Current status of immunomodulatory therapy in chronic hepatitis B, fifty years after discovery of the virus: Search for the "magic bullet" to kill cccDNA.

Abstract:
Chronic hepatitis B (CHB) is currently treated with IFN-α and nucleos(t)ide analogues, which have many clinical benefits, but there is no ultimate cure. The major problem consists in the persistence of cccDNA in infected hepatocytes. Because no antiviral drug has been evaluated which significantly reduces copies of cccDNA, cytolytic and noncytolytic approaches are needed. Effective virus-specific T- and B-cell responses remain crucial in eliminating cccDNA-carrying hepatocytes and for the long-term control of HBV infection. Reduction of viremia by antiviral drugs provides a window for reconstitution of an HBV-specific immune response. Preclinical studies in mice and woodchucks have shown that immunostimulatory strategies, such as prime-boost vaccination and PD-1 blockade, can boost a weak virus-specific T cell response and lead to effective control of HBV infection. Based on data obtained in our preclinical studies, the combination of antiviral drugs and immunomodulators may control HBV viremia during a patient's drug-off period. In this article, we review current immune-modulatory approaches for the treatment of chronic hepatitis B and the elimination of cccDNA in preclinical models. This article forms part of a symposium in Antiviral Research on "An unfinished story: from the discovery of the Australia antigen to the development..."
of new curative therapies for hepatitis.

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