free-ranging members of the Local Group, rather than satellites of their central galaxy.

A curious fact, first noted by Jaan Einasto and colleagues[3] in 1974, is that most of the close satellites of M31 and the Galaxy are elliptical or spheroidal, whereas many of their more distant companions have irregular forms. Unfortunately, some of the newly discovered objects[2] have such low star counts, and the subtraction of light from background sources is therefore so uncertain, that it is difficult to be sure whether they are irregular or dwarf spheroidal galaxies.

Another interesting facet that emerges from these latest discoveries of satellite galaxies is that the radial distances of the known companions of M31 and the Milky Way from the nucleus of their parent galaxy seem to be roughly similarly distributed. For distances of less than 150 kiloparsecs, the number N of companions within a radius R is reasonably well represented by a logarithmic correlation, $\log N = -0.24 + 0.80 \log R$. Perhaps because of the incompleteness of the data, above 150 kiloparsecs the cumulative number drops below that expected from this relation. Even so, half of the known companions of these two galaxies are situated more than 90 kiloparsecs from their host. At that distance, gravity from an unseen source must be acting to keep the companion galaxies in tow, attesting to the enormous size of the haloes of dark matter that must surround the Milky Way and M31.

Numerical simulations[4,5] have predicted the existence of a swarm of smaller, denser dark-mass haloes embedded within the general dark halo of the Milky Way. The gravity of each of these mini-dark-haloes should have attracted a clump of ordinary, visible matter. Thus, these predictions seemed to conflict with the observation that our Galaxy is surrounded by only a handful of companions. But the faintness of Belokurov and colleagues' new discoveries[2] indicates that they might be just the first of a vast population of ultra-faint dwarf galaxies surrounding the Milky Way system that is yet to be discovered. ■

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IMMUNOLOGY

Exposure of an executioner

Michael Carroll

The complement C3 protein binds to pathogens, singling them out for execution by the immune system. Structural studies show how the chemical group responsible for this binding is exposed on activation.

Some of the oldest molecules involved in defence in the animal kingdom are found in the thioester protein family, which dates back more than 500 million years[1]. The power of these proteins comes from their thioester chemical group — a highly reactive molecular 'warhead' that, when activated, binds to chemical acceptor groups on many pathogens and marks them out for destruction by immune cells. Unfortunately, similar acceptor groups are found in host tissues too, so the thioester group must be carefully regulated to prevent it from interacting with host cells and wrongly drawing the immune system to attack them. Perhaps because of this potential for damage, the modern vertebrate immune system retains only a few thioester proteins, including complement protein C3.

Understanding how this potentially dangerous but useful defence protein is kept under control is of great interest, and X-ray crystallographers have been trying to puzzle out its structure for several decades. In September 2005, Janssen *et al.*[2] reported the structure of the human native C3 — the form of the protein before activation. Now, three papers* starting on page 213 of this issue[3–5] report the first X-ray structures of C3b, the active form of human C3.

Complement C3 is a principal component of the complement system, a large family of blood serum proteins and cell-surface receptors involved in the recognition of pathogens and directing the immune response against them, and in protecting host cells from that reaction. C3 is activated in three ways (Fig. 1, overleaf). In the 'classical pathway', it is guided to its target and activated following specific recognition of the pathogen by antibody[6]. Or, it can be triggered through the actions of lectin, a protein that binds to the sugars found on the surface of many pathogens (the 'lectin pathway')[7]. Finally, in the less specific 'alternative pathway', C3 is spontaneously activated at a low level. This results in 'painting' of tissues unprotected by the cell-surface regulators of complement[8]. The alternative pathway not only initiates C3, but also

*This article and the papers concerned[3–5] were published online on 15 October 2006.

50 YEARS AGO

Lord Halsbury introduced the subject [of automation] by saying that the public is substantially misinformed about it... "The automatic factory and the automatic office," he said, "have arrived, but they are no more than the development of improvements in production that have been going on for many years. The only really new technique which has been injected into industry is the digital computer." He said that automation is most likely to affect the section of industry which produces what are called consumer durables, that is, motorcars, radio, television, washing machines, etc. It is very unlikely to be widely used in heavy engineering, shipbuilding, agriculture, mining, textiles and highly mechanized industries... He believes that although automation will cause men and women to change their jobs and perhaps move to new areas, widespread unemployment is not a danger because in any event changes are unlikely to come about quickly.

