corals. Moreover, it is possible that the ENSO system itself may be intensifying as a consequence of global warming[10].

Another common feature of these records is that the increase in sedimentation occurs as a baseline shift around the time of agricultural intensification and not as a long-term, continuing trend. Is this because erosion has levelled off at the new, higher levels? Soil conservation measures and river damming could stabilize the amount of sediment transported to a reef. Alternatively, does the system that allows preservation of the barium signal in the coral saturate at some level, so that higher values cannot occur? Maybe the coral dramatically slows skeletal growth during times of highest sedimentation, so leaving little or no record. To understand these records better, more research is needed on how this tracer behaves as it moves from terrestrial sediments, to rivers and the oceans, and then into the coral skeleton.

Land-use intensification is widespread, so that many reefs close to continents or large islands are likely to have experienced increased delivery of sediment over the past century. As coastal populations increase, this phenomenon is likely to expand. Sedimentation is just one of many large-scale stresses threatening coral reefs[11]. Rising temperatures lead to bleaching, a response that can result in coral death, and increasing concentrations of atmospheric CO_2 make the oceans' carbonate chemistry less favourable for calcification[12].

Reef preservation efforts often focus on stemming the impact of locally significant threats, such as those from destructive fishing, mining and tourism. But mitigating large-scale reef stress from changing climate, ocean chemistry and land use will require regulation of the driving forces of global environmental change — which, thus far, nations have been reluctant to undertake. ■

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Autoimmunity

A case of mistaken identity

Wendy T. Watford and John J. O'Shea

The interleukin-12 protein has been implicated in autoimmunity, but one complication is that it shares a subunit with a related protein. New work looks at the contribution of these proteins to autoimmunity in mice.

It is often quite a straightforward matter to attribute particular human diseases to the action of particular molecules. Sometimes, however, things are less clear cut. For instance, there seems to be considerable evidence that a protein known as interleukin-12 is a major contributor to autoimmune disorders. But on page 744 of this issue, Cua and colleagues[1] argue that this protein has been wrongly accused, at least in the case of a brain autoimmune disease in mice, and that the real culprit is a close relative.

Interleukin-12 is a cytokine — a member of a group of secreted proteins that have diverse roles in cellular differentiation and are especially important in regulating immune responses. Interleukin-12 itself is viewed as being a link between innate and adaptive immunity. The innate immune system consists of cells, such as macrophages and dendritic cells, that respond to generic features of intruders and act accordingly; macrophages, for example, consume microorganisms. Macrophages and dendritic cells also release interleukin-12, and one of its effects is to drive the differentiation of naive T cells into T-helper type 1 cells[2,3], which protect against many intracellular pathogens. T-helper 1 cells in turn produce another cytokine, interferon-γ, which promotes responses by yet more immune cells that are adapted to the unique features of the pathogen in question.

Interleukin-12, then, is important for defence against intracellular pathogens. On the flip side, however, its ability to stimulate T-helper 1 cells and adaptive immunity has led to the proposal that it also actively contributes to several autoimmune diseases, including rheumatoid arthritis and inflammatory bowel disease. Moreover, abnormally high levels of interleukin-12 have been found in people with multiple sclerosis, a disease of the central nervous system in which self-reactive T-helper 1 cells are involved[4].

But although a fair amount of evidence implicates interleukin-12 in the development of autoimmune disease, the protein now seems to have an alibi. Unlike many other cytokines, which are the product of a single gene, interleukin-12 is composed of two proteins that are encoded by distinct genes. These two subunits are named p35 and p40, to reflect their relative molecular masses. The p35 subunit is continuously produced by macrophages and dendritic cells, but p40 is generated only when these cells encounter pathogens. The two proteins then combine to form the biologically active dimer, which is secreted and binds to target cells via a receptor that itself consists of two subunits, designated β1 and β2. The targets of interleukin-12 are T cells, natural killer cells, dendritic cells and macrophages; in response to this cytokine, they release interferon-γ.

This might seem fairly straightforward. The problem is that interleukin-12 is just one member of a small family of dimeric cytokines that regulate interferon-γ production (Fig. 1). And, to confuse matters further, the p40 subunit is a component of both interleukin-12 and the newly discovered interleukin-23. The latter protein also has a p19 subunit[5] and has functions that are similar to, yet distinct from, those of interleukin-12 (reviewed in ref. 6). For instance, it too induces the production of interferon-γ by T cells and dendritic cells[7]. Yet another complication is that the receptor for interleukin-23 comprises the β1 subunit of the interleukin-12 receptor, as well as a second protein.

