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Aim of the thesis

Human herpesviruses (HHV) are ubiquitously present in the human population. They are usually harmless after primary infection but they all possess the ability to remain in a silent and latent stage in the infected host. However, upon malfunctioning or temporary suppression of the host immune system, herpesviruses are reactivated and lead to serious pathological conditions. In particular, HHV-5, also known as the human cytomegalovirus (HCMV), is a major disease-causing agent in immunosuppressed transplant patients and appears to be involved in the development of vascular and proliferative diseases (Soderberg-Naucler 2006). Another well-studied herpesvirus is HHV-4, commonly known as the Epstein-Barr virus (EBV), which is involved in lymphoproliferative diseases such as Hodgkin's and Burkitt's lymphomas (Kutok and Wang 2006).

Herpesviruses have employed multiple ways to persist throughout evolution and to influence the host immune system. They have integrated host genes into their genomes and modified them to their own benefit. In particular, HHV from the beta and gamma families encode viral G protein-coupled receptors (vGPCRs) that derive from human chemokine receptors. For instance, HCMV and EBV genomes contain four (US27, US28, UL33, UL78) and one (BILF1) GPCR, respectively (Rosenkilde, Smit et al. 2008). The characteristic of most of these vGPCRs is that unlike human chemokine receptors, they are able to signal in a constitutive manner. This results in the modulation of intracellular signaling pathways and has profound effects on the biological behavior of the targeted cell. A striking example of the physiological importance of vGPCRs was demonstrated with the ORF74 gene from HHV-8 (also known as Kaposi's sarcoma-associated herpesvirus, KSHV). Numerous *in vitro* and *in vivo* studies demonstrated that the expression of this viral chemokine receptor leads to cellular transformation (Bais, Santomaso et al. 1998) and the development of Kaposi's sarcoma-like lesions in ORF74-expressing transgenic mice (Yang, Chen et al. 2000). This indicates that the expression of one single vGPCR is of crucial importance in KSHV-related diseases.

The aim of this thesis was to understand the biological relevance of the HCMV-encoded chemokine receptor US28 and of the EBV-encoded vGPCR BILF1. We identified that US28 constitutive activity is implicated in HCMV-related diseases, providing US28 as a molecular link between viral infection and subsequent pathologies. Detailed *in vitro* studies

highlighted several important signaling pathways activated by US28 during pathogenesis. We also studied the physiological consequence of BILF1 expression *in vivo* and showed that the role of this vGPCR may be important during the virus life cycle rather than for the development of EBV-related diseases.