Institute of Clinical and Molecular Virology
Chair of Clinical and Molecular Virology

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Research Focus
- Retroviral infections
- Herpesviral infections

Structure of the Chair

Professorships: 4
Personnel: 107
- Doctors (of Medicine): 5
- Scientists: 15 (thereof funded externally: 12)
- Graduate students: 22

Clinical focus areas
- Serological, molecular biological, and virological diagnostics of viral infections
- Drug resistance testing
- Genotyping

Research

Despite substantial progress in our understanding of viral host cell interactions and the interplay between viruses and the immune system, there still is an unmet medical need for prevention, control, and eradication of persistent viruses, particularly in an aging population with decreasing immune competence. Human herpesviruses and retroviruses continue to be major health threats internationally as well as in Germany and are therefore the focus of the Institute’s research efforts.

Retroviral infections

PI: Dr. A. Thoma-Kreß, Prof. Dr. U. Schubert, Prof. Dr. T. Gramberg, Prof. Dr. K. Uberla, Dr. V. Temchura

One HTLV research group and three HIV research groups are working at the Institute. The HTLV research group studies interactions of human T-cell leukaemia virus Type 1 (HTLV-1) with the host cell to decipher molecular mechanisms of HTLV-1 cell-to-cell transmission. The group identified an essential role of the actin-bundling protein Fascin in HTLV-1 release and cell-to-cell transmission. The second research group investigates the late processes of the HIV-1 replication cycle, particularly virus assembly and budding. It was shown that the HIV-1 p6 Gag protein regulates not only those late processes, but also membrane association, ubiquitination, and thus the entry of Gag into the MHC-I antigen presentation pathway. Moreover, it was shown that the accessory protein Vpu induces downregulation of the co-activating NK-cell receptors NTB-A and CD155, and thus subverts NK-cell responses against HIV-1 infected T cells. The third research group is characterizing the innate and intrinsic immune response during retroviral infection. The group focuses on the antiviral restriction factors SAMHD1 and the TRIM protein family. The laboratory found that SAMHD1 has broad antiretroviral activity against which most retroviruses, like HIV-1, have not found an escape mechanism. Furthermore, the group was able to analyze the function of murine SAMHD1 in vitro and in vivo using knockout mice. The fourth research group is exploring effector mechanisms of the adaptive immunity to HIV and aims at developing an HIV vaccine. In a relevant animal model, they could show for the first time that antibodies to HIV Env can block infection of the very first cell after mucosal exposure. For vaccine development, the group uses gene-based vaccine approaches, liposomal vaccines, virus-like particle vaccines and nanoparticles.

Herpesviral infections

PI: Prof. Dr. T. Stamminger, Prof. Dr. M. Mar- schall, Prof. Dr. M. Mach, Dr. K. Korn, Prof. Dr. A. Ensser, PD Dr. B. Biesinger, PD Dr. F. Neipel, Prof. Dr. W. Dörlfer

Several aspects of human cytomegalovirus infections are investigated. A major research emphasis is on the analysis of HCMV effector proteins that exert essential functions for viral replication. During the last two years evidence was obtained that a structure of the cell nucleus, termed PML nuclear bodies, acts both as a direct restriction factor for viral infections and as a coactivator of the interferon response. Consequently, the IE1 protein of HCMV which exhibits significant structural similarity to immunoregulatory proteins of the TRIM family, was found to antagonize both, intrinsic immunity and the interferon response. The regulatory role of protein kinases in the replication of the human cytomegalovirus and related herpesviruses was also studied. In particular, the importance of protein kinases for the nucleo-cytoplasmic egress of viral particles has been demonstrated. A functional involvement of the cytomegalovirus-encoded protein kinase pUL97 in these processes was shown, as well as their regulatory interaction with cellular cyclins. Further viral and cellular components of the nuclear egress complex were identified by the use of proteomics approaches and were functionally characterized. Particular importance had the x-ray-based resolution of the crystal structure of the nuclear egress core heterodimer as a functional platform for the nuclear release of HCMV. Moreover, an investigation of the antiviral potential of protein kinase inhibitors illustrated that these viral and cellular kinase activities can be exploited as promising targets for future antiviral strategies.

