PART V CONCLUSION AND PERSPECTIVES

The aim of this thesis was to describe the intracellular immune activation that follows a herpesvirus infection and how the virus counteracts these intracellular changes. In this respect, the main events evolve around the signaling cascades that activate the three IFN type 1 transcriptional activators; NF-κB, IRF3 (and IRF7) and IP-1. Emphasis was also laid on the notion that a robust set of PRRs surveys the cell and can be activated by many viral compounds that are exposed in their lifecycle. These receptors then initiate signaling cascade, through a meshwork of interconnected adaptors, to converge at the activation of transcription factors. This triggers the expression of a range of cytokines, chemokines and other signaling protein. Among these are the IFN type 1 gene products that trigger several immunological mechanisms, such as induction of direct anti-viral proteins, DC maturation and CD8+ T cell response. These systems are designed to cope with the detected infection in an adequate way. However, human herpesviruses have specialized in dampening, circumventing, and manipulating these systems through millions of years of co-evolution. Their grant anti-immune arsenal contains a significant amount of gene products that intervene with the downstream signaling cascades of innate receptors and IFN type 1 response.

The three types of herpes viruses have developed to adapt the their hostile environment, as is the case in the host, in a random fashion. Additionally, the solutions that circumvent or tackle the host defense mechanisms have arisen separately in the different (sub)types. The randomness and separation make it unlikely that all herpesviruses (i.e. α, β, and γ herpes viruses) share many immune evasive genes and mechanisms. Figure (X) gives an overview on the currently known gene products and/or mechanisms that herpes viruses use to evade an immune activation. Although it is likely that many more gene products (and mechanisms) will be discovered in future research, it is inherent to the randomness of evolution that only few of these newly discovered viral gene products will closely resemble the gene products of (close) relatives. In other words, ortholog search does not seem to be a very effective approach to find viral strategies for immune evasion. On the other hand, the human herpes viruses have an important thing in common; their host. The evolution of anti-viral mechanisms provides common ground in these viruses. In evolutionary terms, the problem (for human herpes viruses) is the same, but their solutions may vary. A better strategy to find new viral mechanisms in immune evasion would be to start from hubs (i.e. RIG-I, TLR3, IRF3, IRF7, etc.) in anti-viral innate (intracellular) immune mechanisms and find viral modulators of these hubs. To find new anti-viral targets (to inhibit the inhibition), one should seek out the newly discovered immune activation mechanisms (i.e. DAI, AIM, RNA polymerase III, etc.) and assay their putative inhibition by viral proteins.

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