And there's the rub: these similarities between interleukins 12 and 23 (and their receptors) call into question functions that have previously been attributed solely to interleukin-12. In the past, mice that were genetically engineered to lack p35 or p40 — and mice deficient in the β1 or β2 receptor proteins — were considered roughly equivalent, reflecting a lack of interleukin-12 activity. Abnormalities seen in people with p40 or β1 mutations were attributed to the same cause. But it is now clear that this simple view is inaccurate, a fact underscored by the finding that p40-deficient mice (which lack interleukins 12 and 23) are more immunocompromised than p35-deficient mice (which lack interleukin-12 alone). Furthermore, autoimmune disease has been seen[8] in mice that lack p35, but not in p40-deficient animals. So it is important to determine precisely what each cytokine does.

In their provocative study, Cua *et al.*[1] addressed this problem by producing p19-deficient mice — which lack interleukin-23, but not interleukin-12. The authors then compared the development of a 'model' of multiple sclerosis, experimental auto-

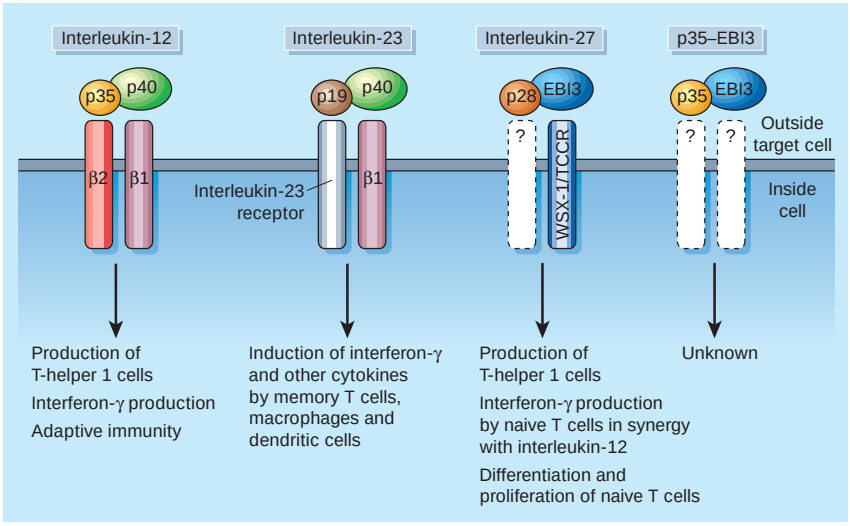

Figure 1 **The interleukin-12 family. These cytokine proteins are released from macrophages and dendritic cells in response to pathogens, and bind to receptors on target cells, activating a variety of functions. In each cytokine a protein akin to p35 (such as p19 or p28) pairs with a soluble protein related to p40 (such as EBI3). p40 is a component of interleukins 12 and 23; their receptors both include the interleukin-12 receptor β1 subunit. Interleukin-27 comprises the p35 relative p28, and the p40 relative EBI3. It binds to the receptor subunit WSX-1/TCCR, and probably another, unknown, receptor subunit. EBI3 can also associate with p35, but the significance of this is unclear. Cua *et al.*[1] show that, because of subunit sharing between these proteins, interleukin-12 has been wrongly assumed to be a major contributor to autoimmune disease. Instead, interleukin-23 is the main culprit, at least in a brain autoimmune disease in mice.**

immune encephalomyelitis (EAE), in p19-deficient and p35-deficient mice. The results show that although p19-deficient mice generate T-helper 1 cells and interferon-γ, they do not develop EAE, but that administering interleukin-23 to these animals is enough to provoke the disease. In contrast, in p35-deficient mice the production of T-helper 1 cells is blocked (as expected, because these mice lack interleukin-12), but the animals are highly susceptible to EAE.

So interleukin-23 can trigger this autoimmune disease, but the role of interleukin-12 is more complicated. The authors find that adding interleukin-23 is not enough to induce EAE in p40-knockout mice (which lack both interleukins). But administration of interleukin-12 followed by interleukin-23 does cause disease. All of this suggests that interleukin-12 contributes to EAE, but that it also has a protective role in this particular model. Although this may seem strange, it is consistent with the finding that interferon-γ also protects against EAE in an 'adjuvant' model[9]. Yet interferon-γ often has a protective effect in adjuvant models, for reasons that are not clear. By contrast, the administration of interferon-γ to people with multiple sclerosis exacerbates the disease[9]. Will the protective effects of interleukin-12 in mice be reflected in humans? The jury is still out.

