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Small molecule inhibitors of HSP70 chaperones influence tick-borne flavivirus infectivity and NS1 protein secretion

Inhalt

Flaviviruses are arthropod-borne RNA viruses that include one of the major tick-borne viral pathogens of humans, tick-borne encephalitis virus (TBEV). The flavivirus non-structural protein 1 (NS1) is a conserved 46–55 kDa protein that exists in different glycoforms and multifunctional oligomeric complexes. Heat shock protein 70 (Hsp70) chaperones are cellular protein folding catalysts. Part of this family is the ER chaperone binding immunoglobulin protein (BiP), a key regulator of the unfolded protein response (UPR). Flaviviruses replicate along the ER membrane and are known to activate and manipulate the host UPR. In this project, we investigate the direct interaction of flavivirus glycoproteins with BiP and its impact on downstream signalling. We could show that infection with the tick-borne flavivirus Langat virus (LGTV) leads to induced cellular BiP expression. Furthermore, we found evidence that flavivirus NS1 proteins interact with BiP and the interaction differs between viral species. We could demonstrate that the interaction is associated with the N-glycans of the NS1 proteins. Direct interaction with the substrate binding domain of BiP is required for LGTV NS1 secretion and can be targeted by Hsp70 inhibitors with little impact on viral infectivity. In contrast, inhibition of the nucleotide binding domain of Hsp70 drastically reduces LGTV infectivity. These results suggest a key role of Hsp70 chaperones in flavivirus synthesis, assembly and NS1 secretion.

Keywords

Tick-borne encephalitis virus (TBEV), flavivirus, ER stress, unfolded protein response (UPR), heat shock protein 70 (Hsp70), binding immunoglobin protein (BiP)

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