provide a more intimate understanding of the connectivity of complex networks. ■

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ASTROPHYSICS

Rays from the dark

Rainer Plaga

The origin of the cosmic rays that bombard Earth has troubled physicists for nigh on a century. Supernova remnants are a favoured source — but we should keep our minds open to alternatives.

Cosmic rays fall in a steady, imperceptible rain onto Earth. Despite their stealth, they are thought to influence both the climate of our planet and the evolution of its inhabitants. They are mainly protons and heavier nuclei, from helium upwards, and come in a wide range of energies. The most energetic are now thought to come from the active nuclei of remote galaxies[1]. But the origin of by far the larger component of the cosmic rain — 'galactic' cosmic rays of lower energies, from around a gigaelectronvolt to more than a million times that, 3 petaelectronvolts (PeV) — is an entirely different conundrum.

One thing we do know is that galactic cosmic rays follow an unbroken power law, decreasing steadily in their frequency of occurrence up to the 'knee energy' of 3 PeV. Beyond that point, the downward slope abruptly steepens. This striking unity in the data invites the conclusion that galactic rays come from one type of source. But what is that source? Last year, Uchiyama *et al.*[2] reported unexpected X-ray observations that seemed to pinpoint it: galactic cosmic rays are produced when a star explodes, creating a supernova that violently expels a proportion of its matter into interstellar space to form a 'supernova remnant'. The propagation of this stellar debris drives a shockwave that, aided by preexisting compressed magnetic fields,