

DEVELOPMENTAL AND CHOLERA TOXIN-INDUCED ALTERATIONS IN THE EXPRESSION OF INTRACELLULAR SIGNALLING MOLECULES

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av

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Avhandlingen baseras på följande arbeten:

- I Slavica L, Nurkkala-Karlsson M, Karlson T, Ingelsten M, Nyström J, Eriksson K.
IDO expression and functional activity in dendritic cells exposed to cholera toxin.
Scandinavian Journal of Immunology 2012; 76(2): 113-22.
- II Slavica L, Nordström I, Nurkkala Karlsson M, Valadi H, Kacerovsky M, Jacobsson B,
Eriksson K.
TLR3 impairment in human newborns.
Journal of Leukocyte Biology 2013; 94(5): 1003-11.
- III Zenić L, Nordström I, Karlsson A, Eriksson K.
Cholera toxin selectively blocks TLR7 expression in human lymphocytes.
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DEVELOPMENTAL AND CHOLERA TOXIN-INDUCED ALTERATIONS IN THE EXPRESSION OF INTRACELLULAR SIGNALLING MOLECULES

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Abstract:

The innate immune system represents the first line of host defence that reacts promptly to microbial attacks. This system relies on several families of pathogen-recognition receptors (PRRs), which recognize pathogen-associated molecular patterns (PAMP) on a broad range of pathogens. Toll-like receptors (TLRs), the best-characterised PRRs, act through the signal transduction pathways to induce production of the pro-inflammatory cytokines that participate in innate responses against pathogens and also provide signals for the activation of adaptive immunity.

At birth, the immune system is characterised by immaturity and undeveloped functions. This is reflected in the greater susceptibilities of neonates to various pathogens, in particular viruses, such as herpes simplex virus (HSV), respiratory syncytial virus, and cytomegalovirus. The aim of this thesis was to characterize in umbilical cord blood cells the expression profiles of PRRs that sense viral nucleic acids, and to ascertain whether these profiles represent a molecular basis for the inadequate neonatal responses to viral infections. Neonatal natural killer (NK) cells, normally involved in anti-viral and anti-tumour defences, were found to lack TLR3 mRNA and protein expression. Consequently, they could not respond to the TLR3 ligand poly(I:C) by producing IFN- γ , which, in contrast, was abundantly secreted by adult NK cells. The neonatal NK cell cytotoxicity against tumor cells, HSV-infected targets, and in stimulation with HSV was also impaired. In similarity to the cord blood NK cells, TLR3 mRNA expression was low in decidual NK cells obtained from placentas at full-term delivery, but not in mononuclear blood cells from pregnant women. In adult mononuclear blood cell populations, the highest level of TLR3 expression was associated with the cytotoxic CD56^{dim} NK cell subset.

Dendritic cells (DCs) link the innate and adaptive immunity systems through TLR signalling. DCs also induce tolerance to host antigens, and regulate the magnitude of immune responses by suppressing immune reactions, partly mediated by the tryptophan-degrading enzyme indoleamine-2,3 dioxygenase (IDO). Cholera toxin (CT), which is a strong bacterial immunogen and a DC-maturation-promoting adjuvant, was investigated in the context of IDO induction. CT-pulsing of DCs induced the expression of IDO mRNA but not the production of IDO protein. However, CT primed for CD40L-induced IDO mRNA and protein activity. The CT-pulsed DCs potently stimulated allogeneic and autologous T-cell responses, and these activities were not regulated by IDO. However, CD40L-induced IL-12p40 production was dependent upon IDO.

The mechanism of CT adjuvanticity has been addressed with respect to interference with viral-recognition receptor pathways. Among the different viral nucleic acid-sensing receptors, CT showed selective inhibition of TLR7 mRNA expression. Although they represent the main mechanisms through which CT exerts its effects, the induction of cyclic adenosine monophosphate and PKA activation were not linked to the CT-mediated down-regulation of TLR7 mRNA. Instead, the PKC signalling pathway was implicated, as was IL-6.

Overall, the results presented in this thesis reveal new thinking about the ways in which TLRs sense infections and how CT acts as an adjuvant, with implications for innovative vaccine development and elucidation of the immune pathways that protect us against infections.

Key words: dendritic cells, IDO, NK cells, TLRs, newborns

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