Fetus-Breastmilk-Breastfeeding-Infant-Cells Cycle: Fetus-to-Infant His/Her Own Fetal Cell External Transmission via Breastfeeding §

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Abstract

The existing literature has recently indicated that (i) fetal cells are present in maternal blood and other multiple maternal tissues and organs during and after pregnancy; (ii) different functional immune cells and stem cells have been found in human breastmilk; and (iii) intact animal milk cells can migrate into the gut wall of suckling offspring and distribute further over the animal neonatal body. Based on these advantages, I propose a novel model called the "Fetus-Breastmilk-Breastfeeding-Infant-Cells Cycle" (FBBIC Cycle), or "the External Transmission of His/Her Own Fetal Cell from Fetus to Infant," to reveal an unrecognized mechanism in which some stem cells and functional immune cells derived from embryonic/fetal cells become part of milk cells and can be ingested by breastfed infants; these regained fetal cells can then be redistributed within the suckling body without potential allogenic or semi-allogenic problems. The completion of the FBBIC Cycle depends on the continuity from gestation to lactation. The FBBIC Cycle theory suggested for the first time that the fetus may contribute milk cells and that acquired cellular immunity during pregnancy may be transferred to the suckling via the FBBIC Cycle. The potential benefits of the FBBIC Cycle in immunology and regenerative cytology warrant further investigation.

Key Words: FBBIC Cycle; Fetal cells; Fetus; Infant; Breastmilk; Breastfeeding; Stem cells; Cell migration

Introduction

It is well known that fetal growth and development within the uterus absolutely depends on nurturing and anti-infection protection supplied by the maternal body through diverse maternal-fetal molecule transferring mechanisms. Traditionally, it has been assumed that the placental barrier might structurally and functionally isolate the eukaryotic cells of the maternal body from those of the fetus [1] and that the cellular component in breast milk was believed to be derived only from maternal host cell lineages, in which fetal cells did not participate.

During the past two decades, accumulating evidence from studies on humans and non-human mammals has indicated that the efficiency of the placental barrier for the structural and functional isolation between maternal cells and fetal cells is relative and that there is a physiologically bidirectional cell transmission between pregnant mothers and their fetuses.[1-5] Moreover, the cell transmission between fetuses, also known as "transmaternal sibling microchimerism,"[6-10] and the cellular migration between the lactating mother and suckling offspring [11-14] have also been proposed.

Hypothesis

In this article, a novel model called the "Fetus-Breastmilk-Breastfeeding-Infant-Cells Cycle" (FBBIC Cycle), or "the External Transmission of His/Her Own Fetal Cell from Fetus to Infant," is hypothesized (see Figure), which consists of the following three major statements: (i) Maternal breasts should be one of the organs where fetal cells can reside. Fetal cells can colonize maternal mammary glands after migration through the placental barrier and into maternal blood; (ii) Milk cells consist of heterogeneous cell lineages from both maternal and fetal sources. Fetal cells in breast milk are expected to consist of stem/progenitor cells and diverse end-differentiated cells including leukocytes; and (iii) Regained fetal cells may reallocate within the suckling body. Fetal cells in breast milk have the capability to cross the intestinal epithelium. After crossing the epithelium, fetal cells may re-spread further and take up residence within a variety of organs and tissues of the suckling without allogenic and semi-allogenic problems.

