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It has been established that the immune system of early life is by some means immature and exhibits a number of 'deficiencies': We and others have shown that antimicrobial phagocytosis may be altered and that T-helper cell-responses and production of selected cytokines are reduced. Moreover, impaired immunoglobulin synthesis contributes to increased susceptibility to infectious diseases during the newborn period. These observations are even more evident in newborns after preterm birth. Preterm infants are at high risk to acquire recurrent bacterial infections during their first weeks of life. Both the permanent exposure to microorganisms due to invasive procedures (e.g., intravascular catheterization or assisted ventilation) and the immaturity of the newborn immune system are responsible for the increased susceptibility to severe infections in preterms. Early onset sepsis (sepsis within the first 72 h of life) remains an important cause of death among very low birth weight (VLBW) infants. Thus, a more precise delineation of these immunological mechanisms will hopefully contribute to approaches improving the outcome.

The fact that, under normal circumstances, the fetus is protected from inflammation by maternal protection mechanisms implicates a lack of stimuli required for functional maturation of the immune system. Studies of leukocytes from preterm newborns are rarely performed, and there are few data available concerning the development and function of the innate immune system during gestational aging. Our research group and others have investigated activation and functional outcome of monocytic cells in preterm- and VLBW- infants. Data from the past decade will be presented and discussed.

In general, most clinical signs observed in the initial phase of sepsis are thought to be triggered by Toll-like receptor (TLR) activation. TLRs have been demonstrated to be pattern-recognition receptors for microbial antigens (components) that contribute to the host defense against infection. The interaction between TLRs and pathogens initiates the activation of an evolutionary conserved immune signaling network leading to the rapid and transient phosphorylation of several downstream signaling proteins. Lipopolysaccharide (LPS) from gram-negative bacteria and lipoteichoic acid (LTA) from gram-positive bacteria are major immunostimulatory bacterial cell wall components and activate the stress-activated protein kinases (SAPKs) p38, p42/ p44 (extracellular regulated kinase [ERK] 1/2), and Jun N-terminal kinase in a myeloid differentiation factor 88 (MyD88)–dependent pathway through TLR4 and TLR2, respectively. The ultimate outcome is the transcription of hundreds of inflammatory mediators.

Our first studies showed that TLR4 expression increases during gestational aging and, similarly, that production of TLR4-induced inflammatory cytokines increases in a gestational age–dependent manner upon LPS encounter. Indeed, similar TLR expression profiles were observed in experimental settings in mice. Because TLRs – as well as other PRRs and their downstream signaling network are essential players in an evolutionary conserved first line of defense, analysis of these key molecules contribute to a better understanding of the ontogenic maturation of host defense against foreign microorganisms.

In my lecture, we will discuss those findings postulating clinical implications and bridge them with experimental models in order to question future therapeutic applications.