Six Models of the Pregnancy-Associated Eukaryotic Cell Transmission among Fetus, Mother and Infant §

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Abstract

Several pregnancy-associated cell transmissions among fetus, mother and infant have attracted increasing attention over the past decades. The two most studied types are fetal-to-maternal cell transmission (FMCT) and maternal-to-fetal cell transmission (MFCT). Recently, a new model called the fetus-breastmilk-breastfeeding-infant-cells cycle (FBBIC Cycle) has been proposed. This model suggests that there is an unrecognized migration of embryonic/fetal cells from fetus to infant him/herself through breastmilk and breastfeeding. Currently, there are six known models of cell exchange and interaction during pregnancy and lactation: (i) FMCT; (ii) MFCT; (iii) gestation-associated fetus-to-fetus cell transmission (FFCT); (iv) breastmilk and breastfeeding-mediated maternal-to-infant cell transmission (MICT); (v) breastmilk and breastfeeding-mediated fetus-to-infant allogenic or inter-sibling cell transmission (FICT), and (vi) the FBBIC Cycle. Of these models, the FBBIC Cycle is the important, as it reflects the most benefit to the offspring during both prenatal and postnatal life from a physiological, immunological, and regenerative cytological perspective, without introducing potential disadvantages from allogenic and semi-allogenic cells. A thorough theoretical exploration of fimpology is essential for accurately interpreting prenatal diagnosis, developing molecular diagnostic techniques further, and deeply understanding tolerogenic mechanisms in transplantation immunology.

Key words: Cell transmission; Pregnancy; Breastfeeding; FBBIC Cycle; Microchimerism; Maternal cells; Fetal cells; Stem cells; Milkcells

Introduction

Based on the existing data from studies on humans and non-human mammals, six models of eukaryotic cell transmission during gestation and lactation have been proposed, although some require further direct supporting evidences: (i) gestation-associated embryonic/fetal cell migration into the maternal body (FMCT), which results in fetal-maternal microchimerism (FMMC) [64,79,80,139-141]; (ii) gestation-associated maternal cell migration into the fetal body (MFCT), which results in maternal-to-fetal

microchimerism (MFMC) [28,34,36,85,142,143]; (iii) gestation-associated allogenic or inter-sibling fetal cell transmission between different fetuses (FFCT), also known as "transmaternal sibling microchimerism" which results in fetofetal microchimerism (FFMC) [94-100,104]; (iv) gestation and lactation-associated maternal host cell migration into the body of suckling infant via breastmilk and breastfeeding (MICT), which results in maternal-infantile microchimerism (MIMC) [30,84,89,106,110,111,144,145]; (v) gestation and lactation-associated allogenic or inter-sibling fetal cell transmission to the suckling infant via breastmilk and breastfeeding (FICT), which results in fetoinfantile microchimerism (FIMC); and (vi) gestation and lactation associated fetus-to-infant his/her own fetal cell external transmission via breastmilk and breastfeeding, known as the Fetus-Breastmilk-Breastfeeding-Infant-Cells Cycle (FBBIC Cycle) [82] (see Figure).

