MED MEDIZINISCHE FAKULTÄT

Forschungsbericht 2021

Institut für Experimentelle Innere Medizin

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1. LEITUNG

Univ.-Prof. Dr. rer. nat. habil. Michael Naumann (Institutsdirektor)

2. HOCHSCHULLEHRER/INNEN

Univ.-Prof. Dr. rer. nat. habil. Michael Naumann

3. FORSCHUNGSPROFIL

- NF-kB, Pathogen-Infektion
- NF-kB, angeborene Immunantwort und Entzündung
- NF-kB, Zellüberleben / Epitheliale Barriere / Micromilieu
- NF-kB, Deubiquitinylasen / COP9 Signalosom
- Deubiquitinylase-Inhibitoren / Biomolekulare Modellierung / Wirkstoffforschung
- Ubiquitin-Proteasom System und Adipogenese

4. SERVICEANGEBOT

Massenspektrometrie

5. FORSCHUNGSPROJEKTE

Projektleitung: Prof. Dr. Michael Naumann, Prof. Dr. Christoph Arens
Projektbearbeitung: Melissa Kantar Weigelt
Förderer: EU - ESF Sachsen-Anhalt - 01.08.2020 - 30.05.2022

ABINEP M3-project 4: Biofilm, microbiome and infection during cancer of the larynx

Die hier beantragte ESF-geförderte internationale OVGU-Graduierten- schule (ESF-GS) *Analyse, Bildgebung und Modellierung neuronaler und entzündungsbe- dingter Prozesse* (ABINEP) soll die Ausbildung internationaler Promovierender in den be- sonders forschungsstarken Profillinien der Medizinischen Fakultät der Otto-von-Guericke-Universität (OVGU) unterstützen und ausbauen. Die durch diese ESF-GS geförderten OVGU-Profillinien sind die Zentren für Neurowissenschaften (CBBS) und für die Dynami- schen Systeme (CDS, einschließlich Immunologie/Molekulare Medizin der Entzündung). Die ESF-GS umfasst 4 thematische Module mit insgesamt 21 Stipendiaten, die den o.g. Schwerpunkten z.T. parallel zugeordnet sind und die organisatorisch unter dem zentralen Dach der ABINEP ESF-GS zusammengefasst werden sollen. Jedes der 4 thematischen Mo- dule wird mit 5-6 Stipendiaten ausgestattet. Die **Module**, die Zuordnung der Anzahl der Stipendien und die durch sie unterstützten OVGU-Forschungsstrukturen sind unten aufgeführt. Weiterhin sind die inhaltlich eingebundenen außeruniversitären Partner benannt:

- 1. Neuroinflammation (5; CBBS, CDS, OVGU, FME, LIN, DZNE)
- 2. Modellierung neuronaler Netzwerke (5; CBBS, OVGU, FME, LIN, DZNE)

- 3. Immunoseneszenz (6; CDS, FME, HZI)
- 4. Bildgebung menschlicher Hirnfunktionen (5; CBBS, OVGU, FME, LIN, DZNE)

Die CBBS-assoziierten Module weisen eine starke Vernetzung mit den Ingenieur- wissenschaften (v.a. dem Transferschwerpunkt Medizintechnik) auf, die über eine unab- hängig beantragte eigene ESF-GS (MEMoRIAL) gefördert werden sollen. Eine enge Koope- ration zwischen diesen beiden ESF-GS ist geplant, um Synergien sowohl in der Ausbildung der Stipendiaten als auch für innovative neue Forschungsansätze in Zusammenarbeit mit dem Transferschwerpunkt Medizintechnik der OVGU und dem Landesprojekt Autonomie im Alter zu erreichen. Insgesamt fördert die ESF-GS ABINEP die Internationalisierung der anerkannten exzellenten medizinischen Forschung der OVGU.

Projektleitung: Prof. Dr. Michael Naumann
Förderer: Deutsche Forschungsgemeinschaft (DFG) - 01.01.2018 - 31.12.2021

Plasticity and cell-type specific functions of OTUB1 in infection

Deubiquitinating enzymes (DUBs) are critical regulators of immune responses and A05 aims to decipher cellular and molecular functions of the DUBs CYLD, A20 and OTUB1 in infectious and autoimmune disorders. Within the 1st funding period, A05 defined that CYLD impairs protective immune responses in listeriosis by inhibiting STAT3-dependent fibrin production in hepatocytes. The 2nd period originated, that CYLD (1) deubiquitinates RIPK2 and inhibits NOD2/RIPK2-mediated autophagy, ROS and NO production in macrophages, and (2) suppresses NF- B-dependent activation in DCs. In contrast, B cell-expressed A20 is essential to prevent spontaneous autoimmunity, whereas DC-specific A20 is required to prevent lethality upon low-dose LPS challenge. In support of a cell type-specific function of DUBs, A05 illustrated that A20 diminishes primary $CD8^+$ T cell responses in listeriosis but augments secondary $CD8^+$ T cell responses by preventing CD95- and TNF-mediated apoptosis and necroptosis of pathogen-specific memory T cells. Importantly, A05 has established a novel conditional OTUB1 mouse strain and has identified that OTUB1 regulates (1) JAK-dependent cytokine receptor signaling in T cells and (2) TLR/MyD88 -mediated NF- B activation in DCs. In T cells, A05 identified that OTUB1 interacts with and stabilizes SOCS1, which suppresses JAK/STAT signaling. In DCs, OTUB1 is required for Toxoplasma-induced TLR11/12-MyD88-dependent NF- B activation and protective IL-12 production. In the 3rd funding period, A05 will finalize its work on T cell-specific OTUB1 in EAE and DC-specific OTUB1 in toxoplasmosis. In collaboration with other projects of CRC854, A05 will extend its studies to the role of OTUB1 in (1) T cells, (2) DCs, (3) macrophages/granulocytes and (4) hepatocytes in the murine model of listeriosis. Preliminary data already show that the plasticity of the function of OTUB1 is determined by the underlying disease and additionally support our concept of a cell type-specific function OTUB. In fact in listeriosis, OTUB1 (1) prevents cell death of hepatocytes, (2) inhibits cytokine production of DC and (3) is required for T-cell- and macrophage-dependent pathogen control. Therefore, the focus of the studies will be to determine the molecular mechanisms of the cell type-specific function and plasticity of OTUB1, i.e. in listeriosis.

