substantially different way from our expectations[9]. As well as providing the motivation to explore new models of galaxy evolution, this is a tantalizing first look at the type of science that will become routinely possible as the next generation of even larger telescopes come online in ten years' time. ■

Gregory D. Wirth is at the W. M. Keck Observatory, 65–1120 Mamalahoa Highway, Kamuela, Hawaii 96743, USA.
e-mail: wirth@keck.hawaii.edu

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Immunology

Polarizing a T-cell response

Sophie M. Lehar and Michael J. Bevan

Signals through Notch receptors regulate many developmental decisions. New evidence suggests that this pathway is also involved in dictating the tone of the immune response to infection.

We are plagued by pathogens ranging from small viruses to large multicellular parasites, and have evolved a corresponding array of protective immune mechanisms mediated by different 'effector' cells. To clear infections, the immune system must first recognize the type of pathogen involved and then mount an appropriate response. Papers in *Cell*[1] and in *Immunity*[2] now show that the Notch signalling pathway, best known for its regulation of cell development, may also determine the type of immune response that occurs.

In this case the effector cells are thymus-derived (T) lymphocytes that express an accessory cell-surface molecule known as CD4. These CD4 T cells can become either Th1 or Th2 effector subsets, as defined by their ability to secrete unique combinations of cytokine signalling molecules[3]. Th1 cells mediate cellular immunity to viruses or intracellular bacteria by secreting gamma interferon (IFN-γ); Th2 cells promote immunity to multicellular pathogens, such as parasitic nematode worms, their signature cytokine being interleukin-4 (IL-4).

T cells do not recognize pathogens directly but rely on other cells — dendritic cells — as intermediaries[4]. Dendritic cells recognize pathogens through receptors that 'see' common determinants found on pathogens. The best characterized of these receptors are the Toll-like receptors[5]. After recognizing a pathogen, dendritic cells migrate to the lymphoid organs, where they interact with T cells, transmitting information about the type of infection encountered and inducing a T-cell response[4]. The upshot of this interaction can dramatically affect the outcome of infection: inappropriate Th1 or Th2 responses are associated with such serious conditions as autoimmunity, allergy or the inability to clear infections[3].

A Th1 response is initiated when dendritic cells are stimulated through their Toll-like receptors; this induces the secretion of interleukin-12 (IL-12), which signals undifferentiated (naive) CD4 T cells to differentiate into the Th1 lineage (Fig. 1). Th2 responses are initiated when dendritic cells encounter multicellular parasites or allergens. But neither the receptors that recognize these 'type-2' antigens nor the dendritic-cell-associated molecules that induce Th2 responses are known.

The key cytokine involved in Th2 differentiation, IL-4, is produced by Th2 cells themselves. This is puzzling. If Th2 cells produce the cytokine required for their own differentiation, how is a Th2 response initiated? One possibility is that Th2 cells arise by default when a strong Th1 stimulus is lacking, but dendritic cells can induce Th2 responses directly, even in the absence of IL-4 signals[6]. So it has been proposed that dendritic cells induce differentiation of Th2 effectors through some as-yet uncharacterized pathway.

Amsen *et al.*[1] and Tanigaki *et al.*[2] provide evidence that the Notch pathway is the missing link. This pathway is an evolutionarily conserved signalling mechanism that regulates lineage choices in a variety of cell types, including T cells[7]. There are four mammalian Notch receptors and five Notch ligands; the latter fall into two structurally distinct classes, Jagged and Delta. When the Notch receptor binds one of its ligands, the intracellular domain of Notch is cleaved to generate an active form of the receptor. This migrates into the nucleus, where it can induce gene expression by activating the transcription factor RBPJκ.

Amsen *et al.*[1] show that under different conditions dendritic cells can be induced to express either the Jagged or the Delta class of Notch ligands. Delta is induced on dendritic cells exposed to a Th1-promoting stimulus, lipopolysaccharide, which is a component of bacterial cell walls. This acts through the conventional Toll-like receptor pathway. In contrast, Jagged is induced under conditions that have previously been shown to induce Th2 responses. The authors present evidence that Notch ligands are involved in polarizing the T-cell response towards producing one or the other type of effector cell. They show that dendritic cells that have been engineered to express either Delta or Jagged on their surface promote induction of Th1 or Th2 responses, respectively. They also show that the promoter/enhancer region of the IL-4 gene contains three binding sites for RBPJκ, and that Notch can activate gene transcription via these sites.

