

SPECIFIC CHARACTERISTICS AND ANTIGENIC PROPERTIES OF THE HEPATITIS VIRUS B

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Abstract. Hepatitis B remains a worldwide problem despite the availability of effective vaccines. The hepatitis B virus surface antigen (HBsAg) induces a natural or postvaccine humoral immune response directed primarily against the “a” determinant of HBsAg. This determinant is part of the large hydrophilic region of HBsAg, located between the 124th and 147th amino acid residues (a. o.) forming 3 loops that are held together by disulfide bridges formed by C124 and C137 a. o. and C139 and C147 a. o. [1]. This determinant has a highly conformational nature and is universal, providing protection against all variants of hepatitis B virus (HBV), so commercial hepatitis B vaccines include recombinant “a”-determinant HBsAg as an immunogen [1].

Keywords: Hepatitis B, HBsAg, monoclonal conjugates, recombinant, immunization.

СПЕЦИФИЧЕСКАЯ ХАРАКТЕРИСТИКА И АНТИГЕННЫЕ СВОЙСТВА ВИРУСА ГЕПАТИТА В

Аннотация. Гепатит В остается всемирной проблемой, несмотря на наличие эффективных вакцин. Поверхностный антиген вируса гепатита В (HBsAg) вызывает естественный или поствакцинальный гуморальный иммунный ответ, направленный в первую очередь против детерминанты «а» HBsAg. Эта детерминанта является частью большой гидрофильной области HBsAg, расположенной между 124-м и 147-м аминокислотными остатками (а. о.), образующими 3 петли, которые удерживаются вместе дисульфидными мостиками, образованными C124 и C137 а. и C139 и C147 а. [1]. Эта детерминанта имеет высококонформационную природу и является универсальной, обеспечивая защиту от всех вариантов вируса гепатита В (HBV), поэтому коммерческие вакцины против гепатита В включают в себя рекомбинантный «а»-детерминант HBsAg в качестве иммуногена [1].

Ключевые слова: Гепатит В, HBsAg, моноклональные конъюгаты, рекомбинантный, иммунизация.

Mass vaccination against hepatitis B promotes the selection and spread of mutant forms of HBV that escape vaccine control (escape mutants). Amino acid substitutions within the “a”-determinant lead to conformational changes and affect antigenicity and immunogenicity to varying degrees. For example, the G145R substitution leads to such drastic changes that HBsAg-

specific protective antibodies almost completely lose their ability to interact with the mutant HBsAg variant [2-5]. However, such structural changes do not completely disrupt the immunogenicity of HBsAg [6]. Infection of chimpanzees with a mutant virus isolate carrying the G145R mutation results in the induction of an anti-HBs response [7]. The antigenic properties of the native G145R mutant HBsAg, first detected in 1990, were analyzed [8]. [8], were analyzed using 4 monoclonal antibodies binding to synthetic cyclic peptides consisting of 124-137 and 139-147 a. o. "a"-determinants.

A study of the interaction of anti-HBs from sera of over-vaccinated or vaccinated individuals with the mutant G145R antigen showed that binding of anti-HBs to wild-type HBsAg was completely inhibited by recombinant ay and ad. In contrast, no inhibition was observed with mutant G145R HBsAg in the serum of vaccinated individuals, and minor inhibition was observed in the serum of re-infected patients [5]. Other mutations in the 145th a. o. region did not have such a pronounced effect. It has been shown that vaccination of humans with preparations containing wild-type HBsAg induced antibody formation to both wild-type HBsAg and the S143L mutant with equal efficacy, but practically did not induce antibody formation to HBsAg carrying the G145R mutation [9, 10]. A study of the humoral response in BALB/c mice after immunization with virus antigens belonging to the ay and ad subtypes of wild-type or mutant G145R ay-type showed that HBsAg variants differ significantly in immunogenicity and specificity of determinants [5]. In mice immunized with wild-type antigens, the anti-HBs response was more than 100-fold higher than the immune response developed in the case of the mutant antigen after the second immunization. When immunized with the ay subtype, anti-Au antibodies were 4-fold higher than anti-G145R antibodies. In contrast, immunization with the mutant antigen produced almost 5-fold more antibodies recognizing this mutant antigen than antibodies recognizing wild-type. The results of the study of various recombinant and natural variants of HBsAg by serological portrayal showed that recombinant wild-type ay and ad antigens are recognized by the entire panel of conjugates. This is consistent with the notion of the universality of the "a"-determinant of HBsAg in wild-type HBV. Serologic portrayal of G145R escapmutated antigens yielded heterogeneous results. Recombinant samples AHBV203 and HBs-878 had no recognition defects by monoclonal conjugates, implying similarity in conformation of these recombinant HBsAg wild-type HBsAg molecules. However, all investigated recombinant antigens of the ESC series (HBsAg ayw2 subtype), also containing the G145R mutation, had multiple deep "failures" in reactivity with most conjugates, and their reactivity was almost identical to that of native HBsAg with the same mutation (ayw2 and adw3 subtypes). Nevertheless, the depth of recognition defects was not the same for different variants of ESC antigens obtained under different experimental conditions.

For example, the recognition impairments of the ESC-1 and ESC-2 antigens by the HB4 conjugate were almost 100-fold and by the X7 conjugate were 20-fold less than those of all three natural isolates with the G145R mutation. In these antigens, the violations on conjugates 11F3 and 10D10 are also smaller than in the native mutant antigens and other recombinant variants from the ESC series. This allows us to conclude that there is some disruption of the correct folding of the ESC01 and ESC-02 antigens, which does not allow them to fully match the natural conformation of the G145R mutant epitope. Therefore, these antigen variants cannot be used in the development of specific vaccine components. In contrast, the serologic portrait of the ESC-03 antigen is closest to the natural G145R HBsAg from sera 1537 and 2043, which have the same subtype (ayw2), and this variant of specific antigen production seems to be preferred. The results obtained indicate that the conditions of its expression and purification play no less important role than nucleotide substitution in the targeting codon in obtaining recombinant HBsAg with the G145R mutation, as the correct folding of the mutant antigen depends on them.

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