

[] HBV PEPTIDE ARRAY DEMONSTRATES CANDIDATE MECHANISMS OF CRV431 ANTI-HBV ACTIVITY

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Background and Aims:

CRV431 is a cyclosporine A analog that reduces HBsAg, HBV DNA, and other HBV markers. Most of the CRV431 activities are thought to occur by blocking participation of cellular cyclophilins, the primary molecular target of CRV431, in the HBV life cycle. However, the specific cyclophilin interactions that influence HBV have not yet been identified. The aims of the current study were to determine whether cyclophilin A can bind directly to HBV proteins, whether CRV431 blocks the interactions, and to identify the specific HBV protein sequences to which cyclophilin binds.

Method:

Soluble, recombinant cyclophilin A was applied to immobilized, 15-amino acid, overlapping peptides representing the entire HBV proteome, and cyclophilin A binding to the peptides was detected with cyclophilin A antibody. CRV431 was additionally applied in some experiments to block the binding. The sequences of the peptides that bound to cyclophilin A were analyzed in detail, and soluble peptides were used in competition experiments to validate cyclophilin A binding to the HBV proteins.

Results:

Cyclophilin A bound to 10 HBV-derived peptides, and all 10 binding events were inhibited by CRV431. The peptides that bound cyclophilin A were derived from preS1 HBsAg, HBV polymerase, precore, and core antigen. Furthermore, the peptides overlapped with sequences implicated in regulation of polymerase nuclear import, HBsAg transport and secretion, and capsid formation. One additional interaction between cyclophilin A and a polymerase-derived peptide was found but only in the presence of CRV431. Current studies are investigating the physiological relevance of the cyclophilin A binding events observed in the peptide arrays.

Conclusion:

These studies identified multiple cyclophilin-HBV interactions that may be the target(s) of CRV431 action.