Surviving Ebola virus infection

The immune response to Ebola virus infection in victims and survivors of two Gabon outbreaks provides insight into immunologic determinants of resistance (pages 423–426)

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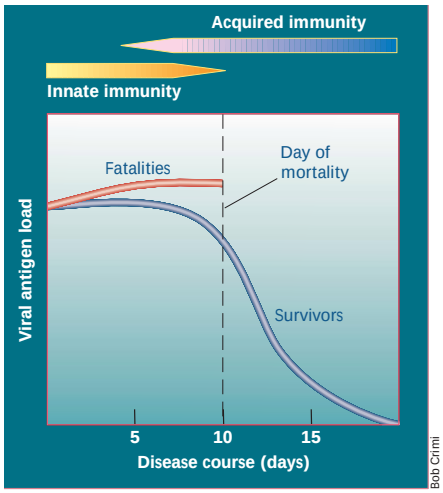
IN THE BEST of circumstances, clinical investigation is difficult. To draw definitive conclusions, well-controlled studies must be done in defined populations, but this is secondary to the obligation to provide care that benefits individual patients. In addition to these limitations, access to patients and the collection of specimens during the relevant time in a disease is often problematic. Such has been the case with studies of Ebola virus infection, which have proven particularly difficult because outbreaks occur in remote locations and because this highly infectious, lethal virus poses substantial risks to medical personnel and scientific investigators. Ebola virus infection causes hemorrhagic fever, a syndrome that begins with flu-like symptoms and progresses rapidly to fever, diffuse bleeding, shock and death[1–3]. Rigorous study of this disease in humans has been nearly impossible, and its immunopathogenesis is poorly understood. For example, determinants of host resistance, mechanisms of viral clearance and prognostic indicators of survival have not been defined. Such information could provide important insights into the natural course of this disease in humans that would facilitate the development of vaccines and antiviral therapies. In this issue of *Nature Medicine*, Baize, Leroy and colleagues have analyzed immune responses in cohorts of patients from two outbreaks in northern Gabon in 1996 (ref. 4). The mortality rates of the epidemics were similar (66% and 75%), and the investigators collected serum and blood samples during these outbreaks from both survivors and non-survivors. Their analyses of immune response and serum biochemical parameters suggest possible mechanisms of protection against this highly pathogenic virus.

Patients who survived showed several features that distinguished them from non-survivors. No difference in the viral antigen load, measured in the serum, was detected in survivors and non-survivors, indicating that host defense rather than inoculum size determines survival. Although non-survivors generated a higher level of gamma interferon (IFN-γ) in the serum early in infection, T-cell cytokine responses, measured by T-cell cytokine RNA levels, were not maintained. In contrast, surviving patients developed more effective antibody responses to the viral nucleoprotein and also generated more sustained T-cell immune responses that persisted into the convalescent phase. Lethal infection was also accompanied by a considerable increase in apoptosis in peripheral blood cells, and cell death increased as disease progressed in fatal cases. This increase in cell death markers correlated with mortality.

These observations are among the most comprehensive analyses of the immune response to Ebola virus infection in humans, and they provide several clues about its pathogenesis. Several similarities between human disease and relevant animal models were found. For example, in guinea pigs immunized with the Ebola virus gene products, successful protection against lethal challenge involves T cell-dependent immune responses[5]. As with immunization in the guinea pig, the nucleoprotein response in humans is mainly humoral, and immunoglobulin production to the viral proteins GP and soluble GP is minimal, although T-cell immunity to these antigens is generated. The findings by Baize *et al*. in infected humans[4] are thus consistent with those in the vaccine model in rodents[5]. The generation of antibody responses correlated with survival in the guinea pig and probably reflected successful T-cell responses that stimulate production of antibody[5], as is suggested now for humans[4]. It is not certain whether the ability to counteract early infection is due to this T-cell immune response in natural infection, and it is possible that an inflammatory response or innate immunity is involved. In addition to these immune parameters, the authors also analyzed levels of apoptosis in peripheral blood cells. These markers reflect the death of immune and non-immune cells. Although the death of immune cells probably contributes to the demise of patients, the significance of this finding is not entirely evident. Apoptosis often accompanies antigen stimulation, particularly when proliferating lymphocytes are deprived of growth factors. As noted by the investigators, these markers of apoptosis could be derived from inflammatory cells, such as monocytes, or endothelial cells. Both cell types are productively infected in primate models of this disease[6–8]. Despite these valuable observations regarding the immune response and its relationship to the progression of the disease, many questions remain. Enhanced apoptosis of lymphocytes has not been demonstrated directly. If this occurs, it will be important to define which subsets are affected and by what mechanism, as the virus does not efficiently infect lymphoid cells[9,10]. The mechanism by which innate immune or inflammatory responses control viral replication in early stages of this disease requires further definition, and the point at which acquired immunity becomes effective has not yet been determined.