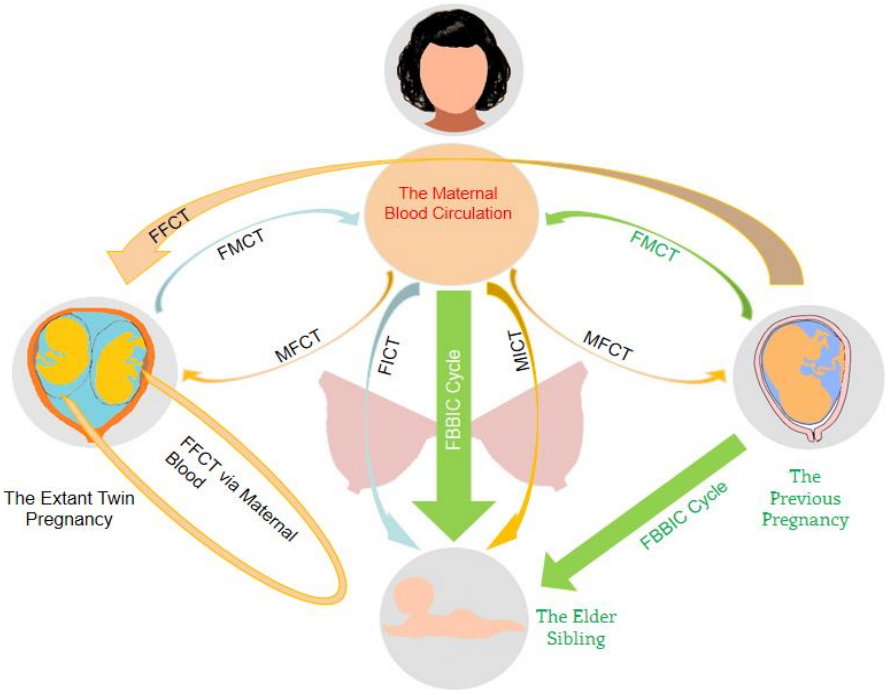

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Figure:

In the imaged mother and her offspring, the gestation-associated embryonic/fetal cell migration into the maternal body (FMCT) and the gestation-associated maternal cell migration into the fetal body (MFCT) exist between the prenatal period of the first born offspring and his/her maternal body, and between the extant fetal twins and their maternal body. The maternal host cell migration into the body of suckling infant (MICT), the allogenic or inter-sibling fetal cell transmission to the suckling infant (FICT), and the fetus-to-infant his/her own fetal cell external transmission (FBBIC Cycle) may arise between the lactating mother and her suckling infants via breastfeeding. In addition, the gestation-associated allogenic or inter-sibling fetal cell migration (FFCT) may take place when residual embryonic/fetal cells of the previous pregnancy migrate into the body of the extant fetal twins via the maternal blood circulation, and moreover, FFCT also exists between twin fetuses.

Interestingly, FMCT, MFCT, FFCT, MICT and FICT share the characteristic of foreign cells migration into tissues and/or organs of a macroorganism's body. MFCT, FMCT, and FFCT occur during gestation, and MICT and FICT may occur postnatally in infants who were breastfed with their own mothers' breastmilk, or with breastmilk from allogenic mothers or donors.

In mammals including humans, there are three major physiological processes for producing offspring: (i) embryonic/fetal growth and development, (ii) production of breastmilk, and (iii) breastfeeding offspring. However, MFCT, FMCT, FFCT, MICT and FICT do not reflect the physiological importance and the biological necessity for the continuity of these natural events. Only satisfies the FBBIC Cycle the most benefit to offspring during their prenatal and postnatal life from a physiological, immunological perspective and regenerative cytological perspective, and should be recognized as the major physiological mechanism in these models. In this manuscript, the six different models of pregnancy-associated prenatal and postnatal cell transmission are briefly summarized.

I. Migration of Gestation-Associated Embryonic/Fetal Cells into the Maternal Body (FMCT)

The migration of fetal cells into maternal organs and tissues (FMCT), also known as fetomaternal microchimerism (FMMC), was the earliest recognized consequence of cellular migration from the fetus to the mother. It was first described by Georg Schmorl in a pathological case in 1893 [58,59]. Studies on humans and non-human mammals have shown that the migration of fetal cell into maternal blood is a normal physiological phenomenon that occurs in all pregnancies [15,59-61].

Detection of Fetal cells in the maternal body

The earliest presence of fetal cells in the maternal body varies among different species. In the murine model, fetal microchimerism begins soon after implantation and increases with gestational age [9,16,18,23,60,62]. In humans, the earliest detectable fetal cells in the body of normal pregnant women have been reported at 4-5 weeks [3], 6 weeks [63], and 15 weeks [64] gestational age respectively.

Migration of fetal cell into maternal organs/tissues in humans appears to increase with gestational age [24]. The number of fetal cells in maternal blood varies widely, ranging from one fetal cell per 10,000 to one fetal cell per 1,000,000,000 maternal cells [6]. Lo and colleagues even showed that at least 17% of the maternal cellular component was positive for fetal DNA [65].

Many maternal tissues and organs in humans and some non-human mammal models have been shown to harbor fetal cells (see Table 1). Furthermore, these co-existing fetal cells have been found to be multiple cell types, including endothelial cells, mesenchymal stem cells /progenitors, and neuronal cells in the relevant maternal tissues and organs (see Table 2).

