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"Mother-Microbe-Infant-Microbe" Synchrony– A Mini Review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Is breast milk nutrition "alive", dynamic and impossible to emulate? This question remains important in the context of the emergence of novel diseases and may be answered by comparing it to a few events that happen in nature, with parallels evident in the breast feeding dyad. Edified by nature, and its myriad coexisting species, including the microbes, there seems to be much interplay between species through symbiosis, perhaps, with a lofty purpose. This is compared to the breastfeeding infant's gut that develops in symbiosis with the microbes that enter it through every feed. Breast milk not only nurtures the infant, but also nourishes the commensal microbes it provides. Milk microbes are influenced by maternal, infant and environmental variables, supporting them differently, parallel to the manner in which microbes and other elements in nature support ecosystems. Reviewing and synthesising information from two different but comparable ecosystems show parallels worthy of appraisal. The lactating mammary gland provides and supports beneficial microbes and microbial environments. Secretory immunoglobulin A (sIgA), the key molecule of mucosal gut immunity, is mutualistic with commensal microbes, capable of mucosal defences, yet preserving equilibrium between pathogen defences and commensal tolerance. Through microbial signals, the nursing mother shares her mucosal immune experiences, commenced in utero, transplacentally and then "translactionally", to mature infant immunity, concluding an exceptional loop of nurture. Technology allows much appreciation that "immune cross- talk" between mother and infant does occur. In this review, commensal gut microbes in the

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infant are conceptualised as miniature ecosystems and, breastfeeding, as a vibrant compartment where being “alive” pivots in and around microbial existence and sustenance - a biological setting that, at best, may be emulated but not reproduced.

Keywords: Microbe; gut; ecosystems; mucosal; breastfeeding.

1. INTRODUCTION

Nature’s forests and their dynamic interaction with the environment, although appearing tranquil, influences holistic health [1]. Seedlings that survive and germinate into young plants shape the nature of plants. Understanding the nature of the seed, for example, the feature of an “erratic seed”, an “unproductive seed”, or a “malingering seed” all prove to be crucial in the ultimate destiny of the tree [2].

Natural eco systems, encompass life forms living in symbiosis with the environment. They adapt to environmental stresses by evolving resilient features. For instance, the nitrogen cycle in Antarctic inland waters and exceptional characteristics of Antarctic ecosystems through unique adaptation evolved to withstand harsh and unpredictable conditions they face [3]. Ecological conditions take no chances at survival, they impact very early stages of evolution by influencing offspring adaptation [4].

Our gut microbial profiles, in many comparable ways are miniature models of nature’s eco systems. Understanding how such microbial profiles are nurtured in the newborn infant, likened to the seedling in nature, through natural feeding, may allow us to draw some interesting inferences. The evolution of natural ecosystems in moulding offspring adaptation towards survival resilience is compared to the myriad actions of gut microbes in supporting a young infant’s immunity through natural feeding. As in nature, early survival modulation is important; breastfeeding provides a template for immune development at a critical time of life, for greater immune adaptability and health resilience [4,5].

Human gut microbes are metabolically active and impactful to us, consisting of a myriad species of bacteria, fungi and protozoans, communicating through a host of cells and genes, presenting a scenario aptly described as a “virtual organ within the gut” [6]. Human microbial flora, our biological ecosystem, is also shaped by lifestyle and environment. Holistic health attributes of natural ecosystems can be compared to the positive health impact balanced gut microbes potentially provide us [7].

Just as fertile soil stimulates growth of flora and favourable yield of crops, such as the ability of soils for water retention, roots development, soils aeration, nutrients availability or nutrients abundance, gut microbial influences are vital to good health, if in homeostasis with the gut environment [8]. This balanced state may also exert far reaching effects beyond the gut, in almost every organ system, possibly through diverse functional links [9].

Like nature that shapes the evolution of its offspring [4], exclusive breastfeeding lays a sound foundation for optimal and beneficial microbial action in the newborn. This is conferred by providing a perennial and significant source of microbes to the infant’s gut through every feed. While there are many contributing factors to the nature of microbes that enter the infant’s gut, such as mode of delivery, hygiene, therapeutic interventions and genetic background [10], as well as stress and diet during late pregnancy, breastfeeding is a crucial variable in the initial colonisation of the newborn gut [11], in the face of anatomic and physiologic gut immaturity.

