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Breast milk: immunosurveillance in infancy

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ABSTRACT

Human breast milk is unique and a natural source of nutrition. However, it also helps to protect against various types of disease, not only infective but also immunological diseases. The wide variety of molecules in milk is responsible for its varied role for the newborn infant. Various breast milk proteins, contribute for its immunological, nutritional as well as its antimicrobial role. The naive immune system, intestinal mucosa and other organs of the neonate are also developed by various cellular factors. Breast milk protects not only during the neonatal period but also beyond it. By educating the neonatal immune system it also protects against the development of diseases later in life.

1. Introduction

In utero the fetus is in a highly protected in germ free environment without exposure to external antigen. Even though immunological defences exist in the new born, they are immature as the immunological development starts in the embryo, continues during fetal life, exists in immature form in newborn and is completed several years after birth.

The neonatal immune system differs from that of an adult. The 'immunosuppressed' state of the fetus is essential during gestation to avoid immunological reactions that would result in termination of pregnancy. This is reflected by an inappropriate chemical barrier[1], frail mucosal barrier[2], immaturity of T and B lymphocytes, poor T lymphocyte response to mitogens, reduced cytotoxic response, inadequate cytokine synthesis, marked deficiency of antibody production, reduced neutrophil, complement and natural killer cell activity[3]. The World Health Organisation and the American Academy of Pediatrics recommend exclusive breast feeding for six months as it provides optimum nutrition to the developing infant. Apart from a nutritional point of view, breast feeding maintains the maternal-fetal immunological link after birth. It also favours transmittance of immunocompetence from mother to her infant and is considered to be the central contributing factor for the immune defense system of the neonate[1].

Supportive data shows the benefit of breast feeding in preventing gastrointestinal and also respiratory diseases in not only developing countries but also developed countries[4]. It has also been shown to give protection

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against urinary tract infections and otitis media[5,6]. Breast milk protects the infant against infections as well as future growth of allergic diseases[7]. Conclusions drawn from a systemic review also reveal that breast feeding protects infants from the development of atopic diseases even if there is a family history[8]. Epidemiological studies have shown a reduced incidence of immune-mediated diseases including celiac disease, inflammatory bowel disease, type 1 diabetes mellitus, rheumatoid arthritis, asthma, eczema, necrotizing enterocolitis and multiple sclerosis in individuals who have been breast fed[9,10].

2. Compounds with immunological properties in human milk

Human milk is tailored for the infant's requirements. It compensates the relative lack of host defense by giving significant quantity of both nonspecific as well as pathogen-specific secretory immunoglobulin A (sIgA). Antibodies were the first bioactive components that were recognized in human milk. The mother's previous exposure to infectious agent results in these antibodies. Other factors in human milk also provide passive protection through immunological, hormonal, enzymatic and trophic activity[11]. During the early period of lactation, certain cells of the innate system like leukocytes and macrophages exert a modulatory effect on the neonatal immunity[12]. The following immuno-modulatory compounds include immunoglobulin G, immunoglobulin M, isoforms of immunoglobulins (sIgA), nucleotides, polyunsaturated fatty acids (PUFAs), specific amino acids (taurine, polyamines), monoglycerides, linoleic acid, cytokines and chemokines, soluble receptors [CD14, soluble Toll-like receptor (TLR) 2], antibacterial proteins/peptides, prebiotics and oligosaccharides that are found in breast milk[13].

3. Anti-microbial properties of human milk

Breast milk has a variety of antimicrobial substances that function against several viruses, bacteria, and protozoa.

3.1. Immunoglobulins

The defensive role of sIgA which is present at very high concentration in the colostrum (~10 g/L) and in mature milk (~1 g/L) is well known. The IgA_2 is resistant to acidic pH of the stomach and to the digestion by enteric enzymes and bacterial proteases[14]. The immunoglobulin G and immunoglobulin M are present at a low concentration[15]. The transfer of highly specific protection from the mother to the infant is because of the entero-broncho mammary link of IgA with B lymphocytes. When the nursing mother is exposed to antigenic stimulus from environmental pathogens, M cells of Peyer's patches in the gut-associated lymphoid tissue or tracheobronchial tree mucosa take up and acquire the antigen to B cells. Plasma cells become active to produce IgA on the basolateral side of the mammary epithelial cell. The IgA attaches to the poly immunoglobulin receptor, the complex traverses the mammary epithelial cell, then cleaved by protease on the apical side as dimeric sIgA and secreted from the apex of acinar cells into the milk. During pregnancy and lactation, because of hormonal stimuli, IgA B lymphocytes colonize mammaryglands and produce specific secretory IgA that may bind to pathogen and prevent infection[16]. The antimicrobial effects of IgA antibodies are related both to immune exclusion, by inhibition of epithelial adherence and penetration or microbial agglutination and neutralization, and immune elimination, by phagocytosis and cytotoxicity[9]. However, the time that elapse between exposure of a mother (and infant) to a novel antigen and protection of the infant by sIgA in the milk makes this mechanism of protection incomplete at best. Also HIV-specific IgA in human milk from HIV-infected mothers do not show a protective role; on the contrary, specific IgA antibodies may be associated with an enhanced transmission of the infection[17,18].

3.2. Lactoferrin

As a proteolysis-resistant, iron binding glycoprotein, lactoferrin is the dominant whey protein. Its protective effect may be linked to competition with siderophilic bacteria and fungi for ferric iron and to the epithelial growth-promoting activity[19,20]. Lactoferrin limits the growth of bacteria and fungi by competing for essential iron. It modulates relocation, and activation of antigen presenting cells like macrophages[21-23]. The action of lactoferrin is also helped by certain soluble mediators like cytokines, chemokines and other effector molecules. Also epithelial growth promoting actions have been linked with lactoferrin[4]. It has been shown to relieve symptoms and increase the suppression of *Helicobacter pylori* in the stomach[24]. Lactoferrin has been shown to ameliorate rotaviral gastroenteritis by interfering with the early phases of infection and also slow up growth of colorectal adenoma[25]. Studies have shown that lactoferrin inhibits the attachment of enteropathogenic *Escherichia coli* (*E. coli*) to intestinal cells by mediating the serine protease activity of lactoferrin[26,27]. Degradation of the protein structures of