

Inflammation

A nervous connection

Claude Libert

The molecular details of a connection between the nervous system and the inflammatory response to disease have been uncovered. This suggests new avenues of research into controlling excessive inflammation.

Sepsis is a complex, exaggerated and chaotic version of the usually well-organized inflammatory arm of our immune defences, and kills over 175,000 people each year in the United States alone¹. Although a great deal of time and effort has been spent researching septic shock, it remains difficult to understand and treat. One promising lead was provided two years ago, when it was discovered that there is a connection between inflammation and the involuntary nervous system. The details of this link have, however, been unclear — until now. Writing on page 384 of this issue, Kevin Tracey and colleagues² describe how they identified a receptor protein that is stimulated by the nervous system and which in turn inhibits a key molecular mediator of inflammation and septic shock. This receptor might make a good target for future drugs to treat sepsis.

Inflammation has several roles in the body, one of which is to contribute to the immune system's ability to fight off intruding microorganisms. For instance, molecules that are produced during the inflammatory response increase blood flow to infected areas, or help to recruit immune cells. One way in which inflammation is triggered is in response to lipopolysaccharides — components of the cell walls of many bacteria — which activate the immune system's macrophages. These cells in turn release 'alarm' molecules, namely cytokines, some of which have powerful pro-inflammatory properties. Tumour-necrosis factor (TNF) is one such molecule. This protein can affect nearly all cell types, and has a range of biological activities. For instance, it induces the expression of a large number of genes that encode essential inflammatory molecules (such as other cytokines; enzymes that help to break down the barriers between cells, allowing the migration of immune cells; and adhesion molecules that again enhance immune-cell migration)^{3,4}.

As long as TNF production remains confined to the site of infection, the inflammatory response is clearly beneficial. But once bacteria, and consequently TNF, invade the systemic blood circulation, blood 'poisoning' and sepsis can develop quickly. Furthermore, TNF has been found to be a central mediator of chronic inflammatory disorders such as rheumatoid arthritis and Crohn's disease. So there is much interest in learning how to control the production, release and

activity of TNF. Several means of doing so have been developed (Fig. 1), and have seen some success in treating certain inflammatory disorders⁵. For instance, there are drugs that inhibit the transcription of the TNF-encoding gene into messenger RNA, the translation of the mRNA into protein, or the release of the TNF protein. There are also antibodies and soluble receptors that bind to and block TNF once it has been released. But, although the value of these approaches is beyond doubt, they all take time to work — and time is usually short when treating patients with sepsis.

Tracey's research team has been studying TNF since this protein was discovered (see, for instance, ref. 6). Recently, Tracey's group described another level of control of TNF synthesis — namely by means of the vagus nerve⁷ — thereby providing a new and exciting link between the involuntary nervous system and inflammation. This 'parasympathetic' nerve emanates from the cranium and innervates all major organs in a subcon-

scious way. It is finely branched and is composed of both sensory (input) and motor (output) fibres. This is of relevance because it means that the vagus nerve can on the one hand sense continuing inflammation (presumably by detecting cytokines through receptors on the nerve surface), and on the other hand suppress it. This suppression is efficient and, above all, a good deal faster than the mechanisms mentioned above. Tracey's group found⁷ that, after injecting lipopolysaccharides into rats, electrically stimulating the vagus nerve prevented both the release of TNF from macrophages, and death. Conversely, surgically severing the nerve not only removed this protection but also sensitized the animals to lipopolysaccharide.

But how does the vagus nerve have this effect on macrophages? It was already known that, after this nerve is stimulated, its endings release the neurotransmitter molecule acetylcholine with lightning speed. Macrophages express acetylcholine receptors known as nicotinic receptors, and respond to the released acetylcholine (or the acetylcholine-mimicking nicotine) by suppressing TNF release. But the precise identity of the nicotinic receptors on macrophages was not known. From a therapeutic point of view, this is clearly important to know. It's also very difficult to find out, as the receptors are pentamers containing different combinations of a possible 16 monomers.