2. ETHICAL CONSIDERATIONS

Comparison between nature and gut microbes is made based on reflections on two very natural events that are suitable for evaluation and assessment for clearer understanding and appreciation of nature’s grand lessons in our limited biological ecosystems. The idea of such comparison may have been previously thought of by others, and I myself have written on such comparisons for public awareness and understanding in news articles, (referenced in this article) but scientific comparisons of natural ecosystems to a biological ecosystem with numerous references, as a narrative review, to the best of my knowledge, is the first.

3. METHODOLOGY

This minireview reviews articles in accordance with the MeSH search strategy, in the PubMed, Scopus, Embasse and other databases. Two hundred twenty publications including original articles, systematic reviews, meta-analyses and

experimental, prospective and retrospective studies were included. Sixty nine articles were finally included. For parallels to be drawn from nature, a few articles relevant to how nature supports its life forms, were chosen, in a subjective manner.

Articles on breastmilk microbes, their diversity and origins, human milk oligosaccharides (HMOs) and other breastmilk substances that support microbial existence were perused and selected. The topic of mucosal immunity was found to be important and was searched by the same strategies. Included were systematic reviews, meta-analyses, narrative reviews, experimental studies and case reports. One news article by the author on the subject is included for completeness of the literature search. Excluded were letters to editor, proceeding abstracts, and publications in foreign language. Information was divided into four sections and were selected based on subjective data analysis and synthesis. Where relevant, information was applied to current knowledge on the subject.

Parallels in nature were integrated to the support of gut microbial survival and nurture, with microbial actions compared to some related methods observed in nature.

4. DISCUSSION

4.1 Microbial Diversity

Biodiversity and ecosystem diversity in nature allude to species diversity and species composition present in a community. The variation of species in nature's ecosystems is of significance in the relationship between species richness and ecosystem functioning [12]. In the gut microbiome, diversity is classified by alpha diversity which quantifies by number and relative proportions, whereas β-diversity is the proportion of specific taxa in the gut microbiome [13].

In nature's ecosystems, specific "spatial environmental heterogeneity is an important driver of bacterial diversity" [14]. When studying habitats and bacterial diversity, soils contained the highest bacterial richness within a single sample or alpha-diversity. There was beta-diversity in sediment, biofilms, and inland water with maximum variation in community composition among geographic locations [14].

The gut microbiome develops dynamically from infancy to childhood and is influenced by a number of factors [15]. Specific differences were observed in children born by Caesarean section compared with those delivered vaginally. Microbial variation was influenced by gender, city where children were born and bred, and in children with constipation and diarrhoea. Preterm infants had unique microbial flora. There was no significant effect of maternal antibiotic exposure on gut microbiota development in early life [15].

Eubiosis, is microbial synergy with the gut environment, a state that favours good health through immune system-microbiota synergy inducing protective responses to pathogens and maintaining regulatory pathways of tolerance to innocuous antigens. A rich and diverse microbiome has alpha diversity, a healthy microbiome contains less than 10% of the facultative anaerobe phylum and the *Firmicutes* and *Bacteroidetes* has a high variation in species among individuals [13].

Dysbiosis is a state of microbial imbalances through selection of microbiota that lack the resilience and diversity required to establish balanced immune responses which contribute to the pathogenesis of diseases [16]. Microbial imbalances are identified by reduced α-diversity or specific changes in β-diversity with an increase in the proportion of the phylum *Proteobacteria* [13].

The healthy adult has an intestinal commensal bacterial composition mainly of anaerobic Gram-positive *Firmicutes* and anaerobic Gram-negative *Bacteroidetes* [13], with an orderly colonization, firstly dominated by facultative anaerobes such as enterobacteria, coliforms and lactobacilli, followed by anaerobes genera such as *Bifidobacterium, Bacteroides, Clostridium* and *Eubacterium*, and this is a sequential multifactorial process [17].

