Breastfeeding - Anti-viral Potential and Relevance to the Influenza Virus Pandemic

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SUMMARY

Essential nutritive and immunological ingredients abundantly present in breastmilk make it the choice infant nutrition. The uniqueness of mother's milk, in contrast to most therapeutics and immunizations, lies in its potential to adapt itself to the requirements of the infant so that timely immune defenses are tapped from its constituents by immune regulation, modulation and immune acceleration to stimulate novel substances; these render it pertinent as defense when faced with challenging organisms. While it is appreciated that immunity can be transferred from mother to infant through breastmilk following maternal influenza vaccination, the immense benefits conferred by breastfeeding per se during influenza pandemics may not be fully valued. This is substantiated by debates and ambiguities for continued breastfeeding in the face of maternal influenza infections. This article emphasises the utmost importance of breastfeeding in viral pandemics in the light of the changing immunological strategies used by viruses at different times and the urgent need for such opportune defenses. The prolific interaction of its constituents is frequently understated as enormous advantages to the suckling infant.

KEY WORDS:
Breastmilk, Defenses, Immune, Influenza, Viruses

INTRODUCTION

Immunologically breast milk is optimally endowed with the capacity to respond to the requirements of the suckling infant in ways such that the infant is protected from many infections. The protection conferred to the breastfed infant encompasses a range of organisms including bacteria and viruses. Remarkably, bioactive and nutritive factors in breastmilk can also function immunologically to augment protection. In the immune responses against viral infections, innate and adaptive immune factors play a distinct role and, in breastmilk, many anti- viral responses are 'fine- tuned ' to organise immune defenses to protect from undesirable side effects. While the benefits of breastfeeding are well recognised,this article reemphasises the manifold protective mechanisms, immunologic and non immunologic that interact to protect the breastfed infant. In the wake of its protective capacity, breastmilk also holds the key to the regulation of the maturation of the immature infant immune system. These benefits add value to continued breastfeeding consistent with and conforming to the recommendations by the Ministry of Health of Malaysia (MOH), WHO and CDC during the H1N1 influenza virus infections.

Influenza viruses

Influenza viruses are RNA viruses that affect birds and mammals[1]. These viruses have striking ability to evade host defenses by virtue of their variability and rapid mutation[2]. There are three main genera: Influenza A, Influenza B ,and Influenza C. Owing to their brisk mutation, Influenza A is further classified into a number of subtypes. Influenza B evolves more slowly; nevertheless it too has many strains.Influenza C is the most stable of the influenza viruses [1]Influenza A (H1N1) virus, a subtype of influenza virus A is the commonest cause of influenza in humans. Influenza A virus strains have an H number and an N number based on the forms of these two proteins the strain contains. There are 16 H and 9 N subtypes known in birds; only H1,2 and 3 and N1 and 2 are commonly found in humans[1]. Influenza A and B viruses have two surface glycoproteins, the haemagglutinin (HA) and the neuraminidase (NA). Both identically recognise sialic acid. HA binds to sialic acid-containing receptors on target cells to initiate virus infection, whereas NA cleaves sialic acids from cellular receptors and extracellular inhibitors to facilitate progeny and virus release; endorsing spread of the infection[3]. The portal of viral entry is the upper respiratory mucosal tract, and influenza viruses can be spread by coughing and as aerosols into the lower respiratory tract .Specific antibody production at the mucosal site prevents infection in the upper and lower respiratory tracts. Protection against influenza virus infection compares with the levels of mucosal immunoglobulin A (IgA) in the respiratory tract and serum immunoglobulin G4. Anti-influenza virus IgA in the mucosa inhibits viral attachment to epithelial cells, prevents or limits infection in the upper respiratory tract. Serum anti-influenza virus IgG precludes infection in the lower respiratory tract [4] Varying surface proteins enable influenza viruses to mutate and deceive host defenses. The unique and evasive attribute of these viruses makes it mandatory that tactful and ingenious mechanisms are executed by the host in order to overcome their strategies. Therapeutics and vaccinations have struggled to keep pace with the tempo of their rapidly changing surface coats. It is proposed, in this review that within the dynamics of breastmilk may lie useful and apt tools of such vital defenses.

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The Protective Role Of Breast Milk In Viral Infections

Defense in breastmilk involves general and specific protective constituents. Categorized separately, there is considerable overlap in their actions. Factors independent of specific antigenic stimulation confer broad protection against a multitude of viruses. Breastmilk is naturally fortified with such immunological, nutritive and bioactive ingredients. General protection embraces mucosal, cellular and colostral features. Specific protection is endowed by more specific factors, a result primarily of antigenic exposure and stimulation. These are targeted, more long enduring and a consequence of the mother's immunological challenge. Such critical protection include virus-specific immune responses with immunoglobulin production, cellular immune responses and specific anti-viral cytokines. These adaptive, targeted immune responses also provide useful immunological memory. Invasion of the respiratory mucosa is a necessary prelude to influenza virus infections where mucosal defenses are vital. Mucous membrane protection grants a barricade against viral invasion without the prerequisite of inflammatory responses or "non immune exclusion"[5]. Breastfeeding enriches the respiratory mucosal milieu with potent anti-viral factors. Inhibitory respiratory mucosal factors in breastmilk, such as N-acetylneuraminic acid containing receptors for HA molecules impair the mechanism of viral invasion[6] Breastmilk mucin has the capacity to aggregate some viruses prior entry into host cells[7]. Breastmilk mucin, plausibly from the human milk fat globule membrane, acts as a pathogen decoy receptor by invading viruses that bind to it and excreting them even before they colonize emphasizing early breast-feeding as integral for innate immune defenses[8].