From *Nature* 10 November 1956.

100 YEARS AGO

Two events during the past few days have shown that men of science recognise the ability of women to originate and carry out scientific research and inspire others with their spirit. One is that on Thursday last the Royal Society awarded the Hughes medal to Mrs W. E. Ayrton, for her experimental investigations on the electric arc and also upon sand ripples; and the other event is the first lecture delivered at the Sorbonne on Monday by Mme. Curie... The Royal Society, by placing Mrs Ayrton's name alone, and not bracketed with that of a man, in the list of medallists for this year has manifested its recognition of individual work by a woman. The Davy medal was awarded by the society in 1903 to Prof. Curie and Mme. Curie jointly, for their researches on radium, though the published work on the subject shows that the discovery of radium was due to Mme. Curie alone.

From *Nature* 8 November 1906.

50 & 100 YEARS AGO

NATURE|Vol 444|9 November 2006

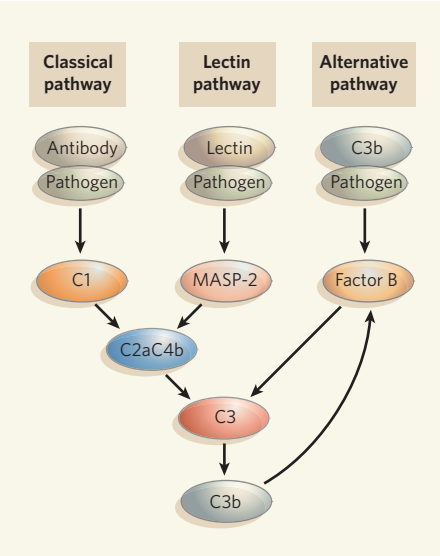

Figure 1 | Complement C3 is activated by three pathways. In the classical pathway, antibody bound to pathogen surface leads to the activation of C2aC4b. This is a 'convertase' enzyme that cleaves C3 into C3a and C3b — the active form (see also Fig. 2). Similarly, the lectin pathway is triggered following recognition of pathogens by the lectin protein, which binds to sugar molecules on their surface. This results in activation of the enzyme complex MASP2 (mannan associated serine protease 2) that forms the C2aC4b convertase. The alternative pathway not only amplifies the classical pathway and the lectin pathway but it can also be activated spontaneously. C3b bound to pathogen surfaces interacts with the blood serum protein factor B, which forms an alternative convertase called C3bBb.

amplifies the other pathways. So, understanding how C3 interacts with initiators of the alternative pathway such as factor B and regulators such as factor H would be of great value.

In the unactivated C3, the thioester warhead is kept wrapped up out of harm's way inside the protein until it is required. In the native C3 structure[2], the thioester domain (TED) is tucked into the body of the protein, beneath the CUB domain (Fig. 2). The protein is triggered when it is cleaved into two fragments, C3a and C3b, and the three papers[3–5] provide striking evidence of how the thioester is exposed at this point. The TED shifts a massive 85 Å following activation, extending out from the body of the protein to resemble a ball on a chain.

This substantial change not only exposes the thioester site, but also opens up binding sites for factor B, which leads to amplification of C3b levels through the alternative pathway (Fig. 1). Notably, sites for complement regulators such as factor H are also exposed along the stretched CUB domain. The interaction with factor H leads to cleavage of C3b within the CUB domain, shutting off further activity and resulting in fragments iC3b and C3c.