In attempts to define the protective antibody response against CMV, a number of monoclonal antibodies specific for glycoprotein B, one of the major antigens for the induction of antibodies, were isolated. In vivo protection experiments in mice, it was shown that both neutralizing as well as non-neutralizing antibodies have the capacity to protect immunodeficient hosts from the lethal course of the infection with neutralizing antibodies being superior. During this work γδ T cells were serendipitously identified as yet another cell type that is involved in protection from CMV infection. The findings could have implications in the stem cell transplant setting, as antigen recognition by γδ T cells is not MHC-restricted and dual reactivity against CMV and tumors has been described. Together with Prof. Dr. W. Holter and PD Dr. M. Lehner (St. Anna Kinderspital and Children’s Cancer Research Institute, Vienna), a translational approach for an antiviral, adoptive immunotherapy of CMV infection using chimeric antigen receptors (CAR) is also pursued. These studies revealed a new

Nuclear colocalization of the two cytomegalovirus proteins pUL50 and pUL53

Using a double-staining confocal immunofluorescence imaging approach, the two proteins that mediate the nuclear egress of cytomegalovirus particles from infected host cell nuclei were detected in their fine-localization at the nuclear envelope (HeLa cells, nuclear DNA counterstaining by DAPI). Note the complete pUL50-pUL53 recruitment and colocalization, in part visible as a fine-speckled structure which is depicted in three different orientations by the use of confocal laser-scanning microscopy. (Figure: Eric Sonntag / Team Marshall)
increases in cellular DNA methylation patterns upon Ad12 or ASFV infection, possibly as part of the apoptotic pathway.

In addition to HCMV, oncogenic herpesviruses are also targeted for research. One group addresses the mechanisms of viral effectors in circumventing cellular restriction factors that are concentrated in the nuclear domain 10 (ND10). These comparative studies of rhadinoviral tegument proteins (in Kaposi’s Sarcoma associated Human Herpesvirus 8, Rhesus Rhadinovirus, Herpesvirus saimiri) revealed a proteasome-independent degradation of major ND10 components SP100 and PML by the KSHV model virus RRV, but also a restriction of this primate virus by DAXX. The mechanisms by which oncoproteins of T-lymphotropic rhadinoviruses are capable to transform human T cells to permanent growth in culture are also analyzed. The studies focused on the interactions with TNF receptor-associated factors (TRAF). It could be demonstrated that the viral oncoproteins utilize these cellular proteins to regulate NF-κB and other signaling pathways which may contribute to viral persistence. For the oncogenic Kaposi sarcoma-associated herpesvirus (KSHV) it could be shown for the first time that the Ephrin receptor tyrosininkase A2 (EphA2) is an essential receptor for KSHV upon infection of endothelial and epithelial cells. It could be demonstrated in 2015 and 2016 that the intracellular part of EphA2 is not required for KSHV infection and that KSHV-RTA regulates EphA2 expression by post-transcriptional mechanisms. Another group investigated the impact of virus infections (Ad12, ASFV, HIV-1, HSV1, and AcMNPV) on epigenetic regulation of transcription and found global increases in cellular DNA methylation patterns upon Ad12 or ASFV infections, possibly as part of the apoptotic pathway.

Teaching

Curricular lectures and courses on virology and immunology for students of human medicine, dentistry, pharmacy and molecular medicine are jointly given by the Institute of Clinical and Molecular Virology and the Institute of Clinical Microbiology, Immunology, and Hygiene.

In collaboration with further colleagues from the UK Erlangen as well as from Würzburg and Nuremberg, members of the Institute engage in the interdisciplinary course on virology and immunology (QM). Furthermore, the Institute of Clinical and Molecular Virology offers a series of elective and compulsory optional courses for students of the Faculty of Medicine and the Faculty of Sciences. Thus, teaching in virology extends to B.Sc. and M.Sc. degree programs in molecular medicine, biology, integrated life sciences and molecular sciences.

The course offerings are completed by the supervision of Bachelor’s, Master’s, MD, and PhD theses.

Selected Publications

Heizner AM et al. Sequence-specific activation of the DNA sensor cGAS by Y-form DNA structures as found in primary HIV-1 cDNA. Nat Immunol 2015, 16 (10): 1025–33


International Cooperations

Prof. J. Ung Jung, University of Southern California, Los Angeles: USA
Prof. W. Britt, University of Alabama, Birmingham: USA
Prof. W.D. Rawlinson, University of New South Wales, Sydney: Australia
Prof. Dr. A. Balasubramanyan, Division of Endocrinology, Baylor College of Medicine, Houston: USA
Prof. Dr. D. Barouch, The Ragon Institute of MGH, MIT and Harvard, Boston: USA