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Commentary

Development of an Allergy Immunotherapy Leads to a New Type of Hepatitis B Vaccine

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Hepatitis B is an old disease and the possibility to successfully vaccinate against infection by hepatitis B virus (HBV) was first shown 36 years ago in a convincing trial (Szmuness et al., 1980). Thus, it may appear unspectacular when in this issue of *EBioMedicine*, a small clinical trial with a new type of hepatitis B vaccine is described (Cornelius et al., 2016). Do we really need this? But the significance of the paper should not be underestimated. The classical hepatitis B vaccine is produced in genetically transformed yeast cells and consists of 20-nm-large particles formed by the small (S) protein of hepatitis B surface antigen (HBsAg). The antibodies against conformational epitopes of HBsAg (anti-HBs) neutralize the infectivity of hepatitis B virus (HBV) in vitro and indicate protection in vivo. However, the classical vaccine has some shortcomings. In spite of multiple injections some persons remain unprotected, particularly those with a weakened immune response. Furthermore, asymptomatic infections by heterologous HBV genotypes with transient viremia are frequent in vaccinated subjects with low or moderate anti-HBs titers (for review see Gerlich, 2015). While the WHO, public health authorities and the main producers of hepatitis B vaccines still consider these drawbacks as insignificant, an enhanced protective capacity against a wider HBV genotype spectrum would not hurt.

A weakness of the current HBV vaccines is that they were designed at a time when the S protein was believed to be the only component of the viral envelope. Soon after, two related, larger HBV envelope proteins (L for large and M for middle) were discovered (Heermann et al., 1984). L protein consists of the S sequence and an amino-terminal preS part which is further divided into preS1 and preS2. PreS2 forms the aminoterminal part of M. The preS1 domain of L was identified as the species-, liver- and differentiation-specific attachment site of HBV to liver cells (Glebe et al., 2005). Currently, a not widely used vaccine is available which is expressed in mammalian cell cultures and contains small amounts of M and L protein as minor components of S-HBsAg particles. It has superior immunogenicity (Shouval et al., 2015), but it remains open whether this is due to the preS components or to better immunogenicity of the S part. Isolated preS antigen without HBsAg had generated neutralizing antibodies in experimental animals (Neurath et al., 1986) but was never administered to human recipients as a vaccine until the study performed by Cornelius et al. It is an irony of medicine history that this study was not intended to improve immunization against HBV but is a side product during the development of an immunotherapy against grass pollen allergy. The Valenta group fused DNA sequences encoding grass pollen allergen-specific peptides to the preS sequence, expressed this construct in *E. coli*, and obtained after purification a vaccine called BM32. This vaccine was adsorbed to aluminum hydroxide and given in doses of 10–40 μg (similar to the classical hepatitis B vaccine) to 30 human subjects. BM32 satisfied the expectations as grass pollen allergy immunotherapeutic, but the question of the current paper was: what was the effect of the preS carrier protein? Soluble monomeric proteins like the preS antigen are usually weak immunogens, but the data suggest that the antibody and T-cell responses against preS partial peptides are comparable to those against the classical HBsAg although no direct comparison was done. It remains open whether the allergen components changed the immune response against preS. It should be noted that a partial lipopeptide of preS1 linked with aminoterminal myristic acid is able to compete with natural HBV for its receptor and is used as the candidate drug Myrcludex in clinical studies for patients with chronic HBV and hepatitis delta virus infection (Blank et al., 2016); but this drug candidate is not a vaccine.

Remarkably, Cornelius et al. report for the first time HBV-neutralizing antibodies in all seven so-far tested human recipients of the BM32 vaccine, i.e., of preS antigen without other HBV antigens. Assay of neutralizing antibodies has been difficult because for long time the only HBV-susceptible cell cultures were human, ape or Tupaia hepatocyte explants which are of very limited availability. Since it is known that the preS1 attachment site binds to the sodium-dependent taurocholate cotransporting peptide (NTCP), a bile acid transporter which mediates entry of HBV (Yan et al., 2012), it became possible to create NTCP-expressing hepatic cell lines susceptible for HBV which the authors have applied. The number of the vaccine recipients evaluated is small and no titers were determined, but the data are sufficient to

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conclude that preS antigen alone can induce HBV-neutralizing antibodies.

The construct contained both preS1 and preS2. The N-terminal part of preS1 is the binding site for NTCP, and antibodies against this part were shown to neutralize HBV (Glebe et al., 2003; Bremer et al., 2011) while the C-terminal part is immunogenic but does not induce neutralizing antibodies. The preS2 part is nonessential for HBV and antibodies against preS2 may be dispensable, but the preS2 part may provide T helper epitopes. An important reason to focus on preS1-based hepatitis B vaccines is the fact that L protein is enriched in the HBV particle while the S and M protein are most abundant on noninfectious HBsAg particles (Heermann et al., 1984). These are present in 3000-fold excess and may consume the neutralizing antibodies against them. Contrary to the protective HBsAg epitopes, the preS epitopes are sequential, relatively well conserved between the HBV genotypes and have not yet been subject to escape mutations. It appears possible that the paper from Cornelius et al. may encourage the field to re-vitalize research on hepatitis B vaccines.

Disclosure

The authors declare no conflict of interest.

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