REVIEW ARTICLE

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Virus Escape CTL or B Cell Epitopes?

Seyed-Mohammad Jazayeri MD PhD[1], William F Carman PhD[2]

[1] Virology Dept. Tehran University of Medical Sciences
[2] West of Scotland Specialist Virology Center, Gartnavel General Hospital

Introduction

For a non-cytopathic virus (such as HBV) to persist, it must be able to evade immune surveillance; there must be either an ineffective antiviral immune response, or the virus must escape an otherwise efficient response. All of these might be involved in HBV persistence.

As tolerance against HBcAg/HBeAg eventually diminishes due to unknown factors, although it appears to be ethnically based, there ensues a battle between the virus and the host, with different outcomes depending on immune status and HLA phenotype. Some progress has been made in teasing out the relationship between host and viral factors in this process. Viral persistence is generally thought to be due to an inadequate antiviral T lymphocyte response. This concept has derived from animal models of viral infection and from the study of patients who spontaneously clear the virus (in whom there is a strong virus-specific CD4 and CD8 response). This view is supported by several observations that patients with concurrent HIV infection or patients receiving immunosuppressive therapy are more likely to develop viral persistence.

HBV core gene has attracted a resurgence of interest recently because it influences the outcome of hepatitis B infection: it is a very powerful T-cell immunogen, it can function as a carrier for non-HBV proteins, it is the principle target for T cell cytotoxicity and, finally, it is a T-dependent and -independent B cell immunogen. Having studied HBcAg sequences from 12 countries, we now know that certain residues allow definition of subtypes and genotypes. Further, specific nucleotide/amino acid motifs are found only in particular ethnic/geographical backgrounds. We also found specific T cell epitopes that were specific for particular geographic regions, and thus ethnic groups [(1)].

The transition from a relative immune tolerance state to the activation of the immune system with generation of anti-HBc results in a strong selection on the viral genome, causing changes in immune targets, i.e. T and B cell epitopes, that could lead to escape of the virus from immune clearance[(2)]. Whether variants of epitopes are under immune pressure or induce a new immune response is explored below.

In Chinese and Japanese patients, an ineffective CTL response has been postulated as the primary determinants of viral persistence in chronic HBV. Several potential CTL epitopes within the HBcAg have been identified (fig-1). There are several HLA class-I-restricted epitopes including: 18-27[(3)]; 48-60 in adw subtype [(4)]; 84-101 in adr subtype [(5-6, 3)]; 141-151[(7)]; and 147-15[(8)]. Similarly, variants were found in envelope-specific HLA-A2-restricted CTL epitopes: amino acid 40 and 44 (in adw strains); amino acid 47 (in adr subtype); residue 53 of small surface protein[(9-10)]; and amino acid terminal domain of pre-S2 protein[(11-12)]. These observations have led to the postulate that the presence of core CTL-escape mutants in those epitopes was responsible for liver injury following viral clearance and might play an important role in the

Correspondence:
Jazayeri MD PhD, Assistant Professor, Virologist; Tehran University of Medical Sciences

Tel: +98 21 8896 2343
Fax: +98 21 8895 4913

E-mail: jazayerism@sina.tums.ac.ir

pathogenesis of chronic infection. However, this hypothesis was in disagreement with the finding obtained by some other authors. In several studies on chronic HB-infected patients, investigators found that in anti-HBe positive patients, who went into remission, putative escape mutations appeared in the T helper epitopes. Conversely, in those with ongoing disease, they occurred in B cell epitopes. They thus speculated that after HBeAg is lost by the selection of a pre-core stop codon, probably driven by the immune response against HBeAg, either an effective CTL response occurs against the core which clears the virus or there is a poor CTL response [13]. In the absence of adequate CTL, anti-HBc kills hepatocytes via complement or killer cells; selection of numerous mutations in humoral epitopes (figure 1) is then inevitable. They suggested a significant role for humoral immune response in terms of T helper cell epitope non recognition on the pathogenesis of HB chronic infection[13-20]. These findings were consistent with the results obtained by Ferarri *et al.*, [21], who found a higher level of anti-HBc antibodies in chronic HB patients than acute patients. They hypothesized that chronic exposure of hepatocytes to HBcAg could lead to a T cell-independent B cell immunogenicity. Jazayeri *et al.* [22] showed that intracellular localization of cAg depended on serology and the presence of mutations in different core gene B cell epitope mutations. Of 26 cloned samples, HBcAg was predominantly localized in nucleus in 13 and in cytoplasm in other 13 samples. 9 of 13 nuclear-localized samples were HBeAg positive, but in cytoplasmic-localized all but one were anti-HBe positive.