4.2 Origins of Breastmilk Microbes

Maternal microbial signals energise offspring metabolism, immunity and organ function, starting as early as during intrauterine life and then, continuing postnatally [17-19]. Breastmilk microbial communities such as *Staphylococcus, Streptococcus, Acinetobacter,* and *Enterobacter* possibly originate from the mother's areolar skin and the infant's mouth [17,18], but other sources could contribute [19]. Since microbes such as the *Bacteroides* and *Clostridiales* in the mammary gland are usually also present in the maternal

gastrointestinal tract, breastmilk microbes could originate from that site and reach the lactating mammary gland by translocation.

Microbes utilise dendritic cells, (DCs), the specialized antigen-presenting cells for transport, via the recognised connection between the maternal gut and mammary gland, or the 'entero-mammary pathway' [20,21]. Additionally, the mammary glands contribute to milk microbial diversity [22]. Maternal microbiota, by maturing foetal or neonatal intestinal innate immune cells and altering intestinal gene expression profiles contribute to the infant's immune development [23] and maternal diet, modified by the microbiota, can be transferred to the infant, crucially modulating infant immunity [24].

4.3 Human Milk Oligosaccharides (HMOs) as "Fertile Soil" for Commensal Growth

4.3.1 Good soil, good crops

In nature, good soils cultivate productive crops [25], without which crops remain unhealthy and cannot sustain the food cycle. Likewise, HMOs in breast milk "cultivate" living microbes and provide a conducive environment [26] for microbial evolution and stabilisation which ultimately proves important nidus for well-being. HMOs are produced by the Golgi apparatus of the follicular cells in the mammary gland [27] and are quantitatively significant. A lactating mother potentially produces 5–15 g of oligosaccharides per litre of milk, with well over 200 diverse HMO types, impacted by time of lactation, environmental exposures and the mother's genes [28,29].

HMOs consist of lactose residues linked to glucose to which other monosaccharides of different types namely, N-acetylglucosamine (GlcNAc), Gal, fucose (Fuc) and sialic acid (Neu5Ac), are attached [28]. Some are fucosylated, others non-fucosylated, sialylated, non-sialylated or with both of these sugars [30]. Modern technology indicate that secretor (Se) and Lewis (Le) genes in the mammary gland regulate HMOs in breast milk and determine peripheral fucosylation which contributes to pathogen defences [27,28]. Mothers differ in breast milk HMO concentrations because non secretor mothers with positive Lewis status, do not produce as much total HMO in milk as secretor mothers [27]. Other maternal variables include, but are not exclusive to, the stage of milk maturation and the time post-delivery [28].

4.3.2 "Fertilisers" that support microbial seeding

Once ingested, most of them escape digestive processes. Undigested HMOs, like the fertile soils of nature, perform important functions that support microbial seeding of the immature gut. Within the gut they help mature intestinal epithelia for a conducive micro-environment, which also safeguards against disease- causing microbial translocation [27,28]. This effect is especially important in the preterm infant who is at increased risk of diseases such necrotizing enterocolitis [28]. However, some microbes utilize and digest HMOs, releasing monosaccharides from their more complex sugars [27,28]. Fucose-linked HMOs selectively promote the growth of certain *bifidobacterium* species and these bacteria in turn can hydrolyse specific HMOs. To do this, the species *bifidobacteria*, encode for digestive enzymes, cleaving monosaccharides from the oligosaccharide chain [26-29].

4.3.3 "Weeding out" pathogens

HMOs contribute to innate immunity in breast milk and can help protect from pathogenic bacteria and by so doing, they shield from early and invasive incursions of pathogenic growth. Pathogenic organisms, if allowed to thrive will result in an unfavourable intestinal environment which can predispose to short-term and long-term diseases [31]. This may be compared to the phenomenon of "colonization resistance", [31] or antibiotic associated susceptibility [32], a concept felt to be of relevance in this context.

Synthesising the occurences in nature where there is a link between species richness, biological events and the climate [33], the "climate" in the gut is enhanced and made conducive by the presence of breastmilk substances and its unique microbial species. These potentially "weed out" disease- causing microbes to support a favourable gut milieu that could well cause immune modulation [34,5].

