Human cytomegalovirus (HCMV) is a herpesvirus that infects humans throughout the world. Most infections with HCMV are asymptomatic, however, both initial and reactivated HCMV infections pose a life-threatening risk in immunocompromised patients, such as transplant recipients and HIV patients. In addition, due to its ability to infect the developing fetus via placental transmission, HCMV is the leading infectious cause of congenital abnormalities worldwide. HCMV has been extremely successful in infecting humans due to its ability to evade the immune system to establish lifelong latency. HCMV expresses US2, US3, US5, US10, US11, UL16, and UL18 proteins that inhibit MHC class I molecules functions to evade T cell-mediated immunity. However, little is known about how HCMV can circumvent antibody immunity.

The neonatal Fc receptor (FcRn) is composed of a membrane-bound heavy chain (HC) in non-covalent association with β2-microglobulin (β2m). Although FcRn shares structural characteristics with MHC class I molecules, it does not present antigenic peptides, instead, it binds IgG antibodies in a pH-dependent manner with FcRn binding IgG at a pH ≤ 5.5 and releasing IgG at neutral or high pH. The FcRn is normally transported to early endosomes and the extracellular neutral pH triggers the release of FcRn at pH > 6.5. FcRn transports IgG antibodies in a pH-dependent manner with FcRn binding IgG at a pH ≤ 5.5 and releasing IgG at neutral or high pH. FcRn is an MHC class I-related receptor, an MHC class I-related FcγR, that shares structural characteristics with MHC class I molecules.

HCMV evades IgG antibody-mediated immunity through endoplasmic reticulum-associated degradation of the neonatal Fc receptor (FcRn) for IgG

**Introduction**

Human cytomegalovirus (HCMV) is a herpesvirus that infects humans throughout the world. Most infections with HCMV are asymptomatic, however, both initial and reactivated HCMV infections pose a life-threatening risk in immunocompromised patients, such as transplant recipients and HIV patients. In addition, due to its ability to infect the developing fetus via placental transmission, HCMV is the leading infectious cause of congenital abnormalities worldwide. HCMV has been extremely successful in infecting humans due to its ability to evade the immune system to establish lifelong latency. HCMV expresses US2, US3, US5, US10, US11, UL16, and UL18 proteins that inhibit MHC class I molecules functions to evade T cell-mediated immunity. However, little is known about how HCMV can circumvent antibody immunity.

**Results**

Figure 1. HCMV glycoprotein US11 interacts with FcRn. A and B. Co-immunoprecipitation of FcRn and US11 in cell lysates from HeLaFcrn+US11 Cells. D and E. Co-immunoprecipitation of FcRn and US11 in cell lysates from US11 expressing cells. US11 selectively inhibited the FcRn trafficking to the endosome by retention of FcRn in ER. Furthermore, US11 recruits Derlin-1, an E3 ligase mediator, and TMEM129, an ER-resident E3 ubiquitin ligase, together with the E2 enzyme, UbE2j2, to engage FcRn. These interactions initiate the dislocation of FcRn from the ER to the cytosol and facilitates its degradation in a ubiquitination and proteasome-dependent manner. Hence, our results reveal for the first time the mechanism by which HCMV infection exploits a Derlin-1/TMEM129/UbE2j2 pathway through US11 to disable FcRn. Because FcRn is vital to IgG transport and half-life of IgG in the cell populations supporting HCMV infection, these results have implications for vaccine development and antibody-mediated immune surveillance in the defense against HCMV.

**Figure 2.** US11 inhibits FcRn trafficking to the endosome by retaining FcRn in the ER. A. The expression pattern of FcRn with early endosome mark EEA1 in HeLaFcrn+-Vs- or HeLaFcrn+-Vs+ cells. B and C. Averages of the EEA1 and FcRn expression in HeLaFcrn+-Vs- or HeLaFcrn+-Vs+ cells. D. Sensitivity of US11-associated FcRn HC to endo-H digestion. Endo H-sensitive (Endo-HS) indicates FcRn retained in ER; Endo H-resistant (Endo-HR) indicates FcRn matured from ER. US11 selectively inhibited the FcRn trafficking to the endosome by retention of FcRn in ER. The level of remaining FcRn (C) and ubiquitination (D) at different time points was quantified as the percentage of initial protein level.

**Figure 3.** US11 induce FcRn protein degradation and is necessary for FcRn degradation during HCMV infection. The FcRn protein expression level in HeLaFcrn+-Vs- (A) and HeLaFcrn+-Vs+ (B) cells after cycloheximide treatment. The endogenous FcRn protein level in US11 expressing cells was monitored by Co-immunoprecipitation of FcRn with Derlin-1/TMEM129/Ube2j2 complex which induces FcRn ubiquitylation and degradation. The level of remaining FcRn (C or G) and β-tubulin (D or H) at different time points was quantified as the percentage of initial protein level.

**Figure 4.** US11 recruits FcRn to Derlin-1/TMEM129/Ube2j2 protein complex which induces FcRn ubiquitylation and degradation. A and B. Co-immunoprecipitation of FcRn with Derlin-1 and TMEM129 in cell lysates from HeLaFcrn+-Vs- or HeLaFcrn+-Vs+ cells. The E3 ubiquitin ligase TMEM129 is required for US11-induced FcRn degradation (B) and ubiquitination (D). The E2 conjugating enzyme Ube2j2 is required for US11-induced FcRn degradation (E) and ubiquitination (F).

**Conclusion**

HCMV glycoprotein US11 interacts with FcRn. US11 inhibits FcRn trafficking to the endosome by retaining FcRn in the ER. US11 induce FcRn protein degradation and is necessary for FcRn degradation during HCMV infection. US11 recruits FcRn to Derlin-1/TMEM129/Ube2j2 protein complex which induces FcRn ubiquitylation and degradation.