Sustained ER Stress Caused by EV71-induced Cytosolic Restraint of Grp78/Bip Is Advantageous to Virus Infection

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Background/Objective

Our previous findings demonstrated that enterovirus 71 (EV71) infection upregulated Grp78/Bip expression, a hallmark of ER stress. The ectopic expression of Grp78/Bip attenuated EV71-induced ER stress and reduced infectious particle formation. The question remains unsolved regarding the virus-mediated upregulation of Grp78/Bip which is disadvantageous to viral replication. We thus set out to explore the modulation of Grp78/Bip in virus-infected cells.

Method

We used subcellular fractionation to investigate the cellular localization of Grp78/Bip upon EV71 infection. Next, cells transfected with individual nonstructural proteins or transfected with poly (I:C), a synthetic analog of double-stranded RNA, were used to explore which of the viral molecules induces redistribution of Grp78/Bip. We also treated the cells with inhibitors for PKR, p38 MAPK, JNK, and apoptosis to determine which of them may participate in the modulation of Grp78/Bip. Finally, we infected cells expressing wild-type or C-terminal KDEL-deleted mutant Grp78/Bip to assess expression level of viral protein and virus titer by western blot analysis and plaque assay, respectively.

Result

EV71 infection induces dsRNA/PKR-dependent, but viral protein-independent cytosolic accumulation of Grp78/Bip. It is significant in that it provides another mechanism of redistribution of ER luminal protein(s) different from translocation of Bax protein to the ER membrane recently described during ER stress-induced apoptosis. It thus facilitates virus replication by blunting Grp78/Bip-mediated alleviation of ER stress.

Conclusion

We found that sustained ER stress caused by EV71-induced cytosolic distribution of Grp78/Bip is advantageous to virus infection. Further work is required to elucidate the mechanism by which PKR mediates redistribution of Grp78/Bip. Additionally, Grp78/Bip localized outside the ER lumen has been shown to play a role in apoptosis regulation. Thus, it is interesting to investigate possible role(s) of cytosolic Grp78/Bip in EV71 replication. Overall, Grp78/Bip can be further explored as potential target for developement of antiviral therapy.