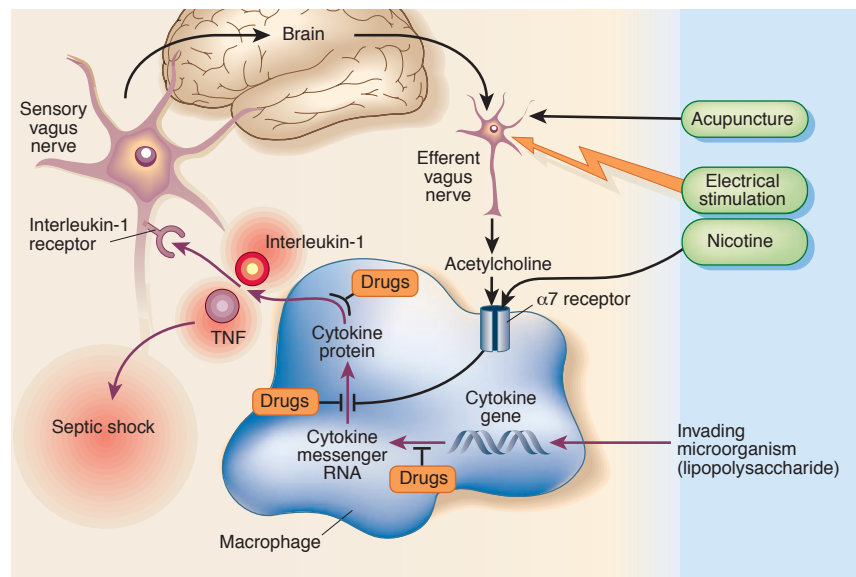


Figure 1 The inflammatory response to microorganisms, and ways of controlling it. Clockwise from lower right: many bacteria contain lipopolysaccharide in their cell walls, which stimulates macrophages. These immune cells then make and release various cytokine ('alarm') molecules, including tumour-necrosis factor (TNF) and interleukin-1. But too much TNF in the blood can be harmful, leading to excessive inflammation and septic shock. Several drugs (orange boxes) inhibit steps in TNF synthesis. In addition, Tracey and colleagues have found that when the vagus nerve detects interleukin-1 (left), it releases acetylcholine (right), which binds to the $\alpha 7$ receptor² on macrophages and inhibits cytokine production. This suggests possible new ways of controlling inflammation: through electrically stimulating the vagus nerve, by acupuncture, or with the use of nicotine (which mimics acetylcholine).

In their latest paper, Tracey and colleagues² pin down the relevant nicotinic acetylcholine receptor: it is one comprising five copies of the monomer $\alpha 7$. They started by using α -bungarotoxin, a molecule that binds to just a subset of receptor monomers, to show that macrophages express the $\alpha 7$ subunit. When the authors blocked the expression of this protein, acetylcholine and nicotine were no longer able to prevent the release of TNF — data that the authors confirmed by studying $\alpha 7$ -deficient mice. In fact, such mutant mice displayed an exaggerated response to lipopolysaccharide in terms of their production of the cytokines TNF, interleukin-1 and interleukin-6. Finally, in a technical *tour de force*, Tracey and colleagues showed that electrically stimulating the vagus nerve of $\alpha 7$ -deficient mice no longer afforded protection against lipopolysaccharide (in contrast to the situation in wild-type mice).

These findings² could have therapeutic implications. The discovery of the connection between the involuntary nervous system and inflammation had already yielded new ideas about treating inflammatory disorders such as sepsis: for instance, a small compound has been developed that can trigger the vagus nerve in rats, thereby reducing inflammation⁸. Looking to the future, it would be interesting to stimulate the vagus nerve electrically in people — as is currently done in thousands of epilepsy patients, showing that the procedure is safe and feasible — and to study the effect on inflammation. More specifically, the new findings suggest that molecules that stimulate the $\alpha 7$ subunit would also be worth developing.

On a different note, nicotine has been found to have powerful immunosuppressive and inflammation-suppressing effects. Of course, the health risks associated with smoking are immense. Yet epidemiological studies indicate that nicotine protects against several inflammatory diseases, such as ulcerative colitis, Parkinson's disease and even Alzheimer's disease. It can also reduce fever and protect against otherwise lethal infection with the influenza virus⁹. The demonstration² that nicotine binds to the $\alpha 7$ subunit on macrophages fleshes out the details of how nicotine produces such effects.

