Insights: Publications

Antagonism of the protein kinase R pathway in human cells by rhesus cytomegalovirus

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While cytomegalovirus (CMV) infections are often limited in host range by lengthy coevolution with a single host species, a few CMVs are known to deviate from this rule. For example, rhesus macaque CMV (RhCMV), a model for human CMV (HCMV) pathogenesis and vaccine development, can replicate in human cells, as well as in rhesus cells. Both HCMV and RhCMV encode species-specific antagonists of the broadly acting host cell restriction factor protein kinase R (PKR). Although the RhCMV antagonist of PKR, rTRS1, has very limited activity against human PKR, here, we show it is essential for RhCMV replication in human cells because it prevents human PKR from phosphorylating the translation initiation factor eIF2α, thereby allowing continued translation and viral replication. Although rTRS1 is necessary for RhCMV replication, it is not sufficient to rescue replication of HCMV lacking its own PKR antagonists in human fibroblasts. However, overexpression of rTRS1 in human fibroblasts enabled HCMV expressing rTRS1 to replicate, indicating that elevated levels or early expression of a weak antagonist can counteract a resistant restriction factor like human PKR. Exploring potential mechanisms that might allow RhCMV to replicate in human cells revealed that RhCMV makes no less double-stranded RNA than HCMV. Rather, in human cells, RhCMV expresses rTRS1 at levels 2 to 3 times higher than those of the HCMV-encoded PKR antagonists during HCMV infection. These data suggest that even a modest increase in expression of this weak PKR antagonist is sufficient to enable RhCMV replication in human cells.IMPORTANCE Rhesus macaque cytomegalovirus (RhCMV) offers a valuable model for studying congenital human cytomegalovirus (HCMV) pathogenesis and vaccine development. Therefore, it is critical to understand variations in how each virus infects and affects its host species to be able to apply insights gained from the RhCMV model to HCMV. While HCMV is capable only of infecting cells from humans and very closely related species, RhCMV displays a wider host range, including human as well as rhesus cells. RhCMV expresses an antagonist of a broadly acting antiviral factor present in all mammalian cells, and its ability to counter both the rhesus and human versions of this host factor is a key component of RhCMV's ability to cross species barriers. Here, we examine the molecular mechanisms that allow this RhCMV antagonist to function against a human restriction factor.

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