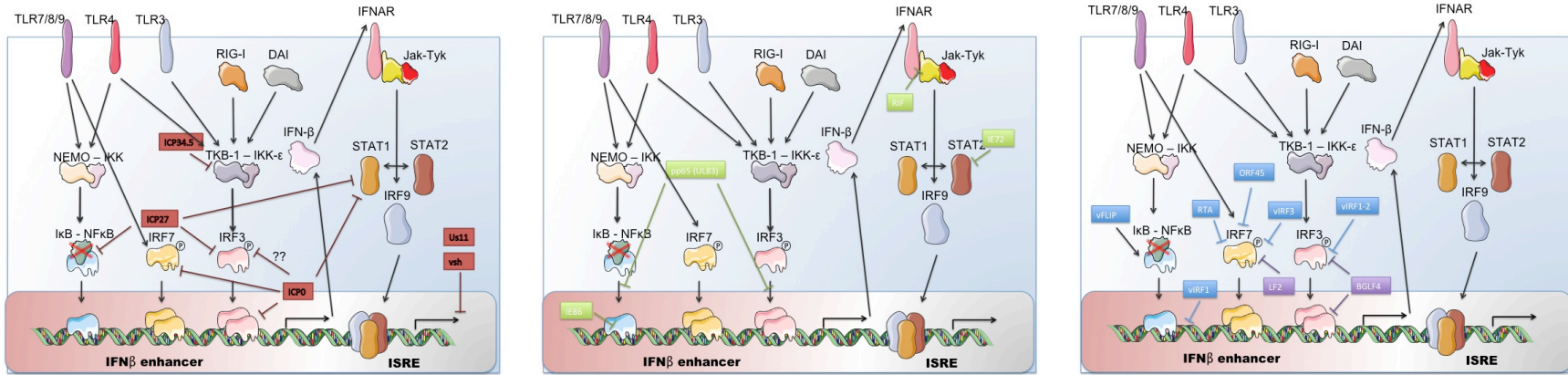


**Figure 4. Innate intracellular immune signaling pathways as targets for Herpesvirus evasion.** The figure represents the signaling meshwork that leads to the induction of an IFN type 1 response and the subsequent transcription of approximately 300 genes in the ISRE-group. The particular viral proteins that are involved in the modulation of these signaling cascades, of human herpes viruses are depicted in the red (HSV-1/2), green (HCMV), blue (KSHV), and purple (EBV) boxes.



**(A) Intracellular immune evasive strategies of HSV-1 and HSV-2.** ICP0 and ICP27 play a central role by acting on most transcription factors in the IFN type 1 pathway. ICP34.5 targets the important adaptor TBK-1. Us11 and vsh alter the immune outcome by working on the gene products.

**(B) Intracellular immune evasion strategies of HCMV.** IE86 and UL83 function by inhibiting the important transcription factors. RIF and IE72 act more downstream (or paracrine) in the signaling by blocking the IFNAR receptor function and Jak-STAT signaling, respectively.

**(C) Intracellular immune evasion strategies of the  $\gamma$ -herpes viruses KSHV and EBV.** The KSHV (blue) vIRF family function as dominant negative forms of the endogenous transcription factors. Additionally RTA and ORF45 block the induction of IRF7. Notably, vFLIP enhances NF- $\kappa$ B signaling. The EBV proteins (purple) BGLF4 and LF2 block the function of IRF3 and IRF7, respectively.