Trine Mogensen

Title: Immunogenetics of infectious diseases and primary immunodeficiencies

Abstract: In recent years, it has emerged that mutations in genes encoding proteins of innate or cell-intrinsic immunity may underlie rare primary immunodeficiencies in humans. Within the framework of my research program, we are aiming at the identification and functional immunological characterization of novel genetic defects predisposing to severe viral infections. This requires studies on basic genetics, cell biology, and immunology on the one hand, and the identification of patients with a rare but severe infectious phenotype, who may directly benefit from our findings in terms of choosing optimal prophylactic and treatment strategies on the other hand. The scope is therefore truly translational medical research focusing on viral infectious diseases, from which we can learn basic immunology and virology and at the same time use this knowledge to inform decision making on diagnosis, prophylaxis, and treatment of these severe viral infections. In the talk I will provide an introduction to how whole exome sequencing and bioinformatics followed by functional immunological studies can be used to unravel the disease causing variants and immunopathogenesis of infectious diseases in humans.

We have previously identified a novel immunodeficiency caused by mutation in the transcription factor IRF3 associated with herpes encephalitis, and we further reported several other defects in the innate TLR3 pathway for sensing of herpes simplex virus in a cohort of patients with this disease. More recently, we investigated the genetic and immunological basis of varicella zoster virus (VZV) CNS infection. These studies demonstrated that defects in the immunological DNA sensor RNA polymerase III (POL III) confers impaired antiviral interferon responses and selective increased susceptibility to VZV infection, thus providing fundamental new insight into VZV immunity. I will present our data on the identification of functionally defective genetic variants in different subunits of POL III in children as well as in adults causing disease manifestations, including encephalitis, vasculitis, and stoke. The roles of POL III in cellular housekeeping and immune surveillance during VZV infection are described and the latest knowledge on POL III and DNA sensing in VZV infection are discussed. Finally, I will high-light emerging outstanding questions related to the roles of Type I interferon in immunity to VZV and other herpes viruses, and how this new insight may be translated into clinical medicine.

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