The notion that Notch signals promote production of Th2 cells is supported by complementary findings from studies of CD4 T-cell responses in mice in which the T cells cannot produce RBPJκ. In separate analyses, Amsen *et al.*[1] and Tanigaki *et al.*[2] both find that the balance between Th1 and Th2 differentiation is perturbed in these mice. RBPJκ-deficient T cells differentiate poorly into IL-4-producing Th2 cells, and preferentially develop into Th1 cells producing IFN-γ. The different subsets of T cells regulate the type of antibody produced during an immune response, and Tanigaki *et al.* report that antibody responses are also skewed in mice lacking RBPJκ in their T cells. The mice have fewer of the antibodies that are normally associated with Th2 responses, and more Th1-type antibodies. Together, these results suggest that Notch signals can alter the balance of CD4 T-cell differentiation into the Th1 or Th2 lineage.

These findings are exciting, but of course questions still remain. How, for instance, are the different Notch ligands able to transduce distinct signals to naive T cells? If the Notch ligands Delta and Jagged can induce CD4 T cells to adopt opposing fates, and Notch promotes Th2 differentiation by activating gene transcription via RBPJκ, then only Jagged should activate this RBPJκ-dependent programme. But it is unclear how this distinction is made: in some settings at least, both classes of ligand are able to activate RBPJκ-dependent signals[8]. Divergent signals could result from the specificity of Notch ligands for different Notch family members. Or Notch ligands might transduce distinct signals through a single receptor, for example through RBPJκ-dependent or RBPJκ-independent pathways. The importance of retaining two classes of Notch ligands is underscored by the fact that simpler organisms, which possess a single Notch receptor, also have two classes of ligands that do not signal equivalently[9]. We eagerly await analyses that will unravel the complexities of Notch signalling in naive CD4 T cells. ■

Sophie M. Lehar and Michael J. Bevan are in the Department of Immunology and Howard Hughes

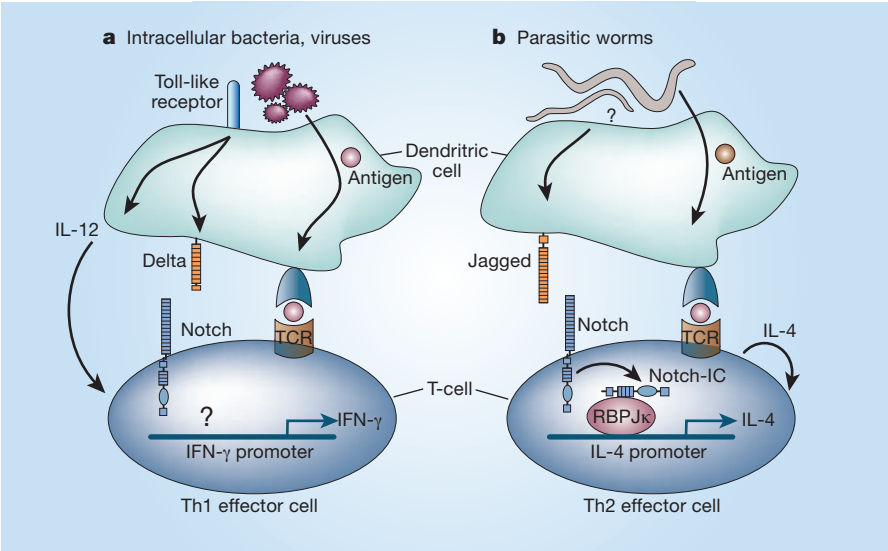

Figure 1 **Stimulating the Th1 or Th2 response. In both pathways, dendritic cells internalize the pathogen. They present its antigens to T cells, which recognize antigens through their T-cell receptors (TCR).** a, **Organisms such as intracellular bacteria or viruses are recognized by the Toll-like receptors on dendritic cells; the resulting signals induce the secretion of interleukin-12 (IL-12) and differentiation of CD4 T cells into the Th1 lineage that produces gamma interferon (IFN-γ).** b, **How dendritic cells recognize larger pathogens, such as parasitic worms, is not known. But the end result is differentiation of Th2 effector cells regulated by T-cell-produced interleukin-4 (IL-4). Information[1,2] on the link between dendritic cells and T cells suggests that the former express different Notch ligands — Delta or Jagged — under different conditions. Jagged is specifically induced by stimuli known to induce Th2 differentiation. Notch signals (Notch-IC) can induce transcription of IL-4 through direct binding of RBPJκ to the IL-4 promoter[1].**

