

Metabolomics, milk-oriented microbiota (MOM) and multipotent stem cells: the future of research on breast milk

Vassilios Fanos

Neonatal Intensive Care Unit, Neonatal Pathology, Puericulture Institute and Neonatal Section, “Azienda Ospedaliero-Universitaria” and University of Cagliari, Cagliari, Italy

“... divine honours cannot be given to the children of Zeus, except for those who suck Hera’s milk; thus it is said that Hermes took Heracles, just-born on Olympus, and put him near her breast so that he could suck. When Hera realised this, she pushed him away and the milk spurted out abundantly to become the Milky Way.”

Eratosthenes, *Katasterismos*, 44 (3rd century BC)

Keywords

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Corresponding author

Vassilios Fanos, Neonatal Intensive Care Unit, Neonatal Pathology, Puericulture Institute and Neonatal Section, “Azienda Ospedaliero-Universitaria” and University of Cagliari, Cagliari, Italy; tel.: +3907051093403 (direct), +3907051093438 (NICU); email: vafanos@jpnm.com.

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Introduction

The more we learn about human milk, the more we are forced to admit to our extraordinary ignorance about this liquid, considered miraculous from ancient times. The diade of the mother breastfeeding her newborn child is a unique model for understanding the importance of diet in a broader sense, both in terms of prevention and protection. Human milk is capable of preventing many diseases. The first moments of life are important for the destiny of an individual: normally this is recognized for the lungs and the first breath, but it is also true for the other organs, in particular for the intestine (“the first meal is like the first breath”).

From Elsie Widdowson’s studies, we know that the duodenum of breastfed piglets gain 42% of their initial weight in the first 24 hours of life [1]. This element emphasizes even more the role of absolute importance of breast milk, when it is available, in the first moments of life. It is like the ideal software inserted in the hardware for which it was created. It influences the rest of an individual’s life and activates a cascade of metabolic processes in the organism. The epithelial mammary cell is considered a bioreactor for complex structures and bioengineering activities that interact in all the physiological processes of the baby: growth and development, microanatomy and function, physiology and metabolism, colonization and maturation of the gut microbiota, immunological orientation and consolidation, setup and organization of the brain [2].

This editorial deals with three themes of great importance today: metabolomics, milk-oriented microbiota (MOM) and multipotent stem cells. Perhaps from the integration of knowledge in these three fields we could take further significant steps towards the understanding of the miracles of human milk.

Metabolomics of human milk and formulas

Metabolomics, also called the “new clinical biochemistry”, is an approach based on the systematic study of the complete set of metabolites in a biological sample, in our case milk. It is a “functional” technology” for identifying, quantifying and characterizing simultaneously hundreds/thousands of low-molecular-weight metabolites. It is capable of producing a snapshot of the metabolome, the entire set of these

metabolites produced by an organism, a mirror that reflects the physiological, evolutionary and pathological state of a biological system. The metabolome is so close to the phenotype that it can be considered the phenotype itself. The metabolic profile is a unique characteristic of all subjects, capable of identifying them with a specificity of 100% [3, 4]. The first metabolomic study of milk was performed by our group in 2012 [5]. With the use of innovative technologies such as nuclear magnetic resonance and gas chromatography mass spectrometry, we demonstrated that human milk presents high levels of lactose and low levels of maltose compared to formula milk. Moreover, the two types of milk also present different levels of oleic and linolenic acid and this has recently been confirmed [6]. Also present is a modification of the panel of metabolites in relation to the maturation of the milk. Comparing the metabolomic data of human milk at one and four weeks, we observe that numerous metabolites increase on progressing towards the first month of life: for example, we can mention oleic, linoleic and palmitoleic acids, which increase as cholesterol decreases [7]. In reality, new studies have made further important contributions leading to the finding of certain characteristics based on genetics (the so-called “secretory” and “nonsecretory” subjects) or drug treatments [8].

Microbiotics of human milk

Up to little more than ten years ago it was thought that human milk was without bacterial contamination and this was considered one of its advantages. We can now state that human milk is anything but sterile! Today we know that it contains a quantity of bacteria (microbiota) of 50 genera and 200 species [9]. They come from sources inside and outside the mammae. In particular, it appears that the microbiota may also derive from the entero-mammary bacterial circle (from the mother’s intestine). The dendritic cells are apparently the transporters of the bacteria which can open the closed junctions and transfer the bacteria, keeping them alive for many days in the mesenteric lymph nodes [10]. We speak of MOM [2]. An average breastfed baby who assumes 800 mL of breast milk receives from 100,000 to 10 million bacteria per day from the milk [9]. The composition of bacteria from human milk normally includes nine groups: *Streptococcus*, *Corynebacteria*, *Bradyrhizobiaceae*, *Staphylococcus*, *Serratia*,

Ralstonia, *Propionibacterium*, *Pseudomonas* and *Sphingomonas*. *Bifidobacterium* and *Lactobacillus* are also common, but less universal. Milk microbiota appears to be rather stable and differs especially in women who are obese and/or quickly gain weight during pregnancy [10]. What is most important in determining an important difference in MOM is the kind of delivery: caesarean or vaginal and, among the caesareans, those that are urgent or repeated. Mothers who have undergone an urgent caesarean section have milk microbiota more similar to that of mothers who have delivered spontaneously [11].

The composition of human milk microbiota is in fact highly individualized and unique for each mother and can have important effects on the colonization of the intestine and the short- and long-term health of the child. What we know is that these consequences for human health begin from the very first moments of life and follow an individual's evolution with a triangular relationship: the guest (the neonate), mother's milk and MOM. When a mother breastfeeds her child, there are two milk consumers: the child and the child's intestinal bacteria (microbiota). To understand how and why the milk influences the infantile microbiota will be of the utmost importance in understanding all the complex macrosystems in which food is strategic. Some questions remain open. How can a specific microbiota protect children and what are its weak points? How can it educate the immune system and present the "sterile" neonate to the real world?

Multipotent stem cells of mother's milk

Finally, we also know that human milk contains stem cells whose function is not yet fully known, but it is not difficult to imagine that they may trigger the beginning of the immune response of the newborn organism [12, 13]. In particular, it is thought that its cholesterol is quite rich. It appears that the stem cells of human milk pass through the intestinal barrier as well as that of the brain and migrate to settle in the brain and other organs and apparatus, among which surely the thymus, pancreas and liver. Once they reach the neonatal tissue of destination, they appear to differentiate to assimilate and integrate in the tissue. For example, at the level of the brain they may differentiate into neuronal stem cells and neurons. Some authors [12] have tested the multipotent potential for differentiation of human milk stem cells and found that they can differentiate along

adipogenic, chondrogenic and osteogenic lines and thus potentially be "reprogrammed" for many different kinds of human tissue. They can thus be considered a source alternative to autologous stem cells, although it is obvious that their role must still be specified more precisely [13-15]. In Hosseini's work, stem cells from human milk have become oligodendrocytes, astrocytes and neurons [14].

Conclusions

This editorial has presented some insights into metabolomics, MOM and multipotent stem cells. Perhaps from the integration of knowledge in these three fields [16-18] we will be able to take further significant steps towards the true understanding of the miracles of mother's milk.

Declaration of interest

The Author declares that there is no conflict of interest.

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