Structural basis for the viral hijacking of Phosphoribosylformylglycinamidine Synthase

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Kaposi's sarcoma (KS)-associated herpesvirus (KSHV) is an etiological agent of KS, pleural effusion lymphoma and multicentric Castleman's diseases [1]. To ensure its own survival and propagation, KSHV employs an extensive network of viral proteins to undermine the host immune system, resulting in lifelong latent infection. Under viral infection, Phosphoribosylformylglycinamidine synthase (PFAS), a core enzyme of cellular de -novo purine biosynthesis is hijacked by viral glutamine amidotransferases (vGATs), putative viral pseudo enzymes of cellular PFAS [2]. vGATs associate with PFAS to exploit the PFAS activity to deaminate retinoic acid-induced gene I (RIG-I), a pattern recognition receptor that senses viral RNA and is crucial for host innate immune defense [2]. This deamidated RIG-I blocks antiviral cytokine production to help the virus avoid the host immune response.

Interestingly, in the presence of vGAT, PFAS changes its catalytic properties. Being a very well-established member of glutaminases, it becomes an asparaginase when complexed with vGAT [2]. Here, we describe our recent studies investigating the structural basis for the mode of action of KSHV_ORF75 (a vGAT) on cellular PFAS. We have successfully expressed and purified KSHV_ORF75 and PFAS from mammalian cells. Using pull down assays, we have also isolated and characterized the KSHV/PFAS heterodimeric complex. We also report on our progress towards solving the cryo-EM structures of KSHV_ORF75, PFAS and their heterodimer. This work is contributing to our understanding of how this viral protein modulates the properties of a cellular de -novo purine pathway enzyme to improve viability and avoid host defenses which likely contributes overall virulence and the progression of KSHV-associated cancers.

References:
{1} Front. Immunol.10, 3084, 2020,
{2} Molecular Cell 58, 134–146, 2015