Nonspecific immunological constituents of breastmilk like lactoferrin, significant in colostrum inhibit pathogenic viruses and modulates and enhances the cellular machinery in breastmilk[9]. Lactoferrin vital for lymphocyte growth, can effectively block and inhibit adsorption and intracellular penetration of some viruses[10]. The intestinal ecosystem of nutrients and selective bifidobacteria accelerate gut maturity especially in preterm infants and is pivotal in competent immunological function of the developing immune system. Bifidobacterium breve exhibits antiinfluenza virus activity[11]. Glycans as soluble receptors on the mucosal surfaces can inhibit pathogens from mucosal adherence chiefly in the gastrointestinal tract[12]. Lipoprotein lipases like purified linoleic acid, a constituent of breastmilk triglycerides inactivates enveloped viruses and causes viral cell lysis [13]. The cells in breastmilk possess innate anti viral activity with immunoregulatory potency and confer developmental direction to the naïve immune system. Every mother has the capacity to adapt and modify immune responses of her breastmilk rooted in her own immunological experience to the advantage of the suckling infant. Living leukocytes in breastmilk, an early pointer to the existence of an immune system within breastmilk, offers immediate and durable immune-modulation of the developing cellular immune system[14]. Neonatal T lymphocytes are distinct from naïve adult T cells. Their T-cell repertoire is certainly not optimal. In contrast to adults, quantitative and qualitative differences in most T-cell subsets are detectable throughout childhood rendering vulnerability to a spectrum of new infections[15] To surmount this susceptibility, lymphocytes in breast milk have a prominent expression and ratio of CD8+ and CD4+ receptors [16]. The modulatory effect of breast milk proteins confers adequate stimulatory effects on T cell growth while carefully guarding against undesirable immunological overreaction. A colostral antiviral factor, with an association with glycoproteins is lymphocyte specific [17] The peak production of colostrums by breast milk lymphocytes postpartum enhances the levels and activity of other immunological factors by producing interferon, a lymphocyte chemotactic factor, and via the ability to transport various immunoglobulins to augment antiviral activity [18, 19]. Macrophages of breast milk regulate the infant's T-lymphocytes and B-lymphocytes by activation markers which are dually phagocytic and immunoregulatory and serve as adaptive immune responses in the younger child [20]. The immunoregulatory role of macrophages in breastmilk is evident by the production of granulocyte–macrophage colony-stimulating factor and differentiation into dendritic cells in the presence of exogenous interleukin-4[21]. Neutrophils and lymphocytes, likewise, also contribute to the powerful immune defense in the face of novel antigenic challenge[22]. Exosomes, nanovesicles with endosome-derived limiting membranes secreted by a diverse range of cell types influence immunodevelopment and contribute to antiviral effects [23]. Fascinatingly, B cells in breast milk are unique phenotypically and primed to secrete antibodies; the majority display a phenotype of memory B cells. The origin of these B cells are linked to the lymphoid tissue in the gut[24]. Colostrum and mature breast milk enhance B cell proliferation and accelerate generation of antibody secretion, a crucial immune antiviral tactic of breast milk [25]. Phagocytic cells, producing interferon are relevant in the resistance to the toxic effects of the influenza virus [26] Type I interferons(IFN) mediate defence against respiratory viruses, particularly influenza viruses. Higher levels of type I IFN in breastfed infants signify the activation of innate antiviral mechanisms in the breastfed [27]. High levels of interferon in colostrum can mitigate the effects of the influenza viruses including H1N1[28]. The feeding of colostrum to infants significantly increases IgA,IgM and IgG by the fifth day of life. Immunoglobulins in colostrums, absorbed from the intestinal tract of newborn infants are pertinent in the resistance to infection during the early neonatal period [29]. At these crucial times, inherent deficiencies of natural killer cell (NK) activity and antibody dependant cellular cytotoxicity (ADCC) are partially overcome by colostral cell cytokine stimulation of NK cell cytotoxicity better equipping the infant against novel viral challenge [30].

