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Stem cells of the maternal milk allow a better development of lactating newborns

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Abstract

Recent findings of stem/progenitor cells in maternal milk and their ability to cross the intestinal barrier of lactating newborns and integrate into neonatal organs to promote optimal child development present a new challenge in perinatal medicine. These findings emphasize the need for all mothers to breastfeed their babies for a long time. According to recent research, breastfeeding protects the lactating newborn from multiple infectious agents that can cause severe and fatal early infancy diseases. The second benefit is that maternal stem cells accelerate the development of several organs, including the brain, protecting lactating infants from severe childhood and adult diseases. The success and diffusion of exclusive breastfeeding, especially in low-resource settings,

depends on mothers' knowledge of the many benefits for their child, including recent discoveries on breastfeeding's powerful benefits. Every mother may need simple booklets to learn about the unique benefits of maternal breastfeeding, including the nutrients and multiple cell types that protect the newborn from infections and accelerate neonatal organ development. Social media should also be encouraged to spread news about breastfeeding and maternal stem cells' impact on lactating infants' health. Health belief model interventions may boost breastfeeding. In conclusion, the discovery of massive amounts of cells in maternal milk and the identification of stem/progenitors with previously unknown potential in newborn development after birth should be considered a new valuable tool for exclusive breastfeeding advocates. Data here suggests that every action to spread this message and educate mothers and families about breastfeeding's irreplaceable role is mandatory.

Introduction

The mammary gland is the only human organ to derive its name from the mother, and this happens in multiple languages including English (mammary gland), Greek (mastikós) and Italian (mammella) languages. The human milk, produced by mammary glands, has been for a long time considered important for the perinatal development of any newborn, due to its peculiar nutrients, differing in composition from the milk of other mammals. Due to this knowledge, breastfeeding has been indicated by the medical community as the preferred method of infant feeding for the first year of life.[1] Exclusive breastfeeding is considered, even nowadays, the healthiest and simplest method for feeding newborns and for preventing malnutrition.[2] More recent studies evidenced a dynamic quality of human milk, with a high interindividual and intraindividual variability regarding the levels of vitamins, minerals, macro- and micro-nutrients.[3]

The human milk stem cells

In recent years, some studies have changed completely the debate regarding the role of maternal milk in neonatal development.[4] The report that maternal stem cells are present in breast human milk, a finding so unexpected that it was defined “a mystery to be unraveled”.[5] These findings encouraged new studies focused on the composition of human breast milk and, particularly, on the cell types detectable in the human milk. First reports from an Indian group evidenced that the human milk is a rich source of multipotent mesenchymal stem cells: colostrum was found to contain about 5 million cells per ml, and a breast-fed neonate has been reported to ingest about 10^8 milk

cells per day.[6] A modern view of the human breast milk was prospected in further studies. Accordingly, the human milk was defined as a dynamic fluid, with all necessary nutrients and growth factors useful for the optimal development of the newborn, but also containing huge amounts of maternal live cells.[7] The mix of all constituents was considered fundamental for the optimal growth of the neonate. In following studies, the lactating mammary gland revealed its intimate nature: to represent a source of a heterogeneous population of breast-derived cells, including exfoliated luminal epithelial cells, immune cells, mesenchymal stem cells and embryonic stem cells, giving rise to a peculiar stem/progenitor cell pool.[8] Further studies carried out on cells freshly isolated from the human breast milk evidenced a heterogeneous expression of stemness markers in milk staminal cells.[9] The recent discovery that a subset of human milk cells may express the transcription factor ISL1, a stem cell factor with relevant roles in human development, reinforced the hypothesis on a major role of milk stem cells in the development and growth of lactating neonates.[10] At this time, a question emerged from the scientists and clinicians involved in the study of maternal milk:[11] which are the potential benefits of the multiple cells detectable in the breast milk for the lactating newborn? An answer to this question was given by a Greek researcher, Foteini Hassiotou, who tried to explain the role of the maternal milk cells in the development of lactating infants. Analyzing the milk stem cells, multiple questions arose: are breast milk stem cells heterogeneous? Can milk stem cells migrate through the intestinal barrier into the newborn organism? And can maternal stem cells integrate into the organs of the lactating infant and differentiate towards multiple cell types?[12] According with this author, breast milk cells should be subdivided into two main groups: immune cells and plastic stem cells. The former may give an immunological support to the newborn, protecting the breast-fed infant from infections, with the production of immunoglobulins, cytokines, lysozyme and lactoferrin. In this vision, immune cells might play a major role in the present of the newborn life, protecting him/her from the infectious agents encountered after delivery, allowing their survival. The second pool of breast milk cells, the stem/progenitor cells, might play a major role in the developmental training of the nursing infant, with short- and long-term positive influences on the infant growth.[13]

Regarding the heterogeneity of milk stem cells, a study by Kaanta *et al.* revealed the existence of different subpopulations inside the milk stem cell pool and identified their immunophenotype. The first group to be identified was that of mesenchymal stem cells, characterized by the following phenotype: CD44+, CD29+, SCA-1+, Nestin+, Vimentin+. The second group included the luminal progenitor cells, characterized by the expression of CD61. The third group included the basal progenitors, with the following immunophenotype: OCT4+, SOX2+, NANOG+. The progenitor cells of the last group were also defined “pregnancy-specific progenitors”.[14]

