Introduction

The family Herpesviridae emerged approximately 400 million years ago [1]. The first members of the class Mammalia arose 200 million years ago, at around the time of the Early Jurassic period, and, since then, herpesviruses and mammals have coevolved and adapted to one another over very long periods of time. Today, members of the family Herpesviridae are numerous and widespread among not only mammals, but also many bird and reptile species; each virus displays a remarkable degree of host specificity. The longstanding interactions between virus and host have likely contributed to the development of the host's innate and adaptive immune system and the mechanisms that viruses use to evade those systems.

The first line of defense against intruding pathogens is the innate immune system. This comprises the complement system, natural killer (NK) cells, apoptosis, pattern recognition receptor-mediated intracellular signaling leading to the production of IFNβ and many other cytokines and chemokines, and phagocytes like neutrophils, macrophages and dendritic cells. Together, these mechanisms enable the host to limit replication and spread of a pathogen and facilitate the induction of specific adaptive immune responses. The adaptive immune system includes antibody-producing B-cells, $CD4^+$ T-cells that recognize antigens presented in the context of MHC (class) II molecules, and $CD8^+$ T-cells that generally recognize antigens in the context of MHC I molecules.

During and following protein synthesis, a proportion of the resulting proteins is rapidly degraded into peptides by the proteasome. The resulting peptides are subsequently translocated into the lumen of the endoplasmic reticulum (ER) via the transporter associated with antigen processing (TAP) [2,3]. Within the ER, the peptides are loaded onto newly synthesized MHC I heavy chain / $\beta_2$microglobulin (β_2m) heterodimers. This process is facilitated by at least five ER-resident molecules that together form the MHC I peptide-loading complex (PLC). Tapasin functions as a chaperone, bridging MHC I molecules and TAP and catalyzing the binding of high-affinity peptides [4–10]. The lectin-like chaperones calnexin and calreticulin promote folding of newly synthesized MHC I molecules; additionally, calreticulin recruits the thioloxidoreductase ERp57. ERp57 and protein disulfide isomerase (PDI) are involved in stabilizing several protein-protein interactions within the PLC via disulfide bond formation [11,12]. Acquisition of peptide allows mature MHC I complexes to leave the ER, pass through the Golgi, and traffic to the cell surface where the peptides are presented to CTLs.

The family Herpesviridae is divided into the subfamilies Alphaherpesvirinae, Betaherpesvirinae, and Gammaherpesvirinae. Members of this family have been identified in many different species, including reptiles, birds, and mammals. There are nine herpesviruses known to infect humans: herpes simplex virus (HSV) types 1 and 2 (HSV-1 and HSV-2 in species *Human herpesvirus 1* and *Human herpesvirus 2*, respectively, of genus *Simplexvirus*, subfamily Alphaherpesvirinae), varicella-zoster virus (VZV in species *Human herpesvirus 3* of genus *Varicellovirus*, subfamily Alphaherpesvirinae), human cytomegalovirus (HCMV in species *Human herpesvirus 5* of genus *Cytomegalovirus*, subfamily Betaherpesvirinae), human herpesviruses 6A, 6B and 7 (HHV-6A, HHV-6B, HHV-7 in species *Human herpesvirus 6A*, *Human herpesvirus 6B* and *Human herpesvirus 7* of genus *Roseolovirus*, subfamily Betaherpesvirinae), Epstein-Barr virus (EBV in species *Human herpesvirus 4* of genus *Lymphocryptovirus*, subfamily Gammaherpesvirinae) and Kaposi's sarcoma-associated herpesvirus (KSHV in species *Human herpesvirus 8* of genus *Rhadinovirus*, subfamily Gammaherpesvirinae) [13]. Most of these viruses are widespread within the human population; for example, in the United States, approximately 90% of individuals of 80 years or older are seropositive for HCMV [14]. VZV is even more abundant, with a seroprevalence of 95% in people from 20 years of age [15]. Herpesvirus infections generally cause only mild symptoms, but in some circumstances they exhibit significant pathogenic properties,