Projektleitung: Prof. Dr. Michael Naumann
Förderer: Deutsche Forschungsgemeinschaft (DFG) - 01.01.2018 - 31.12.2021

Helicobacter pylori type IV secretion system-directed membrane-proximal NF-kB signaling

In the stomach, chronic infection with the pathogen *Helicobacter pylori* represents a risk factor for the development of chronic inflammation, which is a potent promoter for metaplasia, dysplasia and cancer development. Colonization of gastric epithelial cells by *H. pylori* induces fast activation of the proinflammatory and survival factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). Activation of canonical NF-kB is strictly induced only by *H. pylori* strains carrying a cag pathogenicity island (*cag*PAI), which encodes a type IV secretion system (T4SS). Further, it has been suggested that *Helicobacter* outer membrane protein (HopQ), could contribute to NF-kB activation. The detailed mechanism of T4SS-dependent activation of membrane-proximal NF-kB activation is unresolved so far. Regarding the molecular mechanism responsible for canonical NF- B activation and inflammation in infected gastric cancer cell lines we defined as crucial elements the TAK1/TAB complex and the E3 ubiquitin ligase TRAF6, which are situated upstream of the NF-kB inhibitor B

kinase (IKK) complex. To identify *H. pylori*-induced proximal NF-kB signaling molecules which regulate substrate ubiquitinylation, we performed siRNA screens with human ON-TARGETplus siRNA libraries which selectively knockdown F-box and SOCS-box E3 enzymes, or RING-finger and RING-finger-like E3 single protein ligases. Some identified molecules contribute to NF-kB regulation, e.g. Ankyrin repeat and SOCS box protein 3 (ASB3), the Tripartite motif protein containing 28 (TRIM 28) and the ubiquitin-editing enzyme A20. Interestingly, we assigned that *H. pylori*-induced A20 terminates NF-kB activation, but also attenuates host apoptotic cell death. The overall aim of this project is to decipher the complex regulation of the membrane-proximal signal transmission leading to the activation of canonical NF-kB during *H. pylori* infection. In detail, we plan to elucidate bacterial T4SS components and Hop-protein adhesins, and their interplay with eukaryotic surface factors (receptors) to unravel NF-kB control in *H. pylori* infection. Further, a number of evaluated E3 ubiquitin ligases from siRNA screens will be functionally further assessed by a range of established biochemical and cellular approaches regarding their contribution to *H. pylori*-induced NF-kB activity. Finally, molecular traits of NF-kB signal transmission identified in infected gastric cancer cell lines will be investigated in regard to their *in vivo* relevance in experimental infection in mice and paraffin embedded human gastric tissue samples from patient biopsies.

Projektleitung: Prof. Dr. Michael Naumann
Förderer: Deutsche Forschungsgemeinschaft (DFG) - 01.10.2018 - 31.03.2023

Maladaptive processes across physiological barriers in chronic diseases

Graduiertenkollge 2408
Chronische Erkrankungen stellen eine zunehmende gesundheitspolitische Herausforderung dar. Zelluläre Maladaptationen und die fehlgeleitete Zell-Zellkommunikation an physiologischen Barrieren sind mechanistische Aspekte von zentraler Bedeutung bei chronischen Erkrankungen wie Atherosklerose oder chronische Erkrankungen der Niere, der Haut, oder des Gastrointestinaltrakts. Physiologische Grenzflächen werden durch hoch spezialisierte Zellen, z.B. **Endothelzellen** oder **Epithelzellen**, definiert. Störungen in der Regulation und Funktion dieser Grenzflächen führen zu einem pathophysiologischen Mikromilieu, charakterisiert z.B. durch ein spezifisches Sekretom sowie der Aktivierung lokaler Zellen und/oder Rekrutierung von Entzündungszellen. Von besonderer Bedeutung bei chronischen Erkrankungen ist die **Perpetuierung maladaptiver Prozesse,** die auf **posttranslationalen Proteinmodifikationen** beruhen. Das Verständnis molekularer Veränderungen, die maladaptiven Krankheitsprozessen an physiologischen Grenzflächen zugrunde liegen, ist derzeit noch sehr limitiert. Innerhalb des **GRK's** beabsichtigen wir Krankheit-auslösende maladaptive Prozesse an **endothelialen und epithelialen Grenzflächen** zu erforschen.

6. VERÖFFENTLICHUNGEN

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