Commentary

“Dual use”: The anti-allergy vaccine BM32 and its HBV carrier protein

Wolfram H. Gerlich

Institute for Medical Virology, Justus Liebig University Giessen, Schubert Str. 81, Giessen D35392, Germany

In this article of EBioMedicine, Rudolf Valenta and colleagues report on the antibody response to the hepatitis B virus (HBV) component induced by their experimental vaccine BM32 [1]. Originally, the primary purpose of this vaccine was protection against allergenic peptides of grass pollen. The combination of allergy-related peptides with the preS domain of HBV may appear strange. However, in view of this and a previous paper the approach appears logical [2]. The first paper on the use of preS protein as carrier, in this case for a cat allergy antigen explained the rational as follows: "This approach is based on the selection of allergen-derived peptides that lack IgE reactivity and IgE-mediated allergic activity and exhibit reduced T-cell reactivity. Coupled to a non-allergen-related carrier, they should then lead to a vaccine that induces allergen-specific IgG with T-cell help from carrier-derived epitopes."[3] Generation of such a vaccine can be well achieved by expression of fused allergen- and carrier-encoding DNA sequences. It would appear plausible to use an immunogenic carrier which has already safely and successfully been used like the current “recombinant” HBV vaccine.

However, the group selected the preS domain of the large HBV surface protein (LHBs) as carrier. LHBs was the last surface protein which was identified in the HBV envelope. “PreS” does not mean a precursor function for a protein, it is just upstream of the S gene [4]. Initially, preS was neglected as component of HB viruses. In contrast, the small surface protein of HBV (SHBs) has been used since decades as extremely effective prophylactic vaccine [5]. SHBs vaccines have a certain weakness with regard to the presentation of T cell epitopes because the highly hydrophobic, complex-folded and strongly disulfide-crosslinked SHBs protein is not well processed in antigen-presenting cells. The detection of the small hydrophilic preS2 domain in the middle-sized HBV surface protein (MHBs) suggested to increase the immunogenicity of HBsAg vaccines by inclusion of the preS2 domain which could indeed overcome nonresponsiveness to SHBs in certain mouse strains by increased induction of T helper cells [6]. PreS2-containing vaccines have been used in humans for several years but they are no longer used [7].

The entire preS domain (i.e. preS1 and preS2, as in BM32) of LHBs finally was shown to contain an attachment site of HBV to hepatic cells. This discovery immediately suggested to use the preS attachment peptide as prophylactic immunogen. Thereafter, at least two vaccines containing preS and SHBs were developed and were superior to the standard vaccines in large trials [7]. However, these preS vaccines are currently not on the market. One disadvantage of these vaccines is the expression in mammalian cell lines whereas the SHBs vaccine can be inexpensively produced in yeast. The Valenta group recognized the preS protein as preferable carrier for anti-allergen vaccines because it can be easily expressed in E. coli and provides the needed T cell epitopes.

In this article of EBioMedicine, the intensity and fine specificity of the antibody response to preS are described in detail. PreS contains several strong T cell epitopes and B cell epitopes within the HBV attachment and accessory domain. Thus, it is not surprising that BM32 induces high antibody titers against the attachment and accessory domain. In the preceding article, the group provided proof of principle for the HBV infectivity-neutralizing capacity of the BM32 antibody response in a small number of human recipients [2]. Now, they present quantitative data on the concentration of attachment and accessory domain-specific IgG1 and IgG4 antibodies from 76 recipients of BM32 and used for their immune assays peptides covering these sites derived from the 8 known HBV genotypes A-H. No significant differences in the amounts of antibodies against preS peptides from the various genotypes were noted although BM32 contains the preS only from subgenotype A2 and some variability exists between the genotypes in the region preS (1–51). The amounts of induced antibodies, >10 μg/ml up to 1.8 mg/ml, suggest that they may neutralize infectious inocula in exposed patients. But confirmation of this hypothesis requires much more work, e.g. in vitro neutralization assays using susceptible hepatic cell lines, in vivo assays in humanized mice and finally larger trials in humans.

However, the authors put emphasis on BM32 as a candidate for immunotherapy of chronic HBV infection (CHB). An effective immunotherapeutic agent would be highly desirable in view of the difficulties to reach a permanent or so-called “functional cure” of CHB by current HBV therapies with reverse transcriptase inhibitors [8]. However, these therapies suppress production of infectious HBV particles. Thus, it is open whether the very good production of potentially neutralizing anti-HBV antibodies induced by BM32 would add much benefit to the current therapies, even if immunotherapy with BM32 could overcome the immune tolerance to HBV surface antigens in CHB patients. However, the HBV T cell epitopes of BM32 may help to

E-mail address: wolfram.h.gerlich@viro.med.uni-giessen.de

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build an antiviral cellular immune response which could support reaching the desired “functional cure”. PreS by itself is weakly immunogenic, being a small, non-conformational, monomeric protein. PreS has recently been coupled to highly immunogenic ferritin particles and led as therapeutic vaccine to functional cure in a CHB-mouse model [9]. However, for an anti-allergy vaccine a more moderate immunogenicity may be preferable and even for an CHB immunotherapy an overly immunogenic vaccine may precipitate severe immune pathogenesis. Comparing BM32 with other potential pre-clinical candidates for CHB immunotherapy, it has the huge advantage that it has practically passed phase I and II trials in healthy human populations. But it remains to be seen whether it can become a true candidate for clinical trials in CHB patients.

More realistic may be the complementation of the current prophylactic HBV vaccines by BM32 because there are numerous SHBs vaccine recipients with advanced age >40 years or weakened immune competence who do not produce sufficient anti-HBs antibodies. Another aspect is the genotype bias of the standard vaccines most of which contain SHBs of genotype A2 although 99% of the HBV infections worldwide have other genotypes. Vaccine producers consider HBV genotypes not relevant for the worldwide vaccination campaign, but several examples of reduced HBV genotype cross-protection exist [7]. Recently, even a gradual selection of mutated HBV strains heterologous to the major vaccine strains was reported from China [10]. In that respect the broad genotype reactivity of the BM32 induced anti-preS response is highly relevant.

Contributors

Dr. Gerlich wrote the commentary.

Declaration of Competing Interest

Dr. Gerlich has nothing to disclose.

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