But this is not the end of C3's influence — its breakdown products have multiple functions in immunity. C3a, which is released during activation, has potent proinflammatory effects, causing constriction of smooth muscle and activation of leukocyte cells when it binds to cell-surface receptors. The activated product, C3b, is a ligand for multiple receptors including the recently identified CRIg, which helps to get rid of potential pathogens. The structure presented by Wiesmann *et al.*[5] is of C3b in complex with CRIg, and it shows that this interaction shuts off further activity in the alternative pathway by interfering with C5 convertase (the enzyme complex of C3bBb). Notably, it does not seem to interfere with the classical pathway, presumably because of structural differences between the classical- and the alternative-pathway convertases. The authors explored the functional relevance of the C3b–CRIg interaction in a mouse model of collagen-induced arthritis, in which the alternative pathway is a major mediator of injury. Treating the mice with a soluble form of CRIg blocked the arthritis inflammation.

The first product of C3b inactivation, iC3b, is the target of several receptors found on circulating leukocytes, stimulating these cells to engulf pathogens and to activate inflammatory cells. The final breakdown product, C3dg, targets pathogens to surface receptors on B lymphocytes, cells that are vital in ramping up the production of antibodies against the pathogen and in remembering it in case of future encounters[9].

What happens when C3b is not effectively regulated and rapidly shut off? Lessons come from mouse models of immune deficiencies, such as a strain that lacks factor H, where the defunct regulation causes spontaneously active C3, leading to fatal kidney disease[10]. People bearing a genetic variant of factor H have a high susceptibility to age-related macular degeneration, a condition that leaves them blind, presumably because of their limited ability to shut off the active C3b and prevent its amplification by the alternative pathway[11]. A variety of other inflammatory diseases have also been categorized as complement-dependent. Yet there are few generally accepted treatments available to damp this system down.

Now, with the knowledge of the structure of the active form of C3b, there is the promise of therapies to manipulate the complement system. For example, identification of the contact sites of C3b with factor B, which is crucial for initiation of the alternative pathway, should lead to effective inhibitors to block this key interaction. Also, given that the interaction of CRIg with C3b shuts off the alternative pathway, the soluble form of the receptor has potential as a treatment for disorders known to involve the alternative pathway, such as a kidney disorder called membranoproliferative glomerulonephritis type II, and possibly age-related macular degeneration.

Millions of years of evolution provided a great deal of control of the complement system, but it still occasionally runs amok. These structures of C3b could provide us with the means to bring it back in line when it does. ■

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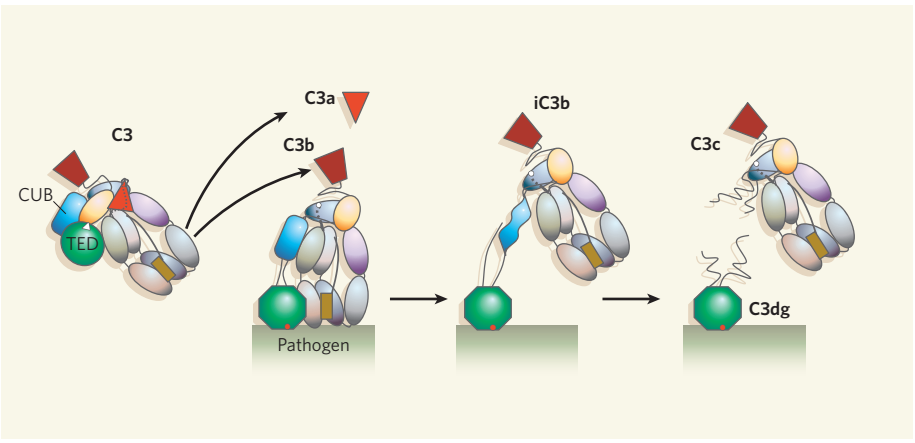

Figure 2 | Breakdown of complement C3. This model is based on the structures reported by Janssen *et al.*[3], Ajees *et al.*[4] and Wiesmann *et al.*[5]. Cleavage of native C3 protein by the enzyme C3 convertase releases C3a and induces a major shift in the overall conformation of the remaining C3b molecule. Full exposure of the thioester domain (TED) facilitates binding of the thioester (red dot) to a target pathogen surface. The opening up of C3b exposes binding sites for components of the alternative pathway such as factor B as well as regulators of complement such as factor H. These regulators aid the sequential degradation of C3b to iC3b, C3c and C3dg. C3c is inactive, but each of the other split products has further functions in immunity.

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