

## ANTIVIRAL IMMUNITY AND PATHOGENESIS

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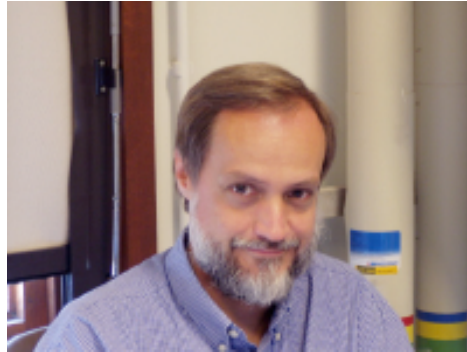
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*The possibility for evolved organisms to survive viral infections depends on the ability of their immune system to eliminate the infectious agent. Therefore, numerous mechanisms, involving different types of immune cells such as cytolytic lymphocytes, T helper and B lymphocytes and macrophages, the molecules that allow those cells to communicate, namely the lymphokines, and the products of those interactions, including antibodies, have been elaborated. On the other hand, viruses have developed strategies to escape the immune system of their hosts, such as frequent mutations or latency, or even to impair this system, which often leads to diseases such as autoimmunity or immune deficiencies. Our project is to investigate, in murine models, some aspects of these relations between viruses and the immune system.*

### **Viral infections result in a dramatic increase in the proportion of IgG2a**

Of particular interest is the fact that all antibody responses are not equal. Indeed, depending on their isotype, immunoglobulins display various properties. For example, IgG1, one of the major IgG subclass in mice, cannot activate the complement system, in contrast to IgG2a, another major isotype of murine immunoglobulins. Such a difference may lead to dramatic variations in the functional effect of antibodies, as their ability to lyse cells they have bound. During the last few years, we found that the isotype of antibody responses was influenced by concomitant viral infections. The effect of the virus resulted in a dramatic increase in the proportion of IgG2a, not only in antiviral antibodies, but also in immunoglobulins with an antigenic target unrelated to viral proteins. A dual regulation of antibody responses by gamma-interferon and interleukin-6 explains this isotypic bias (1, 2). In the case of antiviral antibodies, a possible explanation for this phenomenon could be the selection by the infected host of the most appropriate response against the virus. Using a model of infection with lactate dehydrogenase-elevating virus (LDV), we could demonstrate that IgG2a antiviral antibodies are indeed more efficient than other

isotypes to protect mice against a fatal polioencephalomyelitis induced by the virus (3, 4). The advantage for the host to select IgG2a in non-antiviral responses is more difficult to understand. In addition, the modification of the isotype of antibodies reacting with self-antigens could potentially lead to more deleterious autoimmune reactions. This property of viruses to enhance selectively the production of one immunoglobulin isotype could depend on the preferential activation of a subset of T helper lymphocytes (5, 6). Indeed, different subpopulations of those cells, called Th1 and Th2, respectively, are distinguished in particular by their capability of producing selectively interferon- $\gamma$  (IFN- $\gamma$ ) or interleukin-4, which can selectively trigger B lymphocytes to produce IgG2a or IgG1, respectively.

### **Activation of natural killer cells**

Many of the influences that viruses may have on diverse immune responses can be explained by the production of pro-inflammatory cytokines (7), including IFN- $\gamma$ . Therefore, our analysis of the relationship between viruses and the immune system has focused on the activation, by LDV, of cells from the innate immune system that are able to secrete this cytokine, namely the natural killer (NK) cells.

Within a few days after infection, a strong

and transient NK cell activation, characterized by accumulation of this cell population in the spleen, by enhanced IFN- $\gamma$  message expression and production, as well as by cytolysis of target cell lines was observed. Because NK cells and IFN- $\gamma$  may participate in the defense against viral infection, we analyzed their possible role in the control of LDV titers, with a new agglutination assay. Our results indicate that neither the cytolytic activity of NK cells nor the IFN- $\gamma$  secretion affects the early and rapid viral replication that follows LDV inoculation (8).

### Activation of macrophages

Activation of cells of the innate immune system includes also macrophages and leads to an enhanced phagocytic activity, with potential detrimental consequences for ongoing autoimmune diseases (9). We have thus analysed whether it was possible to modulate such an activation by treating infected mice with clodronate-containing liposomes. Administration of anti-erythrocyte monoclonal autoantibody to mice resulted in the development of a transient hemolytic anemia. Infection with LDV simultaneously with autoantibody injection was followed by a dramatic enhancement of the anemia, leading to the death of most animals. This viral infection induced an increase in the ability of macrophages to phagocytose *in vitro* autoantibody-coated red cells, and an enhancement of erythrophagocytosis in the liver. Treatment with total immunoglobulin G (IVIg) attenuated the autoantibody-induced disease in uninfected mice, but not in LDV-infected animals (10). In contrast, administration of clodronate-containing liposomes resulted in a delay and a decrease of anemia in LDV-infected mice. This treatment decreased also the *in vitro* phagocytosis of autoantibody-coated red cells by macrophages from LDV-infected animals. Thus, regulation of macrophage activation results in modulation of autoantibody-mediated anaemia and may be considered as a possible treatment for autoimmune diseases that involve phagocytosis as a pathogenic mechanism.

### Selected publications

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