27th ECCMID Vienna, Austria 22 – 25 April 2017

The congress of ESCMID

Session: OS066 Host-pathogen interactions provide opportunities for novel therapy

Category: 2b. Severe sepsis, bacteraemia & endocarditis

23 April 2017, 11:30 - 11:40
OS0329

The Trojan-horse hypothesis for the genesis of invasive bacterial infection

Giuseppe Ercoli[1], Vitor Fernandes[2], Peter Andrew[2], E Richard Moxon[3], Luisa Martinez-Pomares[4], Marco Rinaldo Oggioni*[1]

[1]*University of Leicester; Department of Genetics*

[2]*University of Leicester; Infection, Immunity and Inflammation*

[3]*University of Oxford*

[4]*University of Nottingham Medical School, School of Life Sciences*

Background: Despite continuous surveillance by innate and acquired immunity, humans occasionally develop invasive bacteria disease. While the steps leading to full blown host response in sepsis are fairly well understood, the molecular events preceding bacteremia are unknown. During the study of the initial events preceding bacteraemic sepsis by the model pathogen *Streptococcus pneumoniae,* we demonstrated that invasive disease in mice arises from the spleen following an eclipse period during which challenging inoculum is effectively cleared. We hypothesised that invasive disease was initiated by a small proportion of bacteria protected from immune attack through access to an “immune privileged” site within the spleen. The overall aim of this work was thus the identification of the relative molecular and cellular events, in models with increasing translational relevance, in order to develop testable models for the prevention of sepsis.

Material/methods: Confocal microscopy was used to explore the events in the early hours preceding sepsis in spleens of mice infected intravenously with pneumococci. Data were validated using a newly developed *ex-vivo* normothermic porcine spleen perfusion model in order to gain data on organs with a similar microarchitecture and macrophage functionality as humans.

Results: Data show that a subset of CD169 expressing metallophilic macrophages in the marginal zone of the spleen take up single pneumococcal cells and are permissive to bacterial intracellular

replication. At about eight hours post-infection CD169+ macrophages harboring over sixty bacterial cells start lysing. During that time, neutrophils are effectively recruited to the red pulp but no neutrophil recruitment to the vicinity of CD169+ macrophages is observed. This enables the infectious foci of rapidly replicating bacteria within CD169+ macrophages to invade the bloodstream. In accordance with the hypothesis of sepsis originating from foci of bacteria replicating within macrophages, a ultrashort-course treatment with two doses of a macrolide (good penetration into eukaryotic cells) was effective in preventing sepsis, while 77% of mice treated with a beta-lactam (low penetration) developed fatal disease. In an attempt to extrapolate these findings to the human situation, we tested the fate of pneumococcal infection in a porcine spleen perfusion model. In agreement with our findings in mice, we observed uptake and rapid intracellular replication of pneumococci within CD169+ macrophages, which in pigs, as in humans, are located in the peri-arteriolar and peri-follicular areas of the spleen.

Conclusions: These data introduce a completely novel concept into the pathogenesis of invasive bacterial infection, in particular regarding the events preceding sepsis. We expect that our findings showing that active bacteremia arises from foci of bacterial replication in permissive CD169+ splenic macrophages will provide substantial input in strategies to optimize and potentially revise treatment and prevention of sepsis in a clinical setting.