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Diversity of Conformational Epitopes on the Core Antigen of Hepatitis B Virus. D.M. Belnap*, N.R. Watts†, J.F. Conway‡, N. Cheng*, S.J. Stahl†, P.T. Wingfield†, A.C. Steven*, *Lab. Struct. Biol. Res. and †Protein Exp. Lab., NIAMS, NIH, Bethesda, MD 20892, USA, ‡Lab. de Microscopie Electronique, Institut de Biol. Struct. J.-P. Ebel, Grenoble 38027, France.

Antibodies bind proteins at sites termed linear or conformational epitopes. Linear epitopes are consecutive amino-acid residues. Conformational epitopes are discontinuous residues juxtaposed by the protein's three-dimensional structure. Antibodies recognize them only when the protein has a specific conformation. Discontinuity makes it difficult to map conformational epitopes by techniques used to identify linear epitopes (e.g. peptide scanning). Our goal was to identify conformational epitopes in hepatitis B virus (HBV) capsid and to assess the diversity of HBV-capsid epitopes. HBV capsids are comprised of dimeric subunits, with a prominent spike located at the dimer interface. Residues at the spike tip were identified previously as the "immunodominant loop". We characterized one linear and three conformational epitopes on HBV capsids by cryo-electron microscopy of Fab-labeled capsids (at 10-14Å resolution), coupled with molecular modeling. All three conformational epitopes straddle interfaces between subunits. The linear epitope is located on a single polypeptide. The linear epitope and two conformational epitopes are at different sites in the "immunodominant loop". The third conformational epitope is found at the spike base, but Fabs only bind three of seven possible sites—suggesting that small shifts in conformation have large effects on binding affinity. The distinctness of the four epitopes suggests that the full range of epitopes to an antigen may be large. Despite a limited number of accessible residues, epitope diversity could be created by local clusters of exposed peptides.