Modulation of Host Cell Stress Responses by Human Cytomegalovirus

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Abstract  
Human cytomegalovirus (HCMV) induces cellular stress responses during infection due to nutrient depletion, energy depletion, hypoxia and synthetic stress, e.g., endoplasmic reticulum (ER) stress. Cellular stress responses initiate processes that allow the cell to survive the stress; some of these may be beneficial to HCMV replication while others are not. Several studies show that HCMV manipulates stress response signaling in order to maintain beneficial effects while inhibiting detrimental effects. The inhibition of translation is the most common effect of stress responses that would be detrimental to HCMV infection. This chapter will focus on the mechanisms by which cap-dependent translation is maintained during HCMV infection through alterations of the phosphatidylinositol-3’ kinase (PI3K)-Akt-tubercous sclerosis complex (TSC)-mammalian target of rapamycin (mTOR) signaling pathway. The emerging picture is that HCMV affects this pathway in multiple ways, thus...
ensuring that cap-dependent translation is maintained despite the induction of stress responses that would normally inhibit it. Such dramatic alterations of this pathway lead to questions of what other beneficial effects the virus might gain from these changes and how these changes may contribute to HCMV pathogenesis.

**Abbreviations**

4E-BP: eIF4E binding protein; AICAR: 5-Amino-4-imidazole-carboxamide ribose; Akt: The cellular homolog of the oncoprotein of the AKT8 retrovirus; AMPK: AMP-activated kinase; CaMKKβ: Calcium/calmodulin-dependent protein kinase kinase-β; ER: Endoplasmic reticulum; eIF: Eucaryotic initiation factor; FKBP12: FK506 binding protein; HCMV: Human cytomegalovirus; IR: Insulin receptor; IRS: Insulin receptor substrates; mTOR: Mammalian target of rapamycin; mTORC1: mTOR complex 1; mTORC2: mTOR complex 2; PDK1: Phosphoinositide-dependent protein kinase-1; PI3K: Phosphatidylinositol-3′ kinase; PIP2: Phosphatidylinositol-4,5-bisphosphate; PIP3: Phosphatidylinositol-3,4,5-triphosphate; PP2A: Protein phosphatase 2A; PTEN: Phosphatase and tensin homolog; S6K: p70S6 Kinase; TSC: Tuberous sclerosis complex

**Introduction**

Human cytomegalovirus (HCMV) shares a general life cycle strategy with other mammalian double-stranded DNA viruses that replicate in the nucleus: it must adapt the cellular milieu so the host cell can accommodate the increased demand for nutrients, energy and macromolecular synthesis that accompanies viral infection. For example, successful viral replication requires (1) increased glucose uptake, metabolism and oxygen utilization; (2) abrogation of cellular growth controls; (3) manipulation of the cell cycle to a point that is optimal for virus growth; and (4) inhibition of apoptosis during the productive phase of replication.

These massive changes in the cell’s physiology induce cellular stress responses, due to nutrient depletion, energy depletion, hypoxia and synthetic stress, e.g., endoplasmic reticulum (ER) stress. Cellular stress responses are designed to signal the cell when it is in potential trouble and initiate conditions to allow the cell to survive the stress. As a last resort, when the efforts to abate stress fail, apoptosis is induced. Stress responses have many effects on cellular processes; among these some may be beneficial to HCMV replication while others may not. Existing data suggest that HCMV may be able to manipulate stress responses in order to maintain beneficial effects while inhibiting detrimental effects (Isler et al. 2005b; Hakki et al. 2006).

Inhibition of translation is among the most common consequences of cellular stress responses (Kaufman et al. 2002; Arsham et al. 2003; Holcik and Sonenberg 2005; Wouters et al. 2005; Wek et al. 2006). Since translation is an energy-intensive process, its inhibition results in decreased demand for ATP/GTP and decreases the load of proteins entering the ER for processing, consequently relieving ER stress. Translation is well suited to respond to stress, since its inhibition can be accomplished rapidly and reversibly by altering the phosphorylation state of translation regulatory proteins. For example, cap-dependent translation, in which translation initiation depends on