Protection by antibodies

Maternal transplacental antibodies, an expression of the mother's immunological exposure incompletely prepare the infant's immature immune system for its task. In influenza virus infections, protection also entails adequate mucosal defenses; these commence with non-inflammatory antibody shielding of internal body surfaces; a prime function of secretory immunoglobulin A (sIgA), the key player in mucosal immunity [31]. IgA dimers (pIgA) are produced by local plasma cells stimulated by antigens that target the mucosae. The subsequent immunophysiological cascade leading to the formation of the secretory component (SC) and polymeric IgR(pIgR), is now well recognized [31]. The interference with mucosal uptake of soluble macromolecules enhances immune

exclusion in the airways. sIgA interacts with Fc receptors on the virus, trigerring ADCC important for viral protection [32]. Via blood to mucosal migration,antigen-sensitized lymphocytes in the gut-associated lymphoid tissue (GALT) generate the mucosal-associated lymphoid tissue (MALT). Relevant to this, MALT also encompasses the nasopharyngeal associated lymphoid tissue (NALT) represented by the palatine tonsils and adenoids, the bronchial associated lymphoid tissue (BALT), as well as the lactating mammary glands and the products of lactation. The airways also receive such cells from the NALT through different homing receptors[31]. Mucosal protection is heightened in the breastfed infant, by virtue of the intimate involvement of the lactating mammary gland with the MALT. Adaptive immunological memory is also produced;a form of explicit and timely immunisation uniquely present in breastmilk. As a frontline defense against the influenza virus, signals from the NALT can incite the production of anti influenza viral mediators. Maternal exposure to the influenza virus stimulates specific antibody forming cell (AFC) responses in the (NALT) [6]; they generate influenza-specific antibodies. Maternal influenza – specific antibody, crucially and timely transferable mainly through breast milk can be live- saving. Noteworthy too, these antibodies do not interfere with local immunity or the ability to mount a secondary antibody response[33].

Defense by cytokines

Cytokines are a kaleidoscope of pluripotent polypeptides that operate in autocrine or paracrine manner by binding to specific cellular receptors [34]. They are an essential link between innate and adaptive immunity. The concept of a basal cytokine production under physiological conditions in colostrum is well recognized even in unprimed breastmilk [35]. Maternal antigenic exposure efficiently transmits signals where cytokines recall and generate crucial immune mediaters. The complex immunomodulatory potential of the cytokine network with additive or synergistic integration of various cytokines serves as immunological ploys in the face of fast mutating viruses. Soluble receptors of these cytokines, present in breastmilk, further augment their biological activity[36]. Epithelial barrier integrity is modulated by cytokines such as IL-10 and IFN-y while others namely TGF-alpha and epidermal growth factor strengthen epithelial barrier development [37] Cytokines in breast milk usefully collaborate with lymphocytes and the mucosal microenvironment of the breast associated lymphoid tissues of the MALT [38] Similarly, cytokines exert their effects on the NALT and GALT of the newborn[36] Such orchestrated interaction by cytokines is an example of interactive cooperation of the various arms of immunity in the breastfed infant in the immune challenge against viruses. Furthermore, the anti-inflammatory action of breastmilk is of immense impact. The potential damage of inflammation in some infections is evident in avian influenza virus-infected chickens destined to die within two days due to a systemic inflammatory response[38]. In influenza virus infection ,antiinflammatory peptides inhibit the symptoms following infection with H5N1 virus[38]. In breast milk, soluble receptors vie or bind to proinflammatory cytokines restricting or blocking their inflammatory activity[39]. Scavengers of oxygen radicals, degraders of inflammatory mediaters, antioxidants with reduced superoxide generation are all powerful antiinflammatory forces found in breastmilk[37]. The recovery of influenza virus infection is correlated with the appearance of antibodies and decreased virus titers in the nasal area [6]. Recovery and immunological memory in breastmilk are signalled by T cells that selectively colonize the mammary gland during lactation akin to memory T cells ;these cells, once again, reflect the mother's immunological experience beneficially passed on to her suckling infant [40].

CONCLUSION

Influenza viruses are particularly deft at evading both innate and adaptive host immune responses. A spectrum of ingredients that empower the infant's unprimed immune system exist in breastmilk. Its cellular constituents, cytokine composition and antibody responses are the initiators of tactical direction and maturation of the developing immune system. The mother's mature more briskly activated, and effective immune response is capable of reacting to viruses to which she and the infant are exposed, providing much needed activated cells and antibodies through breastmilk. It may also be in this form of ingenious adaptation,that evasive strategies by viruses are put to test to harness maximum benefit to the suckling infant. The role of the lactating mammary gland in mucosal immunity is also fundamental to these immunological interactions. Direct evidence of strain specific maternal antibodies that offer protection in influenza virus infection has been discussed. Here there is no doubt that specific immunity transferred via breastmilk gives a much needed immunological edge to the suckling infant in comparision to the bottlefed infant. The diccovery of the many interactions in breastmilk is far from complete. Yet, some light is shed on the combat by breastfeeding against specifically elusive and complex organisms that constantly deploy change in their strategy to defeat the yet immature immune system. Against these organisms, within the biodynamics of breastmilk, may lie silent and well-timed warfare.

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