COMBINING A WHOLE BLOOD INFECTION ASSAY WITH BIOMATHEMATICAL MODELING TO CLASSIFY INNATE IMMUNE FUNCTION

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INTRODUCTION

- Marked heterogeneity of sepsis as a clinical syndrome
- Caused by highly diverse pathological conditions and shows variable kinetics in individual patients
- Classification of sepsis patients by their immune status is necessary for immunomodulatory therapy approaches

➔ Individualized quantification of altering immune effector functions of septic patients

Are there pathogen-specific patterns of immune activation during whole blood infection?

Are there immune effector functions that allow stratification of sepsis patients?

APPROACH

Human whole-blood infection assay

- Association with neutrophils (PMN) and monocytes (MoC)

Association kinetics

State-based model

- States:**
- P_E = pathogens in extracellular space
 - P_{IE} = pathogens, that became immune evasive
 - N_j = PMN with j killed pathogens
 - M_j = MoC with j killed pathogens

Immune reaction rates:

- ϕ_N = phagocytosis by PMN
- ϕ_M = phagocytosis by MoC
- ρ = acquired immune evasion

Virtual infection model

RESULTS

Pathogen association with immune cells in blood from healthy volunteers

Association with immune cells

Quantification of immune effector mechanisms by biomathematical analyses

Model simulation results

Comparison of infection with either *C. albicans* or *S. aureus*

- Higher association of *S. aureus* cells with MoC
- Larger number of free *C. albicans* cells
- S. aureus* infection causes quicker increase of association kinetics

Immune reaction rates

- Immune defence against *S. aureus* is faster

Pathogen association and innate immune activation in blood from HLM patients

- Within a pilot study, blood samples of 5 patients that underwent cardiac surgery with extracorporeal circulation (heart-lung machine, HLM) were analysed
- Blood samples were obtained before cardiac surgery (pre-operative), immediately after surgery (post-operative), and 1 day after admission to ICU

White blood cell count

Blood cell count was quantified via hematological analyzer.

- Increase in white blood cell count after surgery (maximum at 1d)
- High neutrophil numbers exceeding the reference range after surgery
- Monocyte number increases

Association with immune cells

Immune reaction rates

Immune response after surgery shows increase of

- Association kinetics
- Immune reaction rates

Pathogen-specific patterns of immune response diminished

CONCLUSIONS

To make immunomodulatory therapy approaches for sepsis patients possible it is necessary to develop tools that enable the classification of sepsis patients by their immune status. The use of an *ex vivo* whole blood model of infection combined with advanced biomathematical quantification allows for the quantification of immune effector functions, thereby forming a basis for future patient stratification.