HMOs inhibit fluxes of pathogen colonisation against a broad spectrum of organisms including bacteria, protozoa and viruses [27,28]. The fucosylated HMOs are similar in structure to the sugar chains in the glycoproteins on the surface of the infant's epithelial cells. Soluble fucosylated breastmilk oligosaccharides in the newborn's digestive tract act as decoy receptors by blocking bacterial lectin receptors rendering them incapable of recognizing glycotopes on host

cells, thus inhibiting adhesion and colonization by pathogenic microbes [27,28]. HMO receptors such as galactins, selectins, and siglecs are present in diverse immune cells and receptor binding could influence innate and adaptive immune responses [34,35]. Some commensals such as the *Bacteroides* have even developed mucus-utilization pathways to consume HMOs [35]. There is also more specific antibacterial action against fucose-dependent bacteria such as *Campylobacter jejuni*, enteropathogenic *Escherichia coli* [36] and in the newborn,this may be life-saving when protecting early against *Group B Streptococcus* [37].

HMOs have capacity for early, broad anti -viral activity through decoy receptors inhibiting carbohydrate mediated cell entry but can also block rotaviruses, noroviruses, influenza viruses, and human immunodeficiency viruses by binding to glycans and effectively inhibiting entry [26] while some type of HMOs also block intracellular viral replication [27,38]. HMO -mediated antiparasitic activity in breastmilk lower risk of *E. histolytica* infections in breastfed compared to formula-fed infants [39]. As HMOs resist digestion in the small gut, they reach the colon intact where maximum *E. histolytica* pathogenicity occurs. It is argued that, through this action, they help stabilize commensal gut communities by protecting from potential tissue disruption.

Besides pathogen protection, acidic HMOs have anti-allergic and anti-inflammatory roles. The immunomodulatory effects of HMOs can reduce allergic diseases [40,41]. Beyond local action, neutral and acidic HMOs that are absorbed into the circulation have far reaching effects on holistic health [37,40].

4.4 Mucosa-Associated Lymphoid Tissues (MALT), a "Fence" Against the Critters

There is symbiotic soil - microbial interaction between soil types, soil invertebrates and roots, beneficial to natural ecosystem development [42]. These interactions are felt to contribute to integrity and robustness towards ecosystem habitat survival. As alluded to, understanding the nature of the seed proves to be crucial in the ultimate destiny of the tree [2]. Likewise, many factors in mother's milk have integrated roles, acting in symbiosis, "thoughtful" of the early requisite to successfully nurture the young gut ecosystem to achieve development, stabilisation and "tenacity "of microbial communities.

To realise this end, the intestinal barrier is fortified by mucosal immune factors [43-50]. Just as the nitrogen cycle in Antarctic ecosystems through unique adaptation evolved to withstand harsh and unpredictable conditions they face [3,4], mucosal immune factors function as a "fence" would, by "keeping away" pathogenic disruption by preventing processes such as bacterial translocation external to the gut and maintaining immune balances within the gut milieu. Reflecting on the manner in which nature takes no chances at survival to nurture the young [4], mucosal immunity in the gut takes no chances either, in ensuring optimal survival, by evolving myriad protective strategies at the mucosal portals, favourably modulating early stages of immune evolution [43-57].

4.4.1 Regulation and reinforcement of gut and barriers

Intestinal luminal microbes regulate immune cells and the epithelial barrier. Microbial recognition by immune cells are regulated by low levels of toll-like receptors (TLRs), and microbe-associated molecular patterns (MAMPs) on commensals which do not trigger unnecessary inflammatory reactions [43]. Immune system development during colonization with the gut microorganism, *Bacteroides fragilis,* occurs due to a bacterial polysaccharide (PSA) that supports cellular and physical maturation [44]. MAMPs produced by bacteria and viruses stimulate host innate immunity, on epithelial cells or dendritic cells (DCs). B cells produce IgA and IgG antibodies, which can target bacteria in the lumen [45].

