Old before their time

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The discovery of massive, evolved galaxies at much greater distances than expected — and hence at earlier times in the history of the Universe — is a challenge to our understanding of how galaxies form.

Over the past two decades, astrophysicists have been spectacularly successful in explaining the early evolution of the Universe. Existing theories can account well for the time span from the Big Bang nearly 14 billion years ago until the Universe began to cool and form the first large structures less than a million years later. But detailed explanations of how the original stew of elementary particles subsequently coalesced over time, to form the stars and galaxies seen in the present-day Universe, are still being refined. As they report on pages 181 and 184 of this issue, Glazebrook *et al.*[1] and Cimatti *et al.*[2] have discovered the most distant 'old' galaxies yet. But the existence of these objects at such an early epoch in the history of the Universe seems inconsistent with the favoured theory of how galaxies formed.

That favoured theory is the so-called hierarchical model, in which smaller structures gradually accumulate into ever larger structures, ultimately forming galaxies of the sort we see today[3]. The most massive galaxies are expected to have formed relatively late in the process, with few existing before the Universe was half its present age. Such predictions can be tested, in principle, through the observations made of distant galaxies.

Nature has provided us with a powerful means of observing the history of the Universe: because the speed of light is finite, as we look out into space we actually peer back in time, seeing distant objects not as they are now, but as they were when their light was emitted millions or billions of years ago. Unfortunately, galaxies more than 6 billion light years away are not only exceedingly faint, but are also particularly difficult to identify. The visible galaxy spectra are 'redshifted' to longer, near-infrared wavelengths as a consequence of the expansion of the Universe; at these wavelengths, the Earth's atmospheric emission obscures the key spectral 'fingerprints' that are commonly used to identify galaxies.

For these reasons, virtually all of the galaxies known from the early days of the Universe are those that are still forming new stars, and hence emitting copious amounts of light[4]. Although easier to find, such galaxies are not particularly useful for testing theories of galaxy formation because it is impossible to set strong lower limits on how old they are. However, finding significant numbers of massive, evolved galaxies (which finished forming stars long ago) at distances that correspond to half the present age of the Universe would indicate that such galaxies formed much earlier than the leading theory predicts.

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Figure 1 **Journey to the early Universe. This image, taken in visible light by the Hubble Space Telescope, shows a plethora of galaxies billions of light years away in a random patch of sky called the Hubble Ultra Deep Field. As part of a survey of galaxies in this region, Cimatti *et al.*[2] have found several massive galaxies that were already fully assembled billions of years before they should have been, according to current theories. A complementary survey in the northern sky by Glazebrook *et al.*[1] has revealed similar examples of such galaxies, posing a problem for theories of galaxy formation.**

Several earlier studies[5–8] have found evidence for a population of evolved galaxies in the distant past. These studies used the colours of galaxies as rough estimators of their distance — a method that is easier but also much less accurate than measuring galaxy distances directly through the redshift of their spectrum. By pushing some of the largest ground-based telescopes to their limits, Glazebrook *et al.*[1] and Cimatti *et al.*[2] have now provided the most compelling evidence yet that 'old' (that is, evolved) massive galaxies were numerous at early epochs. Using the 8-metre telescopes at the European Southern Observatory in Chile to survey a small region of the sky in detail, Cimatti *et al.*[2] report the discovery of four massive, evolved galaxies, all of which are considerably more distant than the previous record holder. Supplementary images from the Hubble Space Telescope (Fig. 1) show that these galaxies appear to be massive and old, both structurally and spectroscopically.

Complementing this discovery is the ambitious Gemini 'Deep Deep Survey', which was performed using the Gemini observatory's Hawaii-based 8-metre telescope. This study[1] is notable both for the exceptionally long exposures obtained (30 hours for each target) and for the use of an innovative observing mode, which reduces background noise exceptionally well. As a result, Glazebrook *et al.*[1] were able to measure redshifts for far fainter galaxies than is possible by conventional means. As well as strengthening the evidence that massive, evolved galaxies were a significant component of the young Universe, the Gemini team has estimated the change in the abundance of such objects since that time, by observing additional galaxies at intervening distances. They conclude that, going from the present day back to the earliest epochs they probe, the abundance of massive galaxies decreases much more slowly than predicted by the hierarchical model.

With this first solid confirmation[1,2] that as far back as 10 billion years ago there were already many old massive galaxies, it is clear that even the best models can't fully explain the evolution of galaxies. These studies are forcing astronomers to consider whether massive galaxies grew much earlier than predicted by the hierarchical model, or whether the stars in these earliest galaxies formed in a

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. ■

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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. ■

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