Old Herborn University Seminar Monograph 19:
Defence mechanisms of the innate system: influence of microbes.
Editors: Peter J. Heidt, John Bienenstock, Tore Midtvedt, Volker Rusch, and Dirk van der Waaij.
Herborn Litterae, Herborn-Dill, Germany: 109-111 (2006).

INFLAMMATORY IMMUNITY AT BIRTH

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BIRTH, A TRAUMA-LIKE EVENT

Birth constitutes one of the most dynamic but also potentially hazardous events in the human life cycle. It involves huge changes in most organ-systems of the mammalian body. Cardio-respiratory, endocrine-metabolic, nutritive, nervous and immune functions are affected, including an activation of immune-inflammatory pathways (*Marchini* et al., 2000, 2005a). In many ways this process have striking similarities to "trauma-stress" (*Souba*, 1994). Birth also marks a transition from foetal, sterile life to a terrestrial life in co-existence with the microbial world. Meeting a rapid colonising commensal microflora for the first time, results in a potential danger of a microbial invasion through the epithelial linings. This is one of the reasons why an activation of the immune system, in particular an induction of innate immunity, makes good sense from an evolutionary point of view. Skin and mucosal surfaces are rapidly colonised at birth and a preparedness of the immune system increases the capability to resist the predation of potentially invading microbes.

BIRTH, AN ACUTE PHASE REACTION

IL-6, the principal cytokine mediating the acute-phase reaction, is up-regulated already during normal parturition (*Marchini* et al., 2000). The release of IL-6, a pleiotrophic cytokine with many effects (*Heinrich* et al., 1990; *Molloy* et al., 1993), including that on the hypothalamic-pituitary-adrenal stress axis (*Masturakos* et al., 1993) is followed by a peak induction of acute phase proteins such as C-reactive protein, serum amyloid A and pro-calcitonin during the early postnatal days (*Marchini* et al., 2000). An increase in body temperature, reflecting the interactions between immune and nervous system is also notes in new-born infants (*Marchini* et al., 2000) as part of the of the systemic inflammatory response maybe to the colonisation and/or tissue "damage" connected to birth. Increases in temperature is believed to be important in host defence (*Kluger* et al., 1996). The infant's capacity to secrete gastric acid soon after birth is well described (*Avewry* et al., 1966) as is the importance of the acidification of the gastric content for the microbial ecology of the gastro-intestinal tract (*Wolfe* and *Soll*, 1988). A huge recruitment of circulating leukocytes are found at birth (*Moshfegh* et al., 2005). The enhanced reactivity of neonatal leukocytes, as reflected by an increased transmigrations capacity *in vitro* of eosinophils (*Moshfegh* et al., 2005) as well as increased cytotoxic responsiveness of neutrophils (*Koening* et al., 2005) clearly points out the potential role of inflamers immunity for health and disease in the human new-born (*Diodovich* et al., 2004; *Jiang* et al., 2004; *Thorton* et al., 2004).

SKIN IMMUNE SYSTEM

Protecting the body from infection is critical for survival and the mammals have developed a number of defence systems to reinforce epithelial linings, including the skin immune system. Immediately after birth the human new-born is partly covered by a cream-like white substance, *vernix caseosa*. This substance is to large extent constituted by water but contains also foetal keratinocytes and antibacterial peptides/proteins such as LL-37, psoriasin and lysozyme. (*Marchini* et al., 2002; *Yoshio* et al., 2003). It disappears spontaneously within a few hours after birth and it may have a physiological role in immunoprotection in the immediate postnatal period, before humoral and cellular components are recruited into the skin. Furthermore, there is a powerful upregulation of innate immunity in the skin of the healthy new-born infant during the early days of life (*Marchini* et al., 2001, 2002, 2003). This immune activity may be seen as a rash, known as *Erythema Toxicum Neonatorum* and is most probably a response to the commensal colonisation of the skin at birth. One-day old, healthy new-borns are colonised mainly with coagulase-negative *Staphylococci* (84%), remaining with *Staphylococcus aureus*, Alfa-streptococcus, group B streptococcus, *Enterococcus* species and *Micrococcus* species. Transmission electron microscopy analysis of a typical lesion of *Erythema Toxicum* has revealed microbial-like material into phagosomes of epithelial cells and into immune cell located in proximity to the hair follicle, indicating a penetration of microbes into the skin at birth (*Marchini* et al., 2005b). The findings also suggest that the hair follicle immune system may constitutes the physiologic "room" where microbes are presented to immune competent cells. This exposure may provide signals, possibly mediated by the Toll-Like receptors (TLRs) that alert the immune system and promotes a protective immune response. Preliminary results indicate that TLR 2 and TLR4 are indeed expressed on keratinocytes of newborns. Other factors that may affect immune functions are the high levels of steroid hormones normally present at birth (*Marchini* et al., 2005b; *De Peretti* and *Forest*, 1976). Steroid hormones may influence immune functions both locally in the skin and other epithelial linings, but also in a systemic way (*De Peretti* and *Mappus*, 1983; *Pelletier* and *Ren*, 2004; *Thornton*, 2002).

Previous and recent results clearly indicated that the healthy human newborn mounts an acute and powerful inflammatory immune response in order to face the commensal colonisation of epithelial linings. This event may have implications for colonisation resistance and the induction of tolerance.

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