Medical Institute, University of Washington, Seattle, Washington 98195, USA.
e-mails: smlehar@u.washington.edu
mbevan@u.washington.edu

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Earth science

Kinks and circuits

Norman H. Sleep

Flow in the Earth's mantle buffets ascending mantle plumes, causing surface 'hotspots' to move relative to each other. A chain of deduction offers solutions to an age-old puzzle about hotspot behaviour.

More than thirty years have passed since the advent of the theory of plate tectonics. Rigid plates and the narrow, deformable boundaries dividing them explain much of the action on the Earth's surface. Plumes of hot material rising from great depth in the mantle are thought to feed 'hotspots', producing surface tracks of volcanism in the middle of plates (such as the Hawaiian islands), and regions of very active mid-ocean-ridge volcanism (such as Iceland). Complicating this picture are zones of deformation, such as the Basin and Range province in the United States, that exist within supposedly rigid plates. In their paper on page 167 of this issue, Steinberger *et al.*[1] integrate these processes and make them relevant to both field geologists and geodynamicists.

Their work centres on the Hawaii–Emperor bend, a kink in the chain of islands and seamounts that was produced between about 43 million and 50 million years ago, and is evident from even casual observation of a map of the Pacific basin (Fig. 1, overleaf). This feature has long been the 'poster child' example of a change in plate motions; in this case, movement of the Pacific plate is thought to have changed relative to the underlying stationary hotspot. Viewed more

100 YEARS AGO

OXFORD. – The following is the text of [a speech] delivered by Prof. Love in presenting recipients of the degree of D.Sc. *honoris causa* at the Encaenia, June 22, in the presence of the Chancellor of the University:- THE HON. CHARLES ALGERNON PARSONS. Duobus fere millibus abhinc annis Heron Alexandrinus turbinem quemdam per ludum excogitavit, qui vapore calido actus per tubos inflexos afflante converteretur. Carolus Algernon Parsons inter Hibernos nobilissimus, scientiae etiam laude insignis, ita Heronis vestigiis institit ut, quod ille ludendi causa finxerat, ipse in usum nostrum converteret, quo facilius homines naturae imperarent. Optime sane meritus est de omnibus qui urbes habitant, quibus vias et domos luce electrica hoc invento usus illustravit, neque minus profuit Nerea temptantibus, cum his turbinibus impulsae per altum naves celeritate inaudita ferantur recta semper carina adeo ut navigantium incommoda magna ex parte adleventur.
From *Nature* 7 July 1904.

50 YEARS AGO

The main point I wish to make, therefore, is that success in analysing biological molecules by X-rays may explain to us why they have the structure they have. To make a comparison once more with the mineral world, we see that silicon and oxygen together build very stable structures which are light and have a high melting point, and that is why most of the earth's crust is made of silicon and oxygen. Their tetrahedral frameworks conveniently accommodate certain other elements, and correspondingly it is found that these rank next to silicon and oxygen in order of frequency of occurrence in the rocks. On the other hand, carbon, nitrogen and oxygen, together with hydrogen, build structures which are relatively unstable, but which are capable of an infinite complexity. This is so because the atoms are fastened together by bonds which have definite positions. Hence Nature has used these elements to make the complex structures of living matter. Now, as in the case of the silicates, we shall perhaps be able to see further into the reason for the arrangements of these elements which Nature actually uses. If in due course we make a voyage to Mars by a rocket-ship, we can confidently predict that mineralogy will be very much the same on Mars as it is on this globe of ours. Sir Lawrence Bragg
From *Nature* 10 July 1954.