Are there any other suspects to consider? Interleukin-12-related cytokines that share cytokine or receptor subunits continue to be identified, the newest member of the family being interleukin-27. Composed of the EBI3 protein, which is related to p40, and a p28 protein, akin to p35, interleukin-27 promotes interferon-γ production and drives the development of T-helper 1 cells. EBI3 may also be able to form dimers with other proteins, such as p35 itself. This might add another layer of complexity to interferon-γ regulation. Moreover, cytokine receptors are notoriously promiscuous — exactly which receptors bind which cytokines needs to be sorted out. In short, there is still considerable work to be done to pin down the functions of cytokines in immunity and autoimmunity[10].

What are the implications for treating patients? Antibodies that block interleukin-12 have been widely used in mouse models of autoimmune disease and are being tested in humans. It now seems that interleukin-23 should also be considered a target, although the antibodies against interleukin-12 might serendipitously block this cytokine, too. Treatments aimed at blocking protein subunits that are shared by interleukin-12 relatives (or their receptors) will also be of interest, as it is possible, given their common role in promoting interferon-γ production, that many members of this family contribute to autoimmune disease. Certainly, there is far more complexity here than initially envisioned. But this gives ample opportunity for intervention. ■

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100 YEARS AGO

In the essay to which he refers in his letter in NATURE of January 29, Dr. Wallace attaches less importance to the rearing of a few men of exceptional qualities than to the weeding out of the worst and raising the average; but surely, without giving undue and exclusive credit for advance to the pioneers and prophets, we may take it that men like Darwin and Wallace himself, to mention only one type, will, under natural selection, render the later more conscious steps of man's evolution easier. Dr. Wallace, in the letter referred to, speaks of the "fittest" not surviving under existing civilisation, meaning that many of the specialised types, which form important elements in our polymorphic communities, are not fittest to survive, and continue to reproduce their kind in more primitive or ideal communities. But this, of course, accords well with the principle of the "survival" of those types "fittest" to the actual environment. (Survival, of course, does not postulate direct reproduction any more than it postulates long life; the "worker" bees "survive.") Further, Dr. Wallace's hopeful attitude shows that he really trusts "natural selection" to steer the best races of man to a point whence their further, more self-conscious, progress (still, as always, under natural selection) will be more and more in accord with Nature's will, and so less wasteful and pain-fraught.
From *Nature* 12 February 1903.

50 YEARS AGO

***Chinese Science Revisited (2).* By Dr. Joseph Needham. Another emphasis which must be mentioned is that on popular education. There is a touching and genuine thirst for scientific knowledge among the Chinese people. Shops which sell anatomical models and geological charts have a crowd around the windows all day. If the visitor from the West wanders into one of the modern bookshops on a Sunday, he will almost have to step over rows of children and boys and girls of various ages sitting on the floor and against the bookcases reading popular science, and not paying the slightest attention to him. The assistants never insist on readers buying books, though they usually do, as they are relatively extremely cheap …Will it not make some difference to the world that five hundred million people are awakening to the significance of natural science and all that that implies?**
From *Nature* 14 February 1953.

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Astronomy

Hot gas around the Galaxy

Amiel Sternberg

An extended system of highly ionized gas clouds that surrounds the Milky Way has been detected. This gas may be part of the original matter from which our Galaxy and its nearest neighbours formed.

How did galaxies form? Astronomical observations and theory suggest that the process began with the collapse of density perturbations in an originally smooth distribution of cosmic 'dark matter'. Baryonic matter, the ordinary visible matter that can be incorporated into stars, was then pulled into the growing condensations of dark matter. Eventually the baryons settled into the disks and elliptical structures observable today as galaxies. On the basis of data from the Far Ultraviolet Spectroscopic Explorer satellite (FUSE), Nicastro *et al.* (page 719 of this issue[1]) present evidence for the existence of a large reservoir of baryons around the Milky Way — which, they argue, may be a relic of the original matter that formed our Galaxy and its nearest neighbours.

