Research Interest

Identification of Virus-Host interactions

Our research is devoted to identify and characterize novel RNA and Reverse-Transcribing viruses -host interactions for pathogenic viruses using comprehensive and unbiased systems-based Genomics and Proteomics approaches. Virus systems currently established in the lab are HIV, HBV and Ebola trVLPs.

Our efforts are directed towards gaining a better understanding of the mechanism of viral sensing and restriction as a response of the innate immune system to viral infections. Innate immunity is the first line of defense against foreign pathogen invasion. Viruses must evade these host protective mechanisms to establish productive infections, and thus, targeting these host-pathogen interactions is an attractive strategy for the development of novel antiviral therapies.

Our approach is

1. to understand the virus-host interplay, in particular innate sensing
2. to identify cellular restrictions of various viruses and
3. to establish novel platform technologies

1. Understanding the virus-host interplay and innate sensing

In ongoing projects funded by DZIF TTU Emerging Infections, the Priority Program of the DFG SPP1923 and the funding by the One Health initiative (in collaboration with FLI), we are interested in the innate sensing pathways directed towards Ebola, HIV-1 and vaccine vectors. The (so far mostly unknown) sensing pathways affect the innate response and in consequence shape the adaptive response as a critical step in boosting vaccine effects. Moreover, we are interested in identifying the nucleic acid features that trigger the response and might trigger auto-inflammation.

Recently, we identified in collaboration the proximal sensor for HIV-1 nucleic acid recognition in primary human dendritic cells (Cell, 2015). This seminal work provided evidence that the interplay of regulatory and co-sensing factors within the pattern recognition receptor complex (PRR) is multifaceted, and that the PRR complex composition and PAMP recognition vary for different RNA viruses and therefore it will be crucial to identify the exact PRR complexes for each RNA and Reverse- transcribing virus. Therefore, we are interested to analyze the exact PRR complexes for various viruses, such as Ebola and HBV. We will use innovative methodologies by combining proteomics with genomics and by applying novel ribo-proteomic approaches in infected cells based on next-generation sequencing and mass spectrometry.

The identification of PQBP1 (Cell 2015) as a cytoplasmic sensor of early HIV nucleic acid products, required for activation of the cGAS sensing pathway leading to STING mediated IFN induction, is a big step forward in HIV research. In ongoing projects funded by SPP1923, we aim to investigate in more detail the regulation of this novel sensing pathway. Moreover, we have access to rare patients deficient in PQBP1. We generated an iPSC line from a patient mutated in the polar amino acid-rich domain of PQBP1 (Stem Cell Research 2019). The established iPSC model will serve as a tool to investigate the role of PQBP1 in both pathomechanistic and cellular processes.

By RNAi screening technologies, we recently provided evidence that NLRX1 is a negative-regulator of STING thereby inhibiting virus-triggered innate immune responses (Cell Host Microbe, 2016). In collaboration, we identified novel regulators or Rig-I sensing (Nature Microbiology, 2017). NLRX1 or Rig-I regulators are attractive drug target to screen for adjuvants for viruses sensed by the cGAS-STING or Rig-I-MAVS axis, respectively. In a long-term goal, we would like to screen potential novel adjuvants directed towards these novel targets.

2. Identify cellular restrictions towards viruses

A key to understanding the inefficient innate immunity leading to immune escape by HIV-1 and the potential role of SAMHD1 in tumor escape mechanisms from immunity will be the identification and validation of regulators that control the activity of SAMHD1 (funding by SFB1292). The goal of this ongoing project in the lab is to characterize the proteins that we recently identified in a proteomics approach as binding partners of SAMHD1.

Furthermore, we have set up a high-content imaging platform that enables to identify novel cellular factors that are antagonized by accessory proteins encoded by viruses. Viruses devote a large portion of their coding capacity to counteracting restriction factors by encoding proteins devoted to neutralizing the antiviral function of these intracellular inhibitors. One strategy particularly favored by viruses to achieve these goals is to subvert the host ubiquitin machinery in order to induce the proteasomal or lysosomal degradation of specific cellular factors. We have set up a high throughput screen where we expressed approx. 800 known interferon-stimulated genes (ISGs), potential targets of viral proteins, one-by-one in an arrayed approach in presence or absence of the viral protein of interest. Using an automated high-content imager, ISGs that are degraded can be immediately identified.

3. Establish novel platform technologies in order to identify novel host cellular factors

- CRISPR/Cas9 screening approaches
- Meta-Analysis approach
- High-content imaging platform
- iPSC technology