rugations are that they add a valuable tool for measuring the local ring properties: Although the ring's self-gravity has no role in exciting or maintaining the corrugations, the local nodal regression rate due to Saturn's oblateness increases by the extra gravity of ring particles. Hedman *et al*. verify this feeble effect and obtain a new estimate of the C ring's surface density. Concerning the dynamical evolution of the outer solar system, the amount of cometary debris is probably larger than previously anticipated. The rings, with their enormous surface area, thus provide an effective flypaper detector for interplanetary debris.

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CELL BIOLOGY

# Ancient Neurons Regulate Immunity

**The innate immune system of multicellular animals is regulated by the nervous system.**

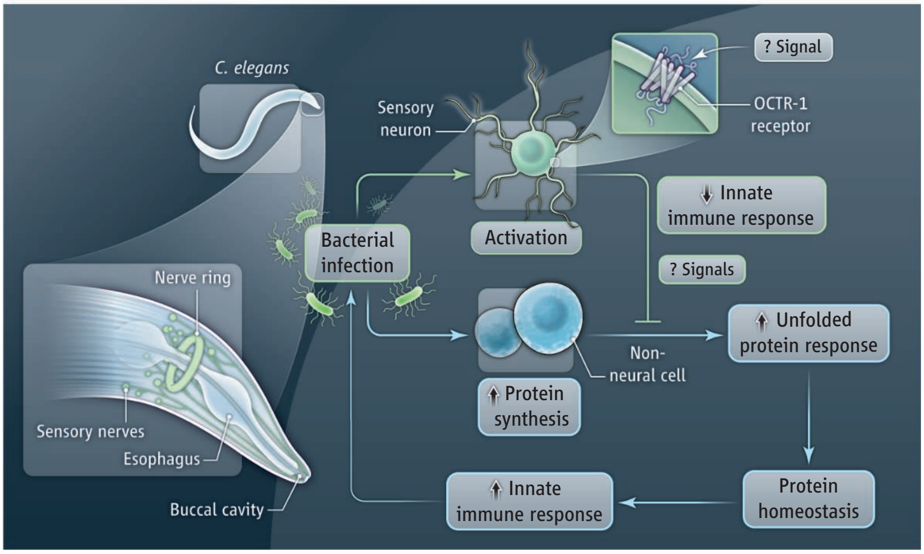
**Kevin J. Tracey**



The most evolutionarily ancient type of immunity, called "innate," exists in all living multicellular species. When exposed to pathogens or cellular damage, cells of an organism's innate immune system activate responses that coordinate defense against the insult, and enhance the repair of tissue injury. There is a modern-day cost associated with these processes, however, because innate mechanisms can damage normal tissue and organs, potentially killing the host. Human life is a balance between dual threats of insufficient innate immune responses—which would allow pathogens to prevail—and overabundant innate immune responses—which would kill or impair directly. What has been the key to maintaining this balance throughout years of mammalian evolution? On page 729 of this issue, Sun *et al*. (*1*) report that neurons in a nematode worm can regulate innate immunity, a mechanism dating back to the early origins of the nervous system itself.

Research on the pathophysiology of infection in the late 20th century revealed that molecules produced by the innate immune system, not pathogens, account for the major physiological, metabolic, and pathological responses to infection in mammals. Cytokines and other molecules were associated with the signs and symptoms of infection, ranging from fever, anorexia, and fatigue, to lethal shock and tissue injury. By understanding the "cytokine theory of disease," it became possible to develop highly selective drugs that neutralize cytokines and experimentally modify the pathophysiology of infection (*2*). This same approach subsequently revolutionized the treatment of inflammatory disease in humans with other, noninfectious, but inflammatory conditions. Today, millions of patients with arthritis, colitis, and other inflammatory syndromes have benefited from therapy with cytokine-blocking agents.

These advances also underscored the importance in understanding mechanisms that control innate immunity and restrain it from injuring the host. Early work focused on soluble factors that control innate immune responses by inhibiting the synthesis or action of cytokines. This "protective mediator" list grew to include glucocorticoid hormones, soluble cytokine receptor fragments, and other anti-inflammatory factors (*3*). More unexpected, however, were later findings that information propagated in neurons controls the magnitude of the mammalian innate immune response. Action potentials traveling in the vagus nerve to the spleen and other organs culminate in the release of acetylcholine, an evolutionarily ancient molecule that effectively inhibits cytokine production by innate immune cells. The cytokine-blocking mechanism requires signal transduction through α7 nicotinic acetylcholine receptors expressed on macrophages and other cytokine-producing immune cells (*4*). Signals generated via this neural circuit tonically suppress innate immunity, because lesions in this pathway enhance the innate immune response to pathogens and injury




**Innate innervation.** Infection of *C. elegans* with a pathogen stimulates the innate immune response and activates the synthesis of new proteins, potentially causing the accumulation of unfolded proteins in host cells. To restore protein homeostasis, the unfolded protein response is activated. ASH and ASI sensory neurons negatively regulate the innate immune response to infection by blocking the unfolded protein response in nonneuronal cells. The OCTR-1 receptor in the sensory neurons is required for this effect.

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