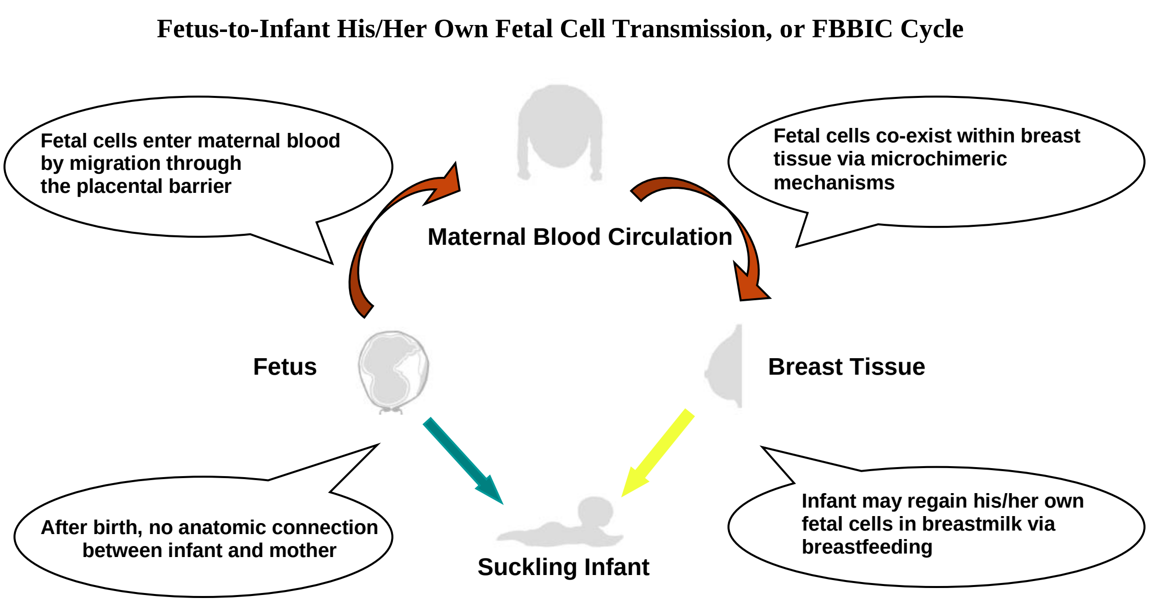

Figure. During gestation, fetal cells enter maternal blood by migrating through the placental barrier, and then spread into multiple maternal tissues and organs including breast tissue and breast milk, where fetal cells co-exist via microchimeric mechanisms. Although the prenatal anatomic connection (umbilical cord and placenta) no longer exists between the infant and mother during lactation, breastfeeding may replace its role. The suckling infant may be able to regain his/her fetal cells in breast milk via breastfeeding from his/her own lactating mother.

Supporting Evidence and Discussion

I. Maternal Mammary Glands as One of Residing Organs for Fetal Cells

Fetal cells, including end-differentiated cells and stem/progenitor cells, are normally present in maternal bloodstream and many other maternal tissues and organs during pregnancy and after delivery;[1-3, 15, 16] and, moreover, fetal cells can persist in the maternal body for as long as 27 years, [2] or even for life.[17]

Interestingly, to the best of my knowledge, the question of whether fetal cells colonize maternal mammary glands has not yet been answered. Moreover, the newly understood fact that normal pregnancy is characterized by a maternal systemic Th2 immune response [18] and that bacterial microorganisms exist in normal breast milk,[19-24] leads to the hypothesis that maternal breasts may be one of the organs where fetal cells can be recruited to and reside.

II. Milk cells Consisting of Heterogeneous Cell Lineages from Both Maternal and fetal Sources

Milkcells have been assumed for a long time to come only from diverse maternal end-differentiated cell lineages, including phagocytes,[25] immunologic memory T cells [26] and B cells.[27] The concentration of milkcells varies widely from 10^3 to 10^8 cells per mL of human milk. [28-30] Recently, human milk cells bearing stem cell markers have been identified by several research teams.[29, 31-33] Embryonic stem cells are defined as cells that come from an organism at its earliest stages of development,[34] and can infinitely renew themselves and transform into multicellular lineages in the body of macroorganisms such as human beings and non-human mammals.[3, 34] However, the source of stem cells in breast milk is elusive, although it was assumed to be from maternal mammary stem cells, not from the fetus.

In the FBBIC Cycle theory, it is hypothesized that (i) milk cells may be derived not only from maternal host cells but also from fetal cells; (ii) the concentration of fetal cells in breast milk is expected to reach its highest level in colostrum and then decline after delivery; and (iii) fetal cells in breast milk may consist of haemopoietic or/and mesenchymal stem cells and diverse end-differentiated cells, including leukocytes.