All samples with cytoplasmic localization contained B cell epitope mutations (especially between aa positions 74-89). Reversion of mutant sequences with cytoplasmic expression back to the wild type led to shifting back to nuclear distribution.

Milich *et al.*[23], presented support for the role of T cell responsiveness rather than neutralizing antibodies in virus elimination during HB disease; they proposed a role for the humoral immune response as an indicator of underlying T cell function or dysfunction. Furthermore, they and some other authors were not convinced by the possibility that the presence of CTL-escape mutants within the core protein was involved in HB chronicity as, so far, direct evidence of CTL escape is lacking. Although it would be tempting to implicate CTL in this process, there are few data to support their role. In fact, according to a few lines of evidence, it seems unlikely that CTL-escape mutants are responsible for viral clearance in chronic HB patients. First, the CTL response during chronic

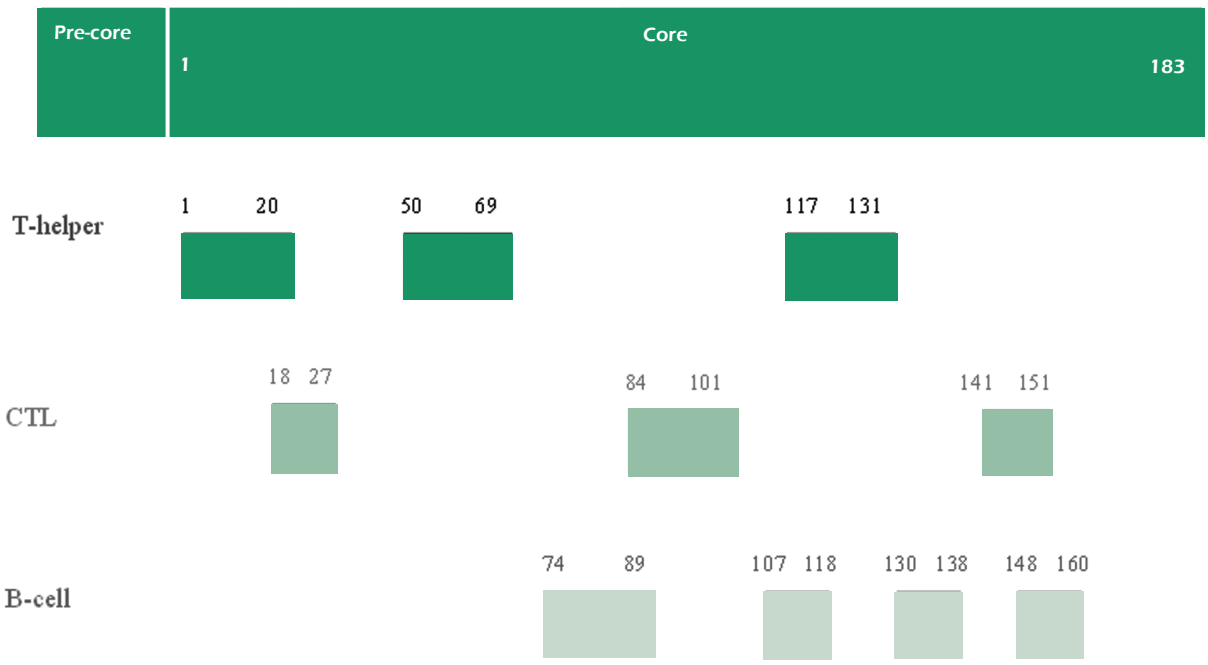

Figure 1. Potential immunodominant domains of HBcAg.

HB is generally too weak or absent. Second, CTL target motifs are very common throughout the core region (there are at least four possible alleles of HLA class-I molecules, fig-1) and also, HBc and HBe antigens share the same CTL epitopes. Third, core amino acid residues 48-60 are within a T helper epitope [24], not a CTL epitope [8]. Fourth, the number of CTL-escaped mutants in published studies was rare at best [13-14, 16-17, 20]. Moreover, as shown before, these discrepancies somehow may be related to the fact that the epitopes for CTL/Th recognition might be different on account of the diverse distribution of HLA antigens in different ethnic groups and/or different genotypes and subtypes [1].

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