Two types of humoral immunity are present in the intestinal mucosa, one for defence and the other to maintain immune equilibrium. IgA class switching after activation of a mature B cell via its B cell receptor, generates the different classes of antibody and either produces a broad spectrum type immune response, to a number of antigens which is independent of T cells [46], resembling innate immunity which is mainly associated with the recognition of commensal bacteria [47]. In T cell dependent reactions, pathogens trigger specific adaptive immune responses [47].

SIgA is a glycosylated molecule, passively transferred in milk, capable of both innate and acquired defences. Following microfold cell (M cell) maturation and antigen sampling in the gastrointestinal tract, an adaptive immune response is induced. Class switch recombinance (CSR) where one antibody type is converted to

another, produces a crucial component of mucosal immunity. SIgA is polymeric and resistant to digestion, with constituents such as the secretory component (SC) also quite capable of both immune defense and immune tolerance [47,48], a much needed equilibrium in the gut environment.

The microstructure within breastmilk is rich in small non-coding RNAs, the micro RNAs (miRNAs) [49], involved in immune "cross talk", reinforcing tenets in mucosal immunity [50]. Breastmilk-derived exosomes and miRNAs can promote growth of intestinal epithelial villus height and crypt [50,51]. MiRNA modulation also represents a mechanism through which commensal bacteria help in the regulation of the intestinal barrier, and breastmilk miRNAs are capable of entering the systemic circulation and protecting specific tissues [52].

Besides HMOs, mucosal immunity and breastmilk factors, microbial symbiosis contributes to a robust network of villus capillaries in the intestinal wall, enhancing angiogenesis which is fundamental to intestinal epithelial growth and development. Commensal microbes that colonize mucosal surfaces regulate the underlying microvasculature by signalling mechanisms [53].

4.4.2 Tolerance

sIgA exhibits immune tolerance towards many types of commensal microbes [54] Glycans in the sIgA molecule provide a template for microbial interactions [54,55]. High and low affinity binding sites on IgA describe the strength of interaction between it and an epitope [54,55]. sIgA can coat bacteria differently and this may vary among different microbes as a mechanism by which immunity differentiates commensals from pathogens. The commensal microbiota may also play a role in inducing and stimulating the production of sIgA or may also limit sIgA production [54,55].

Due to its structure, sIgA, mainly in the mucous outer layer of mucosal secretions is capable of "immune exclusion", a process of non specific defense. sIgA can agglutinate polyvalent antigens or pathogens, as its properties allow crosslinking, clumping, trapping and then, peristaltic clearing. [54]. Besides immune exclusion, sIgA blocks microbial adhesion, inhibiting pathogen interaction with the gut epithelium. Direct receptor-binding or intercepting pathogen virulence by interference with Salmonella motility and impact on cholera toxin are other methods of sIgA defense [54].

Changes in the infant flora may influence the delicate equilibrium of host immune development. For instance, maternal derived milk sIgA prevent excessive expansion of pro-inflammatory segmented filamentous bacteria (SFB) [55]. However, the SFBs are important in protecting against rotaviruses which cause dangerous diarrhoea and dehydration at this age [56]. This bacterium, a potent inducer of mucosal IgA [55], is important in postnatal maturation of gut immune functions. At the same time sIgA can trigger immunity through receptor mediated action by activating immune receptors on a number of important immune cells and initiate activities such as respiratory burst, important for immunological defences and in cell signalling [57].

Maternal dietary metabolites can be modulated by microbes [24], and these may be enhanced by maternal antibodies during lactation, by binding and transferring to the infant [58].

4.5 Bioactive Factors in Breastmilk Nurture Gut Microbes

Nature and maternal nurture rely on signals to reach out and impact what matters. Nature relies on signalling for plant growth and development of its flora and fauna. Bacterial signals for cellular communication are perceived by plants and can modulate important events such as gene expression, metabolism and growth. Plants produce organic acids and vitamins, utilized by microbial populations. Microorganisms release phytohormones and various other substances, which revitalize plant immunity and modulate plant growth [59]. Integrating this observation to the human gut ecosystem, breastmilk micro-signalling modulate microbial immune potentials [60,61], and as occurs in nature, they too could have far reaching implications .