III. Re-spreading of Fetal Cells Within the Body of Suckling Offspring via Breastfeeding

There has been a notion since the 1980s that intact leukocytes in ingested maternal colostrum and mature milk can migrate into the gut wall of suckling offspring. Although, up to now, no direct evidence from studies on human beings is available, many relevant data from studies on non-human mammals have revealed that the trans-epithelial milk cells truly exist within the body of animal suckling neonate.[11-14]

The concentration of milkcells in human colostrum is reported to be as high as 10^8 per ml of milk.[28] Given that human neonates ingest on average 100 milliliters of colostrum per day during the first 3 postnatal days, the total daily acquired cells from maternal breastfeeding would be estimated to be as high as 10^{10} cells. If the trans-epithelium rate of ingested milk cells in human neonates is 0.1%,[35] the total colostral cells regained by a neonatal body would reach 10^7 cells per day. If two per cent of milk cells were stem cells,[36] neonates would regain around 10^5 stem cells from colostrum-feeding daily.

Tuboly and colleagues described a phenomenon in the 1980s that the digestive tract mucosal barrier of suckling newborn piglets was selectively opened to the colostral lymphoid cells from their biological mother, but not to the cells from allogeneic lactating mother, or from blood and heat-treated colostral lymphoid cells.[14] I argue that the Tuboly Phenomenon may also occur in humans.

The intestinal epithelium-transferred animal milk cells have been found to redistribute over the thymus, liver, lung, lymph nodes, spleen and gastrointestinal tissues of the animal suckling.[11-14] Traditionally, these milk cells within the body of animal offspring were also assumed to come only from the animal maternal host cells.

In the FBBIC Cycle theory, milk cells are hypothesized to come from both of maternal and fetal sources, and therefore, it could be deducted that epithelium-transferred and then body-redistributed milk cells may include animal embryonic/fetal cells, from which the third hypothesis may be further inferred: Embryonic/fetal cells in human milk may re-spread within the body of suckling infant via breastfeeding.

VI. Potential Roles and Significances of FBBIC Cycle and Future Prospects

The following is a brief introduction to the potential roles and significances of the FBBIC Cycle in the transmission of cellular immunity to suckling neonates, the immunological mechanisms of transplantation, the regenerative effect of stem cells in human breastfed offspring, and our understanding of human milk and breastfeeding.

Transmission of cellular immunity to suckling neonates

Some studies have already suggested the possible roles played by the FBBIC Cycle in the transmission of cellular immunity to suckling neonates. For instance, three decades ago, breastfeeding was found to deliver a T lymphocyte-mediated immune response to the BCG vaccine in breastfed infants.[37] Recently, vaccine-induced *Mycoplasma hyopneumoniae* cellular immunity at 5 and 3 weeks antepartum was shown to be transferred from vaccinated sows to their offspring via breastfeeding.[38] The transferred immune cells were assumed to be of animal maternal origin.[37, 38]

However, according to the FBBIC Cycle theory, during gestation, fetal cells can migrate into the maternal blood circulation and multiple other tissues or organs where fetal cells have an opportunity to be exposed to novel antigens that the pregnant mother may be experiencing. Some fetal cells have embryonic stem cell-like functions and can differentiate into different cell lineages, including immune cells (such as memory T cells). If these fetal cells return to the body of a breastfed infant, the acquired cellular immunity would undoubtedly be transferred to the suckling. Therefore, the potential role of human fetal cells in generating tuberculin-specific cellular immunity and the specific cellular immunity for *Mycoplasma hyopneumoniae* obtained by animal fetal cells during gestation cannot be excluded.

Recently, CD8(+) or CD4(+) T cells for virus-specific cellular immune responses have been detected in both human and animal milk samples.[39, 40] The question of whether the FBBIC Cycle plays a role in the transmission of virus-specific cellular immunity to suckling neonates needs to be answered in the future.

