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INSIGHTS

Neutralizing hepatitis B

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Despite an effective vaccine, hepatitis B virus (HBV) remains a major public health threat since chronic infection leads to liver disease and cancer. Hehle et al. (https://doi.org/10.1084/jem.20200840) discovered human-derived antibodies that potently neutralize the virus. Will this help a cure?

According to estimates by the World Health Organization, ∼3% of the world's population are chronically infected with hepatitis B virus (HBV), a disease that has been preventable by vaccination for the past 40 yr. 90% of infected people are unaware of their infection status, and <2% are being treated. HBV is transmitted by blood and other bodily fluids and can cause both acute and chronic disease. Perinatal or early infections (first 5 yr of life) are most likely to become chronic, while the opposite is true for those infections that occur during adulthood. Diagnosis often happens late when complications emerge, and a quarter of the chronically infected individuals will go on to develop life-threatening diseases such as cirrhosis and cancer of the liver. Antiviral agents (nucleoside/nucleotide analogues and peginterferons) are effective at suppressing HBV replication. However, they require lifelong treatment, may lead to development of resistance, and are not broadly available in low-income countries. Achieving a cure remains challenging.

Lymphocyte-mediated immunity is important for HBV control and clearance (Bertoletti and Ferrari, 2016; Corti et al., 2018; Ma et al., 2019; Maini and Burton, 2019). The role of virus-specific T cell responses, both CD4 and CD8, is well established. More recently, a significant role for B lymphocytes and the antibodies that they produce has also emerged. For example, HBV reactivates in some HBV controllers undergoing B lymphocyte depletion as part of treatment for lymphoma or autoimmune disease (rituximab). Furthermore, administration of hyperimmune anti-HBV antibody preparations decreases perinatal transmission in chronically infected mothers. A number of laboratories have obtained anti-HBV monoclonal antibodies using phage display methods, humanized mice, or human donors in a few cases, and it was shown that single monoclonals against the virus surface antigen (HBsAg) can in fact be sufficient to reduce infection. However, the molecular features of large collections of antibodies that develop in multiple donors following natural HBV infection or vaccination have not been previously reported.

This task was embraced by Hehle et al. (2020), who report in this issue of *JEM* on the antibodies to HBsAg that were derived from >3,000 virus-specific memory B cells of 14 individuals, including vaccinees and those who spontaneously cleared chronic HBV. Similar to other human infections, IgG memory B cells that bound to HBsAg were rare in peripheral blood. Analysis of their antibody sequences revealed that most of them were somatically mutated, clonally expanded, and preferentially used certain immunoglobulin heavy chain gene segments (IGHV1-69, IGHV1-18, and JH4).

The majority of the antibodies that were cloned and recombinantly expressed by Hehle et al. (2020) recognized conformational rather than linear viral epitopes and displayed neutralizing activities in vitro, with very variable potency (half-maximal inhibitory concentration [IC50] values spread over 9 logs). Of note, outstandingly potent antibodies (IC50s in the low pg/ml range) were found in both vaccinated and naturally infected donors. Remarkably, the three most potent antibodies (IC50s below 1 pg/ml) were all from individuals who naturally cleared the infection. These antibodies are several orders of magnitude more potent than some of the antibodies currently being tested in the clinic, such as libivirumab and tuvirumab. In a mouse model, viremia was transiently reduced by ∼2 logs when the best antibodies were administered in high amounts (0.5 mg/mouse). At even higher doses of antibodies (1 mg/mouse), HBV DNA levels fell below the limit of detection in most mice and for up to a week. Thus, single human-derived monoclonal antibodies to HBsAg can potently suppress HBV in vivo.

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Besides potency, a desirable feature when selecting antibodies for clinical development is their breadth of neutralization: their ability to neutralize antigenic variants of the same virus. At least four serotypes and 10 genotypes of HBV exist worldwide, which are distinct also at their HBsAg sequence. Mouquet's team evaluated their antibodies for cross-reactivity, and about half of them bound to HBsAg proteins corresponding to 9 out of the 10 genotypes. Moreover, one lead antibody neutralized four out of four genotypes that were tested. Importantly, a common escape mutation (G145R) was also recognized by several of the antibodies. Altogether, these findings indicate that, in addition to potency, breadth of neutralization can also be achieved. Hence, the discovery of exceptionally potent neutralizing antibodies from HBV controllers suggests that they could play a role in the spontaneous clearance that occurs in a fraction of HBV infections. Some of the potent and broadly reactive monoclonal antibodies reported by Hehle et al. (2020) hold promise for clinical deployment.

The findings reported by Mouquet's team are complementary to a recent study by Wang et al. (2020) describing antibodies derived from vaccinees and spontaneously recovered individuals who were selected out of ∼140 donors for their high serum neutralization potency against HBV. Notably, we identified in multiple donors clones of antibodies to HBsAg with recurrent combinations of immunoglobulin heavy and light chain genes and with closely related CDR3 sequences. Specifically, antibodies were discovered with either IGHV3-30, IGHV3-33, or IGHV3-23 heavy chains combined with IGLV3-21 light chain. In addition to broadly recognizing different serotypes, select antibodies were potent neutralizers in vitro (IC50 as low as 5 ng/ml). In comparison to Hehle et al. (2020), no antibodies were identified with sub-ng/ml IC50s, although neutralization was measured by different assays. In vivo, the antibodies studied by Wang et al. (2020) conferred complete protection of mice in a pre-exposure prophylaxis model. In the setting of established infection, mice infused with a single antibody had ∼3 logs reduced viremia compared with controls, although virus escape (G145R) was observed after several weeks of treatment with monotherapy. In contrast, administration of a cocktail of two antibodies that recognize distinct epitopes on the virus was effective at suppressing viremia and prevented virus escape.

In sum, the discovery by Hehle et al. (2020) and Wang et al. (2020) of very potent antibodies from natural controllers adds significantly to the evidence supporting an important role for B cells in the pathogenesis of HBV. This prompts the question of whether the antibody response helps determine if acute HBV infections will resolve or become chronic, and if chronic infections will be controlled. The antibody repertoire changes with age (Jiang et al., 2013); is that why infections during infancy are more likely to result in chronic disease? Antibody genes are highly polymorphic (Watson et al., 2017); could this partly explain why some individuals succeed while others fail at clearing the infection? Apart from questions related to disease pathogenesis, more basic biology questions pertaining to the molecular mechanism by which antibodies neutralize HBV remain to be answered. This will likely require detailed structural studies to provide new insights.

In stark contrast to the broad clinical use of monoclonal antibodies in the arenas of cancer and autoimmunity (Chan and Carter, 2010; Weiner et al., 2010), only one antiviral monoclonal antibody is clinically approved (palivizumab, against respiratory syncytial virus, since 1998). Monoclonals are currently being developed and show remarkable efficacy in preclinical and clinical studies against a broad range of viral infections, from HIV-1 to Ebola, Zika, SARS-CoV-2, and more (Caskey et al., 2019; Salazar et al., 2017; Van Rompay et al., 2020). Several anti-HBV monoclonals are currently undergoing clinical evaluation. Because of their potency and breadth of neutralization, the human-derived antibodies reported by Hehle et al. (2020) and Wang et al. (2020) add to the list of promising candidates for clinical development.

Over 250 million people are living with HBV and are at risk of severe health complications. Safe and efficacious HBV vaccines exist, but they are not reaching everyone and there is increasing resistance to vaccination in some populations. Thus, sustained progress toward finding a cure for HBV is needed. Monoclonal antibodies may contribute to this effort, either as a standalone approach or in combination with existing therapies.

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