As for the ability of stem cells to migrate into the neonatal organism, initially it was claimed that milk stem cells could not survive in the newborn stomach, due to the low pH. This hypothesis was abandoned. Old analyses had evidenced that the newborn stomach is characterized by a neutral pH which, associated with the buffering capacity of the milk, may allow the survival of milk stem cells during their passage in the gastrointestinal tract.[15]

The most important open question on the role of maternal milk stem cells regarded their putative ability to integrate into the organ of the lactating newborn. A brilliant and elegant experimental study carried out by Dr. Hassiotou gave an answer to this critical question. Given that mice may express or not the antigen TdTomato (TdT) on the surface of their cells, TdT-negative newborn mice were breast-fed by a TdT-positive mother. When TdT-negative lactating mice were sacrified, TdT+ cells were found in their stomach, thymus, liver and brain[16] of the originally TdT-negative newborns. These findings taken together allowed to state that the milk-derived maternal TdT+ stem cells might cross the stomach wall, reach the portal vein, find homing in the liver and thymus and reach the brain, differentiating into neural stem/progenitors and neurons.[16] These data taken together revealed that breast milk stem cells may transfer from the maternal milk to neonatal organs through lactation, and that maternal stem cells can migrate across the intestinal barrier, differentiate towards different cell types, assimilate and integrate with newborn tissues, accelerating their post-natal development.

These experimental data had the power of changing completely the debate on the utility of breast-feeding in the postnatal development of any newborn. Before the discovery of the huge amounts of cells, particularly of stem/progenitor cells, present in the breast milk, the relevance of breast feeding for the optimal development of newborns was mainly due to the peculiar association of nutrients typical of the human breast milk. The studies demonstrating the ability of maternal stem cells to integrate into the organs of the lactating infant reinforced very much the value of maternal milk for survival and development of lactating newborns. The immune cells of the human milk may assure a big advantage to breast-fed infants against infections, allowing their survival, in spite of the immaturity of their immune system. Moreover, the milk pool of Stem/progenitor cells may accelerate the development of single organs of the newborn, allowing the acquisition of a proper number of differentiated cells, reinforcing the burden of specialized cells which will represent an important tool against the insurgence of chronic diseases later in life. The ability of maternal milk progenitors to differentiate into metanephric stem cells in the kidney will allow the persistence of nephrogenesis, ending with the evolution of new glomeruli in the renal cortex of the newborns.[17] This aid will transform an oligonephronic kidney into a kidney with a burden of glomeruli within the normal range and will transform an individual susceptible to develop renal insufficiency later in

life into an individual resistant to the insurgence of chronic kidney disease.[18] The ability of maternal milk progenitor cells to differentiate into neurons and glial cells will allow a better development of the brain with relevant positive consequences on the newborn life.[19] Maternal progenitors which integrate in the brain cortex might increase the number of post-mitotic neurons and glial cells of the cortex, transforming an individual susceptible for neurodegenerative disorders, such ad Alzheimer disease, into a resistant subject, due to the increased burden of cortical neurons.[20] Maternal progenitors integrating into the dopaminergic neurons of the substantia nigra, would increase the burden of neurons able to synthesize dopamine, ending with the resistance of breast-fed infants to develop Parkinson disease later in life.[21] Similar protective actions exerted by maternal milk stem cells may be hypothesized regarding other organs, with relevant positive consequences on the development of multiple chronic diseases of adulthood, including atherosclerosis,[22] diabetes,[23] infectious diseases like COVID-19,[24] metabolic syndrome,[25] and cancer.[26]

Concluding remarks

The recent findings regarding the presence of stem/progenitor cells in the maternal milk, and their ability to cross the intestinal barrier of lactating newborns and integrate into the neonatal organs, contributing to the optimal development of children represents a new challenge in perinatal medicine. These findings reinforce significantly the message on the absolute necessity for all mothers to utilize breastfeeding of their infants for a long period. Breastfeeding is characterized, at the best of the more recent knowledge, by two main advantages: it assures an immunological protection of the lactating newborn towards the multiple infectious agents, which may be responsible for severe and lethal diseases of early infancy. The second advantage regards the ability of maternal stem cells to accelerate the neonatal development of several organs, including brain, protecting the lactating infants from multiple severe diseases insurging in childhood and in the adult life. Mother's knowledge of the multiple advantages for their little daughter/son, related to the more recent discoveries on the powerful positive effects of breastfeeding, represents a key factor for the success and diffusion of exclusive breastfeeding, particularly in low-resource settings.[27] To improve the knowledge of the peculiar value of maternal breastfeeding regarding the nutrients and the multiple cell types able to protect the newborn from infections and able to accelerate the development of the neonatal organs, may need the distribution of simple booklets to every mother, in order to improve their knowledge regarding the gift they are giving to their lactating infant.[2] Moreover, even the use of social media should be encouraged for a better diffusion of all the news regarding the key role of breastfeeding, adding news regarding the relevant role played by the

maternal stem cells for the actual and the future health of lactating infants.28 Health belief model interventions may also enhance the breastfeeding success.[29]

In conclusion, the discovery of the presence of huge amounts of cells in the maternal milk and the identification among them of stem/progenitors with a previously unknown potential in the newborn development after birth, should be considered a new precious tool for people involved in the diffusion of exclusive breastfeeding. Every action aimed to diffuse this message, enhancing mothers and family knowledge regarding the irreplaceable role of breastfeeding, appears, on the basis of data here reported, mandatory.[20]

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