Best Practice & Research Clinical Endocrinology & Metabolism 32 (2018) 47–56

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

5

Cytokines in milk and the role of TGF-beta

Julia Brenmoehl, PhD, Scientist, Daniela Ohde, PhD, Scientist,
Elisa Wirthgen, PhD, Scientist,
Andreas Hoeflich, PhD, Group Leader *

Leibniz Institute for Farm Animal Biology (FBN), Dummerstorf, Germany

ARTICLE INFO

Article history:
Available online 2 February 2018

Keywords:
breast milk
cytokines
TGF-β
immune system
mammary gland
dairy products

Cytokines are required for normal growth and development of the mammary gland and TGF-β prominently represents an established effector of apoptosis, e.g., during involution of the mammary gland. By the control of intracellular signaling pathways, including JAK/STAT, MAPK, PI-3K, and NF-κB, cytokines efficiently regulate cell proliferation and inflammation in the breast. Therefore, cytokines are discussed also in a context of malignant mammary growth. As a group of tissue hormones produced by somatic cells or by cells from the immune system, cytokines are defined by their immunomodulatory potential. Over the past 40 years, multiple cytokines were identified in colostrum and milk. Importantly, cytokines derived from mammary secretions after birth are required for maturation of the immune system in the developing gastrointestinal tract from the suckling. Moreover, recent studies have further assessed the particular interactions between probiotic bacterial strains and cytokines. In light of the increasing prevalence of inflammatory diseases of the gastrointestinal system, the effects of probiotic microorganisms during milk fermentation may have immunotherapeutic potential in the future.

Introduction

Breast milk provides the newborn with a variety of bioactive factors protecting against infection and inflammation and is required for immune maturation, organ development, and healthy

* Corresponding author. Leibniz Institute for Farm Animal Biology (FBN), Institute of Genome Biology, Signal Transduction Unit, Wilhelm-Stahl-Allee 2, D-18196 Dummerstorf, Germany. Fax: +49 (0) 38208 68 902.
E-mail address: hoeflich@fbn-dummerstorf.de (A. Hoeflich).

https://doi.org/10.1016/j.beem.2018.01.006

microbial colonization [1,2]. Breastfed infants have a reduced prevalence of allergic diseases, insulin-dependent diabetes mellitus and other pathological disorders, like Crohn's disease or ulcerative colitis [3]. The composition of milk is altered during lactation, affecting the concentrations of proteins, carbohydrates and lipids, but also of hormones and cytokines. The latter are peptides that have critical roles in immunology and include interleukins (IL), interferons (IFN), lymphokines, chemokines, tumor necrosis factors (TNF) and transforming growth factor beta (TGF-β). They are produced by mammary epithelial cells [4,5] or by various cells in milk, such as leukocytes [6], especially T-cells and macrophages [6]. Interestingly, there is a substantially higher percentage of cytokine-producing cells in breast milk than in cord blood [7]. Cytokines are involved in immune response, health status and tissue development and can act as tissue hormones in an autocrine and paracrine fashion. They serve as pro- and/or anti-inflammatory agents on one hand, as a neutralizer of harmful pathogenic effects, and on the other as inducers for maturation and development of the immune system.

The discovery of cytokines in milk

Almost 40 years ago, the presence of cytokines in human colostrum and milk was suggested based on enhanced proliferation and differentiation of B lymphocytes in cord blood [8]. In 1990, Munoz and colleagues identified pro-inflammatory IL-1β in human colostrum and early milk [9], a monomeric cytokine secreted by monocytes and macrophages. Milk-derived IL-1β exists in a precursor form and mature IL-1β may survive proteolytic digestion in the intestinal tract of the infant because of greater resistance against trypsin [10]. In 1993, IL-6 was identified [11] and quantified in human milk by a specific radioimmunoassay [12]. Column chromatography revealed the presence of monomeric IL-6, characterized by a molecular weight between 25 and 30 kDa but also of a higher molecular weight form of IL-6 ($\geq$100 kDa), possibly owing to association with other binding partners in milk [12]. It was assumed that IL-6 has immunomodulatory functions in the breast because stimulated mononuclear cells isolated from human milk produce less IgA in the presence of IL-6 antibodies [13]. IL-6 is produced by monocytes, macrophages and Th2 cells, but also by human mammary epithelial cells. It is involved in humoral immunity (regulation of interferon production) [14], stimulation of IgM and IgA [15], and down-regulation of pro-inflammatory IL-1 and TNF-α production [16]. TNF-α was detected in early milk [17] bound to the soluble receptor or other molecules [18], emanating from monocytes, macrophages and adipocytes [19]. In addition, secretion of various components, such as mucin, by the intestinal and lower airway epithelium, is triggered by TNF-α [20]. Bioactive IFN-γ was initially described in 1993 in colostrum from lactating women at much higher levels if compared to plasma samples from the same individuals [11]. With IL-10 another bioactive cytokine was discovered at high concentrations, particularly in the lipid phase of human milk during early lactation [21]. IL-10 may act on the gastrointestinal tract of the suckling in an anti-inflammatory manner [21]. Pathogen clearance and antigen acquisition of dead cells are mediated by IL-10-stimulated survival and proliferation of B-cells as well as natural killer cells (NKC) [22]. In human, but not in bovine milk, colony-stimulating activity was demonstrated using human or mouse marrow cultures in 1983 [23]. It took more than 10 years from that point before granulocytes (G-CSF), macrophages (M-CSF) and granulocyte-macrophage colony-stimulating factors (GM-CSF) were identified in human milk samples [5,24,25]. In human colostrum, the greatest concentrations of G-CSF are detectable, followed by GM-CSF and M-CSF [26]. With this, immunoreactive TGF-α was found in early human milk samples at low concentrations and discussed in a context with growth and development both of the mammary gland and newborn [27]. In fact, TGF-α can enhance cell proliferation of gut epithelial cells [28]. Furthermore, TGF-β isoforms were detected in maternal breast milk, with TGF-β2 established at higher concentrations compared to TGF-β1 [29]. The levels of different cytokines are regulated during lactation [30]. In early human milk, TGF-β2 is present at more pronounced concentrations versus later time-points of lactation [31], and TGF-β2 concentrations are inversely correlated with gestational age and birth weight [29]. In addition, cytokine IL-18 was found at higher levels in human colostrum versus milk [32]. Comparative analysis of a variety of cytokines by protein array technology uncovered the additional presence of IL-2, -3, -4 and -12 in human milk and colostrum [26]. Beyond all interleukins detected,