The data also make me reconsider the possibilities and molecular biology of 'alternative' medicine. Pavlovian-type conditioning, hypnosis and meditation are well known (since the beginning of the twentieth century in some cases) to reduce inflammation¹⁰. It might be worth finding out whether these effects, as well as the reported beneficial effects of prayer and acupuncture on inflammation (the last of which is known to depend on acetylcholine)^{11,12}, are mediated by the vagus nerve and the $\alpha 7$ subunit. ■

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Astronomy

Feeding the first quasars

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Quasars, the oldest known objects in the Universe, are powered by gas falling into black holes at their centres. How black holes formed so early in time has been hard to explain, but a new model might have the answer.

The excitement that has, in recent years, accompanied the study of supermassive black holes mirrors the excitement that followed the discovery of quasars in the early 1960s. Quasars — short for 'quasi-stellar objects' — are characterized by a prodigious outpouring of energy: hundreds of times that of a regular galaxy, but produced in a region that is only a few light days or weeks across. Quasars are also among the most distant objects known to astronomers; as such, the light reaching the Earth from them paints an invaluable picture of the history of our Universe. Supermassive black holes have long been accepted as the only viable energy source for quasars, but only now are we beginning to understand the complex connection between black holes and the formation of galaxies.

Quasars are thought to reside at the centres of massive haloes of dark matter — the mysterious, unseen matter that is needed to explain many features of our Universe. Indeed, this is a crucial assumption that underlies some of the most popular models of black-hole formation. On page 341 of this issue, Barkana and Loeb¹ suggest that if a dark-matter halo is pulling gas towards a quasar at its centre, a distinctive signature should be seen in the light reaching us from the quasar. There are few data to go on so far, but if this signature is confirmed, it would provide the first observational evidence that quasars are embedded in great haloes of dark matter.

In the local Universe, there is now airtight evidence for the presence of supermassive black holes in two galaxies — the Milky Way^{2,3} and the nearby Seyfert II galaxy, NGC 4258 (ref. 4). Compelling, although more indirect, evidence of black holes exists for at least two dozen additional galaxies⁵. These supermassive black holes have masses that range from a few million to a few billion times that of our Sun. Their host galaxies are sufficiently disparate in nature that it is now possible to search for connections between their large-scale properties and the masses of

their central black holes. Some connections have already been identified, most notably between supermassive black-hole masses and the velocity distribution of the surrounding hot stellar component^{6,7}. Another connection may exist between the mass of the central black hole and the mass of the surrounding dark-matter halo⁸.

The demographics of more distant supermassive black holes can be inferred from a census of quasars. In the past few years, the Sloan Digital Sky Survey (SDSS) has dramatically increased the number of known quasars at 'high redshift', where redshift is a measure of an object's recession velocity due to the expansion of the Universe. The SDSS^{9–12} has found several quasars with redshifts larger than 5, including the current record holder at a redshift of 6.43. Assuming that these high-redshift quasars are radiating at the Eddington limit (the maximum luminosity that can be sustained by accretion), their luminosities imply central black holes with masses at least several billion times that of the Sun.

It has been pointed out¹³ that at a redshift of 5 we are looking back in time to when the age of the Universe (about 1 billion years) was approximately equal to the dynamical timescale of a typical galaxy — roughly speaking, the stellar orbital time, or the time it takes a galaxy to communicate with itself through its own gravitational potential. Thus, the very existence of quasars at such high redshifts is a challenge to models of structure formation^{14,15}. Although the details vary, the basic assumption underlying virtually all models is that, at all redshifts, the history of supermassive black holes follows the evolution of galactic dark-matter haloes. In particular, the black-hole mass is assumed to scale with halo mass, and black-hole growth proceeds through gas accretion triggered by galaxy mergers.

A relation between black-hole and dark-halo mass is a feature of models that account for supermassive black holes within this 'hierarchical' framework, in which structure