Lactoferrin, an important breastmilk protein contributing to the bioavailability of breastmilk iron, promotes survival of *Bifidobacteria* species [60]. Lactoferrin sequesters iron from bacterial pathogens and directly interacts with bacteria. Lysozyme supports infant gut flora through both anti-bacterial and anti-viral activities [61]. Breast milk lysozyme selectively excludes non- human-residential bifidobacteria (non-HRB), and with other factors, inhibits growth of adult-type strains [61].

Following birth, calprotectin, a protein of the S100 family, is found in large amounts in breastmilk. It chelates metals and inhibits the growth of manganese sensitive bacteria such as S. aureus and group B streptococci, important neonatal pathogens [62]. The essential amino acid tryptophan and its metabolites in breastmilk influence gut microbial composition and metabolism in the infant [63]. Kynurenines which are tryptophan metabolites, act as substrate with impact on gut microbiota [63]. Aryl hydrocarbon receptor (AHR), a protein transcription factor that regulates gene expression and signalling, in breastmilk, originates from the mother's diet as well as from the maternal microbiota, transferred through milk [64].

Innate immunity in breastmilk pertaining to the presence of soluble Toll-like receptors (TLRs) which are the transmembrane glycoproteins that recognize conserved molecular structures, as well as their immunoreactivities, provide novel insights on intestinal homeostasis [65]. TLRs in colostrum and mature milk were found mainly in milk samples from women who delivered preterm infants, in the milk fat globule membrane [65].

Lipid profiles and bile acids modulate gut microbiota [66], and breastmilk fatty acid profiles were associated with the *Bacteroides and other microbes* in the gut microbiota of breastfed neonates [66] Pathogens carrying antibiotic resistance genes (ARGs), make infections challenging to treat and there are risks associated with resistant pathogens in infancy. When breastfeeding and intrapartum antibiotic prophylaxis are halted, higher numbers of specific ARGs may be influenced by commensal type in the infant gut [67].

4.6 A Biological Loop of Unceasing Energy Flow

4.6.1 "Maternal gut- milk- infant gut" energies

There is energy flow through biotic and abiotic signals in an ecosystem, as energy cannot be created nor destroyed [68] and such energy flow is compared to the human system where microbial signals as dynamic "energies" could also harvest, store, and utilise energy obtained from the diet [69]. When this is obtained from the maternal diet, the energies harvested would "flow" into breastmilk nutrition.

These "energies" may well be "perceived" by many organ systems. Eubiosis or dysbiosis may positively or negatively impact the microbiota-gut-liver axis, microbial associations from the gut to our lungs, skin, kidney, heart or brain viz-a-viz impulses, mediators and pathways [70]. Bidirectional signals, for instance, in the microbiota-gut-brain axis, functioning through metabolites, cytokines and enteroendocrine mediators are crucial to holistic health [11,71].

4.6.2 Placental metabolites and their energies

In nature, plants and microbes communicate through "trans-kingdom" signalling pathways [59]. In the unborn foetus, during gestation, maternal microbial signals reach the offspring via the placenta [72]. Maternal antibodies may help transfer microbial products from the maternal intestine to accelerate foetal innate immune maturity [72]. This function may then be replaced by microbial signals in breastmilk that continue to support developing immune processes.

5. CONCLUSION

Our gut feelings may indeed be palpably linked to intestinal microbiota [73], and gut microbes have immense potential towards holistic health, through tangible substances and energy flows.

In the human gut, it is necessary to be cognizant that an ecosystem is enriched, diversified and stabilized by breastmilk and the micro-signals that have commenced long before birth, in a trans-biological system, where the lactating mammary gland completes placental function in the nurture of the young, embracing the "mother-microbe -infant-microbe" transmission loop. By observations highlighted in the article, it is hoped that the reader, the teacher and the researcher appreciate a greater synthesis and integration between nature's majestic events with dynamic biological evolution in us, initiated by the early and natural act of breastfeeding.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Not relevant as this is a review article

COMPETING INTERESTS

Author has declared that no competing interests exist.

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