Table 1. Bilateral Cell Migration between the Maternal Body and the Fetal Body

Maternal Tissues/Organs Harboring Fetal Cells	Refs.	Offspring Tissues/Organs Harboring Maternal Cells	Refs.
blood	1–9	blood	28
bone marrow	9–12	bone marrow	29–32
brain	9, 13–16	heart	31–35
breast tissue	17	kidney	34
heart	9, 18	liver	31, 34–36
kidney	9, 18, 19	lung	31, 34, 35
liver	9, 13, 20–21	lymphoid organs	31, 32, 35, 37
lung	22–25	muscles	38–40
lymph nodes	13	pancreas	34, 41, 42
pancreas	18	skin	34, 36, 43
spleen	9, 10, 11, 13	spleen	36, 44
thymus	9	thymus	30, 36
thyroid	13, 26, 27	thyroid	36

Table 2. Multiple Cell Lineages in the Maternal and Fetal Bodies

Multiple Fetal Cell Lineages in the maternal body	Refs.	Multiple Maternal Cell Lineages in the offspring body	Refs.
endothelial cells	45, 46	erythrocytes	58
nucleated red blood cells	47, 48	leukocytes	59
haematopoietic progenitors	49	platelets	59
hepatocytes	13, 18	beta cells	34
insulin-producing islet β cells	50, 514	cardiomyocytes	33
leukocytes	1, 13, 53, 54–55	hepatocytes	34
mesenchymal stem cells	8, 15	renal tubular cells	34
myocardial cells	18	stem cells	32
neuronal cells	18		
pancreatic acinar cells	18		
renal tubular cells	18		
trophoblasts	56, 57		

Clinical significance and potential challenge

The potential physiological significance and pathological consequences of FMCT have attracted researchers' attention for the past two decades [55,59,63,66-68]. The existing literature suggests that fetal cells may be involved in the pathogenesis of some clinical diseases during pregnancy, such as preeclampsia, rheumatoid arthritis, systemic lupus erythematosus (SLE) and systemic sclerosis [7,13,66,67,69-74]. They may also play a role in maternal tissue repair during and after gestation [13,22,26,63,75,76]. O'Donoghue even proposed that the coexistence of fetal cells in the maternal body may be one of answers to the question of "Why is maternal life longer than paternal life?" [78].

The possible role played by fetal cells in anti-breast cancer has attracted the attention of Gadi and colleagues [79,80,81]. However, while exploring the anti-breast-cancer

hypothesis, Gadi revealed that fetal cells coexisted in normal breast tissue of parous healthy women [17]. To the best of my knowledge, this may be the first direct supporting evidence of the Fetus-Breastmilk-Breastfeeding-Infant-Cells Cycle (FBBIC Cycle) theory [82].

Another reason for studying FMCT is its potential value in prenatal genetic diagnosis [4,8,78]. However, interpreting the results of prenatal genetic diagnosis properly is a challenge, given the possibility of FFCT and FMCT from silent aborted pregnancies or older siblings. Sato and colleagues showed that after abortion, the level of fetal cells in maternal blood circulation quickly declines to an undetectable level within one month [83].

II. Migration of Gestation-Associated Maternal Cells into the Fetal Body (MFCT)

Gestational maternal immunity transmission to the fetus was described as early as in 1892 by Paul Erlich using experimental mouse models [59,84]. Although the distinction between humoral and cellular immunities wasn't established until the emergence of modern immunology during the second half of the 20th century, some researchers believed that in Paul Erlich's mouse models, the transmission of maternal cell-mediated cellular immunity to the fetus should be included [59,84]. Maloney and colleagues further showed that maternal cells persisted in the body of healthy offspring for up to 49 years [59,85], which has therefore been recognized as a physiological phenomenon [59]. Studies on humans and some non-human mammals have shown that maternal cells are found in multiple tissues and organs of fetal, neonatal and adult offspring (see Table 1). Many maternal cell lineages that have been found in offspring tissues and organs include erythrocytes, leukocytes (granulocytes, T and B lymphocytes) and platelets (see Table 2).

