The Roles of HBV Viral Proteins in HBV Persistence: A Study Using an HBV-persistent Mouse Model

Chun-Ta Lin[1*], Lih-Hwa Hwang[1], Shih-Hui Chen[1]

[1.] Institute of Microbiology and Immunology, NYMU

Background/Objective
The mechanism behind the HBV chronicity has remained unclear, mainly due to the lack of an immunocompetent animal model for persistent HBV replication and for investigation of the mechanisms underlying HBV immune escape. We have previously established an HBV-persistent model in FVB/N mice by hydrodynamic injection. Using this model, we investigated whether HBV viral proteins antagonized host immunity and thus induced viral persistence.

Method
We knocked out the expression of each individual viral gene, while keeping the expression of the other genes intact. Five null clones were constructed, including E- (eAg knockout), S- (sAg knockout), P- (polymerase knockout), X- (xAg knockout), and S/E (sAg and eAg knockout)-null clones. These null clones were delivered into FVB/N mouse livers through hydrodynamic injection. HBV persistence was followed for up to 24 weeks and immune responses in the mouse livers were analyzed by qRT-PCR and flow cytometry.

Result
All but P-null clones were cleared from mouse livers albeit with different rates. Among them, the S- and S/E-null clones were cleared the most quickly (< 2 weeks). Immunological analyses indicated that significantly stronger NF-κB activation and higher levels of cytokine and chemokine expression (e.g., TNF-α, CXCL9 and CXCL10) were observed in the liver non-parenchymal cells (NPCs), representative of innate immune cells, of the mice injected with S- or S/E-null DNAs than those injected with wild-type DNA.

Conclusion
HBV eAg and sAg play significant roles in antagonizing host immune response in vivo, which may contribute to HBV persistence.