Respiratory virus infections and lung immunity

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Background and preliminary data:

Respiratory virus infections are a major cause of mortality worldwide. Some members thereof have a zoonotic background and may pose -upon further evolution with respect to airborne transmission- a serious pandemic threat. Our laboratory has identified the cellular import machinery as a key host factors in promoting virus evolution and adaptation upon avian-human transmission of avian influenza A viruses (Gabriel et al., PNAS 2005; Gabriel et al., Nat. Commun. 2011; Hudjetz & Gabriel, PLoS Pathogens 2012). Herein, particularly the importin-α3 isoform plays a key role in regulating innate immunity in the human lung. Influenza viruses have adapted specific mechanisms to circumvent importin-α3 mediated immunity in the lung thereby causing serious lung pathologies (Thiele et al., Cell Reports 2020). There is now increasing evidence that other emerging viruses, such as SARS-CoV-2, hijack the cellular import machinery to circumvent innate immunity and thereby establish high-level virus replication in the lung.

Hypothesis:

We hypothesize that respiratory virus infections (influenza, RSV, SARS-CoV-2) have evolved common mechanisms to circumvent key factors regulating innate immunity in the lung.

Aims and Work Programme:

1. To study replication kinetics and innate immune responses upon respiratory virus infection in human lung organoids.
2. To identify the human lung innate immune atlas upon respiratory infection using multi-omics.

In Aim #1, we will generate human lung organoids, which will be infected by influenza A viruses, RSV or SARS-CoV-2 respectively. Using a variety of molecular techniques (e.g. plaque assay, real-time PCR, Western Blot,…) we will measure replication kinetics, determine cytokine/chemokine responses and analyze importin-α expression profiles in the human lung organoids. This comparative approach will identify common and distinct innate immunity landscapes upon respiratory virus infection in the human lung.

In Aim #2, we will use the in aim#1 established setting to perform an unbiased transcriptomics and proteomics approach in the respiratory virus infected human lung organoids. The obtained molecular data will be analyzed by artificial intelligence based programs to unravel new infection mediated immune response pathways. By combining the specific pathways identified in aim#1 with the unbiased pathways identified in aim#2, we will generate a new immune atlas of respiratory virus infection in the human lung.

Overall, the in aim#1 and aim#2 obtained data will provide new insights for the design of future antiviral strategies that aim targeting common factors used by the three major respiratory pathogens currently circulating in the human population and causing high morbidities and mortalities.

Project-related publications:

Zickler M, Stanelle-Bertram S, Ehret S, Heinrich F, Lange P, Schaumburg B, Mounogou Kouassi N, Beck S, Jäckstein MY, Mann O, Krasemann S, Schröder M, Jarczak D, Nierhaus A, Kluge S, Peschka M, (...), Ondruschka B, Heeren J*, Gabriel G* (2021). Replication of SARS-CoV-2 in adipose tissue determines organ and systemic lipid metabolism in hamsters and humans. Cell Metabolism. 2021 Dec;10. *equally contributed;

Thiele S, Stanelle-Bertram S, Beck S, Kouassi NM, Zickler M, Müller M, Tuku B, Resa-Infante P, van Riel D, Alawi M, Günther T, Rother F, Hügel S, Reimering S, McHardy A, Grundhoff A, Brune W, Osterhaus A, Bader M, Hartmann E, Gabriel G (2020). Cellular Importin-α3 Expression Dynamics in the Lung Regulate Antiviral Response Pathways against Influenza A Virus Infection. Cell Reports 2020 Apr 21;31(3):107549.

Engels G, Hierweger AM, Hoffmann J, Thieme R, Thiele S, Bertram S, Dreier C, Resa-Infante P, Jacobsen H, Thiele K, Alawi M, Indenbirken D, Grundhoff A, Siebels S, Fischer N, Stojanovska V, Muzzio D, Jensen F, Karimi K, Mittrücker HW, Arck PC* and Gabriel G* (2017). Pregnancy-Related Immune Adaptation Promotes the Emergence of Highly Virulent H1N1 Influenza Virus Strains in Allogenically Pregnant Mice. Cell Host and Microbe, Mar 8;21(3):321-333. *equally contributed; Article reviewed in Ghedin & Schultz-Cherry, Nature Microbiology 2018 and reviewed in Bordon, Nature Reviews Immunology 2018.

Gabriel G#, Klingel K, Otte A, Thiele S, Hudjetz B, Arman-Kalcek G, Sauter M, Shmidt T, Rother F, Baumgarte S, Keiner B, Hartmann E, Bader M, Brownlee G., Fodor E, Klenk HD (2011). Differential use of importin-α isoforms governs cell tropism and host adaptation of influenza virus. Nature Communications, 18(2):156. #corresponding author.

Gabriel G, Dauber B, Wolff T, Planz O, Klenk H, Stech J (2005). The viral polymerase mediates adaptation of an avian influenza virus to a mammalian host. PNAS, 102:18590-18595.