HOST PDZ-CONTAINING PROTEINS TARGETED BY HEPATITIS B VIRUS AND SARS-COV-2

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PDZ domains are very common modules of protein-protein interaction, essential in many signaling pathways. They mainly interact with PDZ-binding motifs (PBMs) at the C-terminal of partner proteins. PDZ-containing proteins have various roles in human cells such as trafficking of membrane receptor, cellular junctions and polarity, signaling and scaffolding.

Many viruses target host PDZ domains to ensure their propagation during infection. Some viral PBMs such as those of the glycoproteins expressed by the Rabies virus and by SARS-CoV are factors of virulence.

Here, we focus on two viral proteins from Hepatitis B Virus (HBV) and SARS-CoV-2 that present a PBM targeting PDZ-containing proteins to illustrate how viruses have selected different strategies to improve their dissemination by interacting with host PDZ proteins. We have characterized the interactions between the HBV core protein (HBc) and the SARS-CoV-2 protein E and host cell PDZ-containing proteins. To this aim, we used a combination of high-throughput technique (Holdup) and biophysical and structural characterization (NMR/crystallography), coupled with validation of partners in a cellular context. We have identified specific PDZ binders that interact in vitro with the PBM of HBc or protein E by the Holdup assay. Most of these binders are also found targeted by other viruses.

For HBV, we showed that the PDZ domain of the non-receptor tyrosine phosphatase type 3 (PTPN3) binds to the full-length HBc protein within the capsids in vitro. We hypothesized that PTPN3 interact in vivo with HBc forming capsids through a PDZ/PBM interaction. We solved the structure of the PDZ domain of PTPN3 in complex with the PBM of HBc to specify the determinants of interaction. We studied the impact of PTPN3 overexpression on HBV replication after infection on HepG2 NTCP cells and we concluded to the potentially pleiotropic role of PTPN3 in HBV replication.

Protein E PBM of SARS-CoV is involved in virulence and replication interfering with the cellular polarity/junction of infected cells. We identified five candidates targeted by the SARS-CoV-2 protein E and involved in cell junctions and polarity. We have characterized the interactions in vitro between the protein E PBM and these partners using X-ray crystallography and microscale thermophoresis. Pull-down assays between PDZ domains and the full-length E protein wild-type or mutated in the PBM were also performed.

All our results will contribute to a better understanding of the hijacking of host machinery by the viruses.