Transplantation immunology

The survival of grafts at the individual macroorganism level involves a complicated tolerogenic mechanism, one aspect of which is the tolerance to noninherited maternal antigens (NIMA) mediated by maternal-fetal-microchimerism. [41] Recently, the role of human regulatory T cells (Tregs) in transplantation tolerance has been attracting much attention.[42] The development of tolerogenic fetal Tregs during gestation was found to be enhanced by maternal alloantigens, and these tolerogenic fetal Tregs play a role in the mechanism of tolerance to NIMA. [43, 44] In addition, many other cell lineages, such as mesenchymal stem cells, embryonic stem cells, myeloid-derived suppressor cells, tolerogenic DC, and B cells, have also been shown to have immuno-regulatory properties.[42]

Based on Mold and colleagues' finding,[43] the fetus-to-fetus eukaryotic cell transmission model and the FBBIC Cycle, the following possibility cannot be excluded: Paternal alloantigens-tolerogenic fetal T regulatory cells (PATF-TRCs) may also be induced during gestation, in addition to maternal alloantigens-tolerogenic fetal T regulatory cells (MATF-TRCs). Once these MATF-TRCs and PATF-TRCs return to the body of a suckling infant via breastfeeding, they survive much more easily than allogenic and semi-allogenic cells do. These fetal cell-derived MATF-TRCs and PATF-TRCs may participate in suppressing postnatal anti-maternal or anti-paternal immune reactions to maternal or paternal grafting.

Regenerative cytological role in human breastfed offspring

The ultrasound assessment of the thymus revealed that the thymus size of breastfed infants is significantly larger than that of formula-fed infants.[45-47] Jeppesen and colleagues showed that thymus index and thymic index/weight-ratio of healthy infants who were fed exclusively with pasteurized donor milk were significantly lower than those of exclusively breastfed infants,[46] which cannot be easily explained by the difference in the molecular components between the two kinds of human breastmilk. However, it can be accounted for by the lack of the FBBIC Cycle in those infants fed with pasteurized donor milk.

Studies on human beings and nonhuman animal models have shown that fetal cells may be involved in maternal tissue repair.[48-53] However, according to the FBBIC Cycle theory, the critical question of whether regained fetal cells participate in the tissue repair of breastfed infants also has clinical significance. The potential regenerative protection from regained fetal cells through the FBBIC Cycle may provide a novel mechanism for explaining the finding in epidemiological studies that breastfeeding decreases the infant mortality and morbidity from infections in the gastrointestinal tract or respiratory tract.[54-57]

Significance in our understanding on human milk and breastfeeding

To date, our understanding on human milk and breastfeeding has focused on the aspects of nutrition and immunology: (i) at the nutritional level, breastmilk offers various essential nutrients including carbohydrates, lipids and proteins, for the growth and development of suckling offspring; and (ii) at the immunological level, breastmilk acts as a vector to transfer maternal acquired and innate immune defense factors to suckling babies. The FBBIC cycle may further suggest that the fetal cellular benefit of human milk and breastfeeding for infants to obtain from their healthy biological mothers is individually unique. It is may be true that discarding biological mother's breastfeeding means abandoning the chance for offspring to regain their own fetal stem/progenitor cells and functional immune cells that were stored in breastmilk during pregnancy.

Breastfeeding has been consistently advocated as the best feeding method for human suckling by academic institutes and international organizations, such as WHO and UNICEF, over the past decades.[58; 59] The FBBIC Cycle may provide a new theoretical basis for supporting human breastfeeding, especially colostral feeding.

Concluding Remarks

During the past decades, the advantages in cellular embryology, fetology, regenerative cytology, immunology, and human milk research have presented many indirect pieces of evidence supporting the FBBIC Cycle theory. For the first time, the FBBIC Cycle theory explains theoretically that the fetus may play an active role, or be a co-contributor, in the formation of maternal breast milk, and breastfed infants may regain their own fetal cells from ingested breastmilk.

The FBBIC Cycle is one of the pregnancy-induced cell transmissions that occur among the fetus, infant, and the maternal body, and its completion absolutely depends on the continuity from gestation to lactation, meaning that the FBBIC Cycle may not be completed in infants who are never breastfed by their own mothers. The probably irreplaceable benefits of the FBBIC Cycle for infants in immunology and regenerative cytology are worth further investigation, which will undoubtedly improve our understanding of human breast milk and breastfeeding.

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