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New insight into strategies employed by HCMV in immunomodulation

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The immune system has evolved to protect against the many pathogens that are encountered throughout the lifetime of an individual. In turn, the selective pressure that is exerted by the immune system has shaped pathogen evolution. This co-evolutionary relationship between host and pathogen is particularly clear for viruses that establish persistent infections, such as human herpesviruses. Human cytomegalovirus (HCMV, a β-herpesvirus), is a large double-stranded DNA virus that causes a lifelong, persistent/latent infection in ~50-80% of the US population. While HCMV infection is largely asymptomatic in healthy persons, it can induce serious disease in those with naïve or compromised immunity, and the high incidence of congenital infection has spurred a strong initiative for vaccine development. Primary clinical isolates carry at least 19 additional genes within the UL/b' genomic region that have been lost in several commonly used HCMV strains, with several of them targeting signaling by the TNF superfamily. Here, we show that the immunomodulatory function of HCMV UL141 is associated with its ability to bind diverse proteins, while utilizing at least two distinct binding sites to selectively engage TRAIL DRs or CD155. Binding studies revealed high affinity interaction of UL141 with both TRAIL-R2 and CD155 and low affinity binding to TRAIL-R1. We determined the crystal structure, which revealed that UL141 forms a homodimer that engages two TRAIL-R2 monomers 90° apart to form a heterotetrameric complex. The breadth of UL141-mediated effects indicates that HCMV has evolved sophisticated strategies to evade the immune system by modulating multiple effector pathways. Reference: Nemcovicova, et al. 2013 and 2014.

Biography

Ivana Nemcovicova has completed her PhD from University of South Bohemia in Czech Republic and Post-doctoral studies from Vienna University in Austria as well as La Jolla Institute for Allergy and Immunology in California. She has a Junior Project Leader position at the Institute of Virology at the Slovak Academy of Sciences and is proudly using a status of Marie Curie Fellow. She has 8 publications and more than 60 citations in reputed journals.

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