INTRODUCTION

The immune system is of central importance in the course of viral diseases and increasing evidence suggests that this is also true for viral hepatitis B and C. On the one hand immune responses to viral antigens are believed to be responsible for viral clearance in acute hepatitis B and C, and on the other hand, if they fail to eliminate or control the virus, they most likely cause chronic inflammatory liver disease. The uncompromised human immune system is equipped with humoral and cellular components, that in most viral infections can eliminate the virus or at least achieve viral control. In the natural course of viral hepatitis, however, persistence of the infecting virus is common and numerous observations suggest that both viral and host factors may contribute to viral persistence. Since HBV and HCV are non-cytopathic viruses, liver tissue damage in chronic hepatitis is the result of a permanent inflammatory process within the liver mediated by effector cells of the immune system which obviously cannot eliminate the virus-infected hepatocytes and therefore cannot terminate infection. The decisive role of the immune system becomes evident in acute hepatitis B and C virus infection when the immune system of the infected host holds the key to decide whether there will be viral clearance or control and self-limited disease or viral persistence and chronic hepatitis. Although acute infection displays similar features in hepatitis B and C there are numerous and not only virologically important differences in the course of both viral infections. In acute hepatitis B infection, at least in healthy adults, only a minority (5–10%) of infected individuals will develop chronic disease. In acute hepatitis C infection the majority will run an asymptomatic course of disease that in about 85% will progress to chronic hepatitis. Only those patients who display symptomatic acute hepatitis C, however, clear the infection in about 50%, suggesting that a vigorous immune response contributes to viral clearance in these patients.

Medical strategies have focused on prevention, and sophisticated antiviral treatment has been developed for both virus infections. Potent prophylactic vaccines
IMMUNOLOGY AND LIVER

for hepatitis B are increasingly available all over the world and, as shown by results from research into antiviral immune responses, first trials with therapeutic T cell vaccines in patients with chronic HBV infection are being conducted.

A decade after the identification of hepatitis C virus as the causative agent of most cases of transfusion-associated and community-acquired non-A non-B hepatitis, research efforts in different fields from laboratories throughout the world have contributed towards a substantial improvement in our knowledge of HCV, and have helped to prevent new infections. However, a protective vaccine for HCV remains to be developed.

This chapter will introduce the participants of the immune response in viral hepatitis, but will focus on the key players in acute and chronic viral hepatitis, the virus-specific T lymphocytes.

IMMUNOLOGICAL EFFECTOR MECHANISMS

Antibodies

Virus-specific antibodies of different immunoglobulin subclasses to distinct viral proteins define the course of infection with hepatitis B virus and enable us to differentiate between acute, chronic and self-limited infection. In contrast antibodies against anti-HCV are detectable during the chronic course of HCV to each structural and non-structural – protein. However, there is no pattern of anti-HCV antibodies known so far which indicate the stage of infection (acute vs chronic) or confer immunity. This is consistent with the observation of HCV reinfection in chimpanzees after viral challenge with the same strain (See ref. 23). The presence of antibodies directed against certain epitopes within the hypervariable region 1 (HVR1) of the E2 protein have been shown to principally display neutralizing activity in patients and chimpanzees, but their neutralizing capacity and their contribution to viral clearance or evolution of disease is still under debate\textsuperscript{1-3}. Finally the decline of HCV core-specific IgM antibody titres during successful interferon-alpha-induced viral elimination argues against a decisive role of antibodies in viral elimination\textsuperscript{4}.

Antigen presenting cell

The cellular components of the immune response (Figure 1) consist of specific antigen-presenting cells, B and T lymphocytes. In order to induce a strong immune response antigens have to be presented by antigen-presenting cells (APC). The most potent APC appear to be the highly specialized dendritic cells (DC) which present antigen as peptides to CD4\textsuperscript{+} T helper cells via HLA class II molecules or to CD8\textsuperscript{+} cytotoxic T cells via HLA class I in combination with co-signals. DC are classified according to their stage of development into immature and mature DC. Immature DC are present in most tissues and capture antigen in a very effective manner (e.g. by phagocytosis, endocytosis, and by viral infection). Antigen itself supports the maturation process of immature DC which then migrate into the T cell areas of lymphoid tissues (i.e. lymph nodes) and complete their maturation. Mature DC attract and prime T cells and may be of great importance for the maintenance of a long-lasting T cell response.