Viral load and immune responses during actue Ebola virus infection.

The remarkable inverse correlation between the serum IFN-γ levels and mortality indicates that this marker may be useful in predicting the outcome of infection. Semi-quantitative PCR analysis may also be helpful. In the absence of effective therapy, the utility of this information is limited; however, antiviral compounds are being investigated[11] and may prove useful in the future. In the interim, Baize, Leroy *et al*. have provided insight into the

natural history of the immune response to infection by this highly pathogenic virus. Successful immune protection and vaccination against viral infections other than Ebola have been demonstrated in humans. Despite these successes, the specific contribution of innate and acquired immune responses to viral infections in general remain poorly understood[12,13]. Ebola virus infection can be regarded as a paradigm for other viruses and for other infectious causes of hemorrhagic fever. Such information will help to unravel the pathophysiology of this aggressive infection and will contribute to strategies for vaccine development and treatment.

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Mahogany adds color to the evolving story of body weight regulation

Cloning of the *mahogany* gene opens new avenues for the study and treatment of obesity.

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MELANOCORTIN SIGNALING HAS been recognized for years mainly for its ability to darken skin and fur color; now it seems to be an essential component of normal body weight maintenance (reviewed in refs. 1,2). Adding to this new understanding of the melanocortin system is the positional cloning of the mouse *mahogany* gene by two groups, reported in the 11 March 1999 issue of *Nature*[3,4]. Interaction of this gene with the melanocortin system was originally suggested because *mahogany* mutations darken coat color—hence its colorful name. The paper by Gunn *et al*.[3] now demonstrates that *mahogany* is widely expressed in human tissues and that it is a close relative of attractin, a recently discovered immunoregulatory protein made by human T lymphocytes. But mahogany also influences energy homeostasis. The report by Nagle *et al*.[4] shows that *mahogany* is expressed in the hypothalamus and that *mahogany* mutation can prevent diet-induced obesity in mice. These findings support the idea that mahogany affects melanocortin signaling both in hair follicles and brain[5].

Most mammals maintain a relatively constant level of body fat over time, despite highly variable energy requirements and sometimes intermittent availability of food. As body fat mass is determined mainly by cumulative differences in energy intake and expenditure, stability of the adipose depot implies an active matching of the two sides of the energy balance equation. For nearly half a century, investigators have puzzled over a possible mechanism, wondering if obesity arises from defective energy homeostasis rather than from a gluttonous personality.

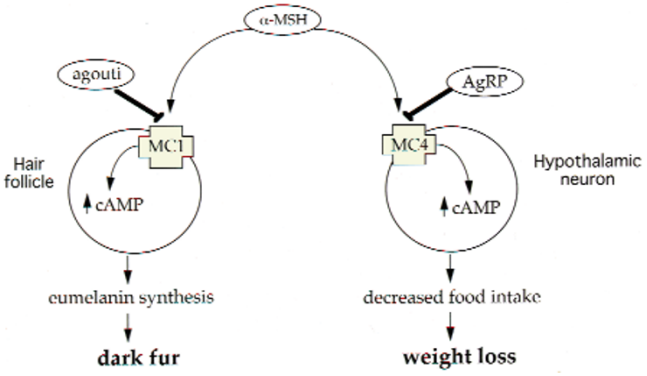

Fig. 1 Melanocortin (MC) signaling in skin and brain. Reduced MC1 receptor signaling induced by agouti causes yellow coat color; reduced MC4 receptor signaling induced by AgRP causes hyperphagia and obesity. ∝-MSH, ∝-melatonin-stimulating hormone; AgRP, agouti-related protein.

In recent years, a remarkable series of discoveries has established that body adiposity is indeed highly regulated, convincing many that new drugs for obesity treatment are on the horizon. Among the new arrivals in the panoply of hypothalamic peptides that control food intake are the melanocortins. Melanocortins are peptides such as ∝-melanocyte stimulating hormone (∝-MSH) that are cleaved from the pro-opiomelanocortin precursor. These peptides mediate pleiotropic effects as ligands for melanocortin (MC) receptors, a family of G_s-coupled receptors, of which five isoforms are known. For example, circulating ∝-MSH (secreted by the pituitary gland) acts on cutaneous MC1 receptors to promote pigmentation of skin and fur, whereas in the hypothalamus, neuronal release of ∝-MSH activates MC4 receptors and thereby reduces food intake. An essential role for melanocortins in weight regulation was established when mutation of the MC4 receptor was shown to cause obesity, first in mice[6] and then in humans[7,8]. A unique feature of the melanocortin system is the existence of two related proteins that block the effect of ∝-MSH at melanocortin receptors, called agouti (usually made in skin) and agouti-related protein (AgRP, made in the hypothalamus). Agouti's physiological role is to lighten coat color by antagonizing the ac-