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Plasmacytoid dendritic cells and type I interferon in the regulation of the humoral response to *Streptococcus pneumoniae* and *Staphylococcus aureus.*

Fach/Einrichtung: Infektiologie

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Infection by *Streptococcus pneumoniae (S. pneumoniae)* is the major cause of pneumonia, otitis, septicaemia and meningitis in young children. *Staphylococcus aureus (S. aureus)* permanently colonizes the epithelium in the anterior nares, causes skin infections or serious invasive diseases such as septic arthritis, osteomyelitis and endocarditis. Both Gram-positive bacteria constitute a leading cause of morbidity and mortality worldwide. Plasmacytoid dendritic cells (pDC) are leukocytes of lymphoid origin localized in the peripheral blood and tissues, specialized in the production of type I interferons upon microbial stimulation, mainly after viral infection. In the human body, IFNα secretion is almost exclusively due to the stimulation of these cells. It is known that pDC play a defined role at the interface of innate and adaptive immunity. However, not much is known about the pDC function in the immune response against extracellular bacteria. The aim of this study was to investigate the role of pDC and type I IFN in the immune response to *S. pneumoniae* and *S. aureus*. It explores the bacterial recognition and evaluates how it can affect the B cell activation. Proliferation of B cells and immunoglobulin production was used as a read-out system. Host-pathogen interaction was assessed *in vitro* and *in vivo*.

A key initial question was addressed: the ability of pathogenic Gram-positive bacteria *(S. pneumoniae, S. aureus)* or *S. pneumoniae* polysaccharides to activate B cells. *S. aureus* induced strong B cell response. The rest of the stimuli induced weak proliferation or immunoglobulin secretion. The presence of other immune cells and soluble factors in the culture was crucial to upgrading the response. I showed that pDC represent essential mediators of B cell proliferation and immunoglobulin secretion upon challenge with CpG-ODN, *S. aureus* and *S. pneumoniae.* Remarkably, pDC cannot be substituted by type I interferon. This indicates that pDC support the B cell activity in a cell contact-dependent manner. I further demonstrated that differences in Pneumococcal structure and virulence targets such as capsular polysaccharides and choline-binding proteins modulate the host immune response. *S.*

pneumoniae choline mutants, despite their reduced virulence, were able to induce immunoglobulins and pro-inflammatory cytokine secretion. Data further show that the expression of cytosolic PRR in human B cells is strongly increased in the presence of type I IFN. The secretion of IFN I may result from Fcy receptor-mediated uptake of pDC. Overall the results obtained in this study indicate that pDC can enhance microbe-induced immunoglobulin secretion. The identification of soluble factors or molecules involved in B cell/pDC interaction. This represents an important issue which may provide a new approach to vaccine development against *S. pneumoniae* and *S. aureus.*