**CRC685 TPA03 (Autenrieth/Peschel):**

**Evasion and exploitation of innate and adaptive immunity by *Staphylococcus aureus***

*Staphylococcus aureus* is a highly successful human pathogen whose virulence depends largely on sophisticated strategies to evade and exploit innate and adaptive immune responses. Virulence of emerging community-associated methicillin-resistant *S. aureus* (CA-MRSA) relies on phenol-soluble modulin (PSM) peptide toxins. We could show that CA-MRSA use PSMs to attract and stimulate neutrophils via the formyl peptide receptor 2 (FPR2), a G-protein coupled receptor, and to disrupt neutrophils when sufficiently high PSM concentration are reached (Kretschmer/Peschel). Furthermore, PSMs appear to interfere with adaptive immunity by counteracting the stimulation of DCs by TLR ligands thereby diminishing DC maturation, proinflammatory cytokine secretion, and antigen uptake, leading to reduced Th1 but more pronounced regulatory T cell response *in vitro* (Autenrieth, see Figure 3). The underlying mechanisms and their relevance for host defense and inflammation have remained elusive. We want to address the following questions:
(1) FPR2 represents a previously unrecognized player in innate immunity whose role in infection and inflammation has remained largely unclear. In order to study FPR2 in mouse models we will elucidate, which of the various mouse FPR2 homologs senses PSMs and investigate the impact of FPR2 and its endogenous antagonist lipoxin on the course of *S. aureus* infections using different available transgenic mice. (2) PSMs do not only stimulate FPR2, they are also important for strong TLR2 stimulation, probably by facilitating the release of lipopeptides, the major staphylococcal TLR2 ligands. How PSMs affect lipopeptide release and how they shape pro- or anti-inflammatory responses will be investigated with defined *S. aureus* mutants and transfected human cell lines.
(3) What are the underlying molecular mechanisms responsible for the induction of the regulatory T cell response by PSM-treated DCs? (4) What is the relevance of PSM-modulated DCs *in vivo*? Therefore, DC functions will be examined upon infection with CA-MRSA wild-type and PSM mutant strains using different *in vivo* mouse models e.g. systemic, soft-tissue, skin and lung infection models.
These studies will increase our understanding on the complex immune evasion immune evasion strategies of *S. aureus* and will uncover possible strategies for immunotherapy.

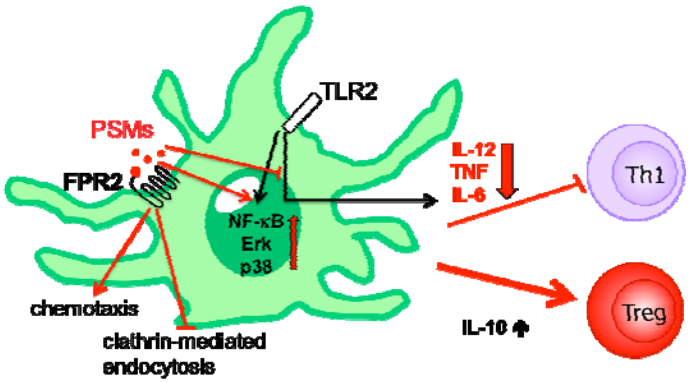


Figure 3: *Staphylococcus aureus* PSM peptides modulate dendritic cell functions and increase in vitro priming of regulatory T cells