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Transfer of maternal cytokines to suckling piglets: In vivo and in vitro models with implications for immunomodulation of neonatal immunity

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Abstract

Maternal cytokines may play instructive roles in development of the neonatal immune system. However, cytokines in colostrum and milk and their transfer from mothers to neonates have not been well documented, except for TGF-β. Swine provide a unique model to study lactogenic cytokines because the sow's impermeable placenta prohibits transplacental passage. We investigated IL-6 and TNF-α (pro-inflammatory), IFN-γ and IL-12 (Th1), IL-10 and IL-4 (Th2) and TGF-β1 (Th3) concentrations in sow serum and colostrum/milk and serum of their suckling and weaned piglets and in age-matched colostrum-deprived gnotobiotic piglets. All cytokines were detected in colostrum/milk and correlated with concentrations in sow serum except for mammary-derived TNF-α and TGF-β1. Detection of IL-12 and TGF-β1 in pre-suckling and colostrum-deprived gnotobiotic piglet serum suggests constitutive production: other cytokines were undetectable confirming absence of transplacental transfer. Peak median cytokine concentrations in suckling piglet serum occurred at post-partum days 1–2 (IL-4 > IL-6 > IFN-γ > IL-10). The effects in vitro of physiologically relevant concentrations of the two predominant lactogenic cytokines (TGF-β1 and IL-4) on porcine naive B cell responses to lipopolysaccharide (LPS) and rotavirus (RV) were investigated. High (10 ng/ml) TGF-β1 suppressed immunoglobulin secreting cell responses to LPS and rotavirus; low concentrations (0.1 ng/ml) promoted isotype switching to IgA antibody. Interleukin-4 induced inverse dose-dependent (0.1 ng > 10 ng/ml) isotype switching to IgA and enhanced IgM secreting cell responses to LPS and rotavirus. In summary, we documented the transfer and persistence of maternal cytokines from colostrum/milk to neonates and their potential role in Th-2 biased IgA responses and reduced immunologic responsiveness of neonates.
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Keywords: Cytokines; Milk; Neonate; Swine; Th2 bias

Abbreviations: ELISPOT, enzyme-linked immunospot; IgSC, immunoglobulin secreting cells; LPS, lipopolysaccharide; MNC, mononuclear cells; PPD, post-partum day; PWD, post-weaning day; RV, rotavirus; SIC, small intestinal contents; TMB, tetramethylbenzidine; Tr1, T regulatory type 1

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1. Introduction

Neonates depend on transfer of immune factors from their mothers via the placenta and/or breast feeding to be protected from pathogens until the maturation of their immune system. The maternal immune factors transferred to the neonates include soluble molecules (i.e. antibodies, growth factors, cytokines, etc.) and lymphoid and non-lymphoid cells. A few studies, mainly of humans, of the transfer of cytokines via the placenta and the components of colostrum/milk have suggested possible roles for maternal cytokines such as TGF-β, IL-1, IL-6, TNF-α, etc., in immunologic protection of neonates and in modulating neonatal immune development during colonization by commensal bacteria (Bocci et al., 1993), but most of these studies did not assess multiple types (Th1, Th2, Th3 and T regulatory type 1 [Tr1]) of cytokines or their profiles over time in infants.

Cytokines have effects on and are produced by different T helper (Th) CD4+ cells that are classified into Th1, Th2, Th3 and Tr1 types based on studies in humans and mice. Interferon (IFN)-γ and interleukin (IL)-12 are produced by Th1 cells and they promote inflammatory and cytotoxic T lymphocyte responses. IL-4 and IL-5 are produced by Th2 cells and they promote B cell responses. T cell growth factor (TGF)-β is produced mainly by Th3 cells that have immunoregulatory functions. IL-10 is produced by Th2 and Tr1 cells and plays an important role in antibody production and anti-inflammatory responses (Foussat et al., 2003). The presence of these cytokines in mammary secretions likely influences development of the neonatal immune system. Of the maternal cytokines, TGF-β has been studied the most experimentally in humans, mice and rats. In mammals, three isoforms of TGF-β (β1, β2 and β3) have been identified of which TGF-β1 is the most abundant form in tissues whereas TGF-β2 is more abundant in body fluids (Miyazono et al., 1993). However, TGF-β1 is of particular interest as it has been reported to play an immunoregulatory role during pregnancy and at birth in humans as well as a role in the Th2 bias of neonatal immune responses (Laouar et al., 2005; Power et al., 2002). Both IL-10 and TGF-β1 were detected in the maternal and fetal circulation in humans (Power et al., 2002). The latter cytokine could favor Th2 memory responses by suppression of memory Th1 cells in the fetus predisposing neonates to the observed Th2 bias (Ludviksson et al., 2000; Wegmann et al., 1993). TGF-β1 supplied to the fetus by injection into the mother's circulation during gestation or to the neonate via milk during suckling was shown to rescue TGF-β1 −/− newborn pups from severe cardiac abnormalities (Letterio et al., 1994). In suckling rats, feeding of formula lacking TGF-β2 led to inflammatory responses to food antigens including accumulation of IL-18 and recruitment of high numbers of activated dendritic cells, eosinophils and mast cells to the intestine (Penttila et al., 2003). These inflammatory responses in suckling rat pups could be alleviated by addition of TGF-β2 to the feeding. In humans, TGF-β1 and TGF-β2 in colostrum correlated with increased serum IgA concentrations in infants during the first month of life (Ogawa et al., 2004). IL-4 is an important Th2 cytokine that antagonizes Th1 related IFN-γ production, and may contribute to Th2 biased immune responses in neonatal pigs, similar to the responses observed in human infants and neonatal mice (Adkins et al., 2001; Early and Reen, 1996). The presence of early pro-inflammatory cytokines such as IL-6 and TNF-α has also been documented in human milk, but the effects of these cytokines on the neonatal immune system were not well studied (Rudloff et al., 1992, 1993).

In swine, the Th1/Th2/Th3/Tr1 functions of these cytokines have not been clearly defined. There is limited information concerning the level and function of cytokines transferred from milk to suckling neonates or their impact on neonatal immune development in swine or other species (Wagstrom et al., 2000). Porcine milk contains abundant TGF-β, which has been suggested to play a role in regulating the intestinal immune system in neonatal pigs (Xu et al., 1999). The presence or transfer of other cytokines has not been studied in porcine colostrum/milk. There is also a lack of information for humans and animals about the persistence or function of these maternal cytokines in neonates after transfer by suckling.

The goals of this study were to investigate the transfer efficiency of various cytokines representing proinflammatory, Th1, Th2, Th3 and Tr1 cytokines (according to the classification in humans and mice) from the colostrum and milk of the sow to the serum of neonatal piglets, to determine the persistence of the passive cytokines in the serum of neonatal piglets, and to provide a basis for comparison of milk cytokine components between pigs and humans to establish their universal roles in neonatal immune development. In addition, we investigated the effects in vitro of various physiologically relevant concentrations of the two predominate and immunomodulating cytokines (TGF-β1 and IL-4) transferred via colostrum into piglet sera on porcine naive B cell responses to lipopolysaccharide (LPS) and rotavirus (RV). Our findings contribute new information to support a previously unrecognized role

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