Nayla Jbeily

Ceramide formation in host response to bacterial and fungal infection and development of organ failure

In addition to the function in membrane stabilization, sphingolipids and its metabolites were increasingly approved as key players in mechanisms of cellular stress response such as recognizing and elimination of microbial pathogens. The limiting step in sphingomyelin metabolism is the hydrolytic activity of sphingomyelinases, of which the secreted isoform has been shown to be increased in sepsis, chronic inflammation and organ failure. Own results and data from other groups emphasize its activity essential during the early phase of host response in gram negative infection as shown by overwhelming secretion of cytokines, increased mortality as well as reduced phagocytosis in loss-of-function studies. However, there is also increasing evidence, that ceramide formation is involved in the development of organ failure during severe infection. In this project, we will characterize the putative dual function of secreted sphingomyelinase to define the consequence for ceramide formation and orchestration of host response. For this purpose, the kinetic and dynamic of sphingomyelin hydrolysis in clearly defined models of inflammation and organ failure will be analyzed, i.e. polymicrobial cavity infection (peritonitis/sepsis), infection with gram negative rsp. gram-positive bacteria/with fungi and non-infectious conditions such as endotoxic shock and zymosan-induced multiple organ failure. Furthermore, it will be tested, whether (and from which time point) a pharmacological inhibition of ceramide generation may have a benefit with respect to organ function and survival. Comparative transcriptomics will be performed by Illumina-technology. Finally, we aim at the elucidation of differences of adherence, chemotaxis and diapedesis of activated leukocytes in living mice by intravital microscopy.

Publications

Press AT, Traeger A, Pietsch C, Mosig A, Wagner M, Clemens MG, Jbeily N, Koch N, Gottschaldt M, Bézière N, Ermolayev V, Ntziachristos V, Popp J, Kessels MM, Qualmann B, Schubert US, Bauer M (2014) Cell type-specific delivery of short interfering RNAs by dye-functionalised theranostic nanoparticles. *Nat Commun* 5, 5565. Details PubMed

Gonnert FA, Recknagel P, Seidel M, Jbeily N, Dahlke K, Bockmeyer CL, Winning J, Lösche W, Claus RA, Bauer M (2011) Characteristics of clinical sepsis reflected in a reliable and reproducible rodent sepsis

model. *J Surg Res* 170(1), e123-e134. Details PubMed

Supervisor

Ralf A. Claus

Co-Supervisors

Bernhard Hube

Start of PhD

January 8, 2010

Doctoral Disputation

July 1, 2013