The total baryon content of the Universe is a key cosmological parameter. Observations of the cosmic deuterium-to-hydrogen abundance ratio, a quantity that was fixed by nucleosynthesis in the hot Big Bang, imply that baryons constitute 4% of the total 'mass-energy' density of the Universe[2]. Remarkably, the same percentage is inferred from studies of the 'acoustic' oscillations in the primordial plasma, evident today as fluctuations in the cosmic microwave background radiation[3].

Observations of intergalactic atomic hydrogen in clouds that existed when the Universe was about a tenth of its current age, the epoch when galaxy formation began, reveal a cosmologically expected baryon content. At that time, most of the baryons were distributed in a diffuse intergalactic medium, which was photoionized and heated to a temperature of around 10^4 K by the first stars and quasars. But in the present-day Universe, the baryon budget comes up short. Observations of stars, galaxies, clouds in the intergalactic medium and very hot (10^8 K) X-ray-emitting plasma in galaxy clusters account for only a third of the expected cosmological baryon density[4].

So where are the 'missing' baryons? One possibility is that they are contained in massive astrophysical compact halo objects (MACHOs), a collective term for objects such as isolated neutron stars, brown dwarfs or planetary masses that are faint and hard to detect. Alternatively, they could be hiding as dilute 'warm–hot' ionized clouds at temperatures of 10^5–10^7 K. Such gas would be difficult to detect by conventional methods: it would be too highly ionized to allow it to be identified by observations of atomic hydrogen, yet too cool to be evident as thermally emitting X-ray plasma.

Hydrodynamic simulations[5] of galaxy formation suggest that much of the baryonic mass today could indeed be present in a warm–hot intergalactic medium (WHIM) at 10^5–10^7 K. In this picture, WHIM is produced by the shock waves that inevitably occur as gas falls out of the much cooler, diffuse intergalactic medium and into the collapsing filamentary web of 'over-dense' regions where galaxies form. The shocked gas cannot cool efficiently because the WHIM densities are low, and as much as half of the primordial baryonic material is predicted to survive as WHIM, rather than condense into stars and galaxies.

Can the WHIM be detected? One possibility would be to detect the absorption-line signatures of highly ionized trace 'metals' (elements heavier than helium) that may be present[6–8]. The oxygen ions O^{5+}, O^{6+} and O^{7+} — designated O VI, O VII and O VIII by astronomers — are particularly important candidates for this purpose. The available spectroscopic line transitions of the oxygen ions occur at ultraviolet and X-ray wavelengths, however, meaning that observations must be carried out above the Earth's atmosphere. This is now possible with the revolutionary spectroscopic capabilities of the FUSE satellite, and the Chandra and XMM-Newton orbiting X-ray observatories. Distant quasars serve as (point-like) sources of ultraviolet and X-ray radiation, and clouds are detected as intervening oxygen-line absorbers along the lines of sight.

Indeed, one of the spectacular results of the FUSE mission has been the detection of many discrete O VI absorbers, distributed all over the sky[9,10]. They probably represent a heterogeneous collection of clouds that are at widely varying distances and have widely different origins. Some absorption probably originates in ionized gas close to, or within, the interstellar medium of the disk itself; some, however, may occur in clouds located well outside the Milky Way.

The 'radial velocities' of the O VI clouds, as determined by the Doppler shifts of the absorption lines, provide clues to their origin and location. Nicastro *et al.*[1], and, independently, Sembach *et al.*[10], have analysed high-velocity O VI absorbers, with absolute radial velocities in excess of 100 km s^{-1}, and as high as 550 km s^{-1}. Such velocities are larger than would be expected for motions confined to the Galactic disk. Nicastro *et al.* show that the kinematic properties of this ensemble may imply that most of the high-velocity O VI absorbers are distributed in a volume encompassing the entire Local Group of galaxies, consisting of the Milky Way, Andromeda and 30 or more less-massive galaxies. They note that an extended distribution of hot gas is consistent with very low gas densities inferred from X-ray absorption-line detections of O VII and O VIII. For such an extended distribution, the total mass of hot ionized gas is comparable to the dynamical mass of the Local Group, and the hot gas represents a major reservoir of baryons.

Is the extended distribution of high-velocity O VI absorbers the original WHIM? Nicastro *et al.* argue that it is. Given the uncertainties in the distance estimates, however, the clouds could also be reprocessed, metal-enriched gas that was ejected from the Milky Way (or its neighbours) by supernova explosions. Measurements of the metal abundances in the hot clouds will help to clarify this issue. ■

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