Clinical significance

The initial impression of maternal cells in the body of offspring was associated with their pathological role [59,86,87]. Microchimeric maternal cells in offspring may be involved in the pathogenesis of some pediatric diseases, such as neonatal lupus syndrome [34,68,73], juvenile dermatomyositis [68,88], and type 1 diabetes [41]. In addition, the migration of maternal cells into the fetal body was considered a prenatal mechanism for the vertical transfer of viral pathogens [89,90].

Maternal-donor related renal transplant

As early as in the 1950s, animal experiments and clinical studies showed that maternal eukaryotic cells within the fetal body may be involved in tolerance genesis [91]. The tolerance to noninherited maternal antigens (NIMAs) through exposure to maternal cells in the fetal body was proposed as one of tolerogenic mechanisms [89,92,93]. However, in mammals including humans, exposure to NIMAs may occur during gestation and/or

lactation through the following routes: (i) molecular exchange between mother and fetus, and/or between lactating mother and her suckling infant, and (ii) the migration of maternal cells into the fetal body, and/or the migration of maternal cells into the body of her suckling infant, which depends on whether the infant is being breastfed by his/her own mother. Therefore, at the cellular level, tolerance to NIMAs may occur as early as during gestation through MFCT. Postnatal MICT may play a role in strengthening tolerance to NIMAs. More discussion can be found in the following MICT section.

III. Gestation-Associated Fetal Cell Transmission between Different Fetuses (FFCT)

In the gestational fetus-to-fetus fetal cell transmission (FFCT) model, "fetuses" are different individuals, and fetal cells from one fetus can co-exist within the fetal body/bodies of the other/others. FFCT could occur theoretically in the following pregnant circumstances: (i) multiple pregnancies including twin pregnancy [94-98], in which, more than one fetus usually grows and develops simultaneously within one uterus; (ii) silent or identified abortion, in which, the residual fetal cells in the maternal body from previously early aborted embryo enter the body of another fetus in the next pregnancy [99,100]; and (iii) remaining fetal cells in the maternal body from previously born brothers and/or sisters migrate into the fetal body of younger brothers and/or sisters [101,102].

It is worth pointing out FFCT in the existing literature of animal studies on microchimerism has often been overlooked. In fact, many non-human mammal models used in experimental studies are multiple pregnancy animals, such as mice, rats, and pigs [103,104]; therefore, theoretically, there should be a fetus-to-fetus cell transmission or exchange during their normal gestation, which was supported by the latest laboratory evidence from studies on porcine littermates [103,104].

In humans, despite normal fetus-to-fetus microchimerism in plural pregnancies [94,98], there may be FFCT in the extant pregnancy of multiparous women who previously experienced a silent or identified pregnancy. Nelson's group revealed an interesting phenomenon in which male DNA or cells were often detected in healthy women who had never given birth to a son [99,100], for which FFCT was discussed as one of the possible explanations by the authors [99].

Clinical significance

The inherited paternal antigens (IPAs) of one fetus in previous/or extant pregnancy may be noninherited paternal antigens (NIPA) to the other fetus of next/or extant pregnancy. The clinical significance of FFCT is elucidated in a noninherited-paternal-antigens-centric model for understanding transplantation immunology (see the article titled "A Noninherited-Paternal-Antigens-Centric Model for Understanding the Birth Order and Sibship Size Effect in Transplantation Immunology" in this issue).

Offspring may contact NIPA via prenatal FFCT and postnatal FICT at the cellular level. Roelen and colleagues showed that no differences in the frequencies of cytotoxic T cell precursors (CTLp) and IL-2-producing helper T cell precursors (HTLp) against the

noninherited maternal and the paternal HLA-A and -B antigens, and moreover, similar frequencies of CTLp and HTLp were observed between breastfed and non-breastfed children [105], which suggested the efficiency of gestational exposure to NIPA via prenatal FFCT may be superior to that of lactational exposure to NIPA via breastmilk and breastfeeding-mediated FICT. Perhaps, the significance of exposure to NIPA via postnatal FICT is strengthening NIPA-tolerogenesis.

IV. Migration of Breastmilk and Breastfeeding-Mediated Maternal Cells into the Infantile Body (MICT)

The migration of maternal cells into the body of suckling infant through breastmilk and breastfeeding, resulting in maternal-infantile microchimerism (MIMC), has been supported by many laboratory studies on non-human mammals such as murine [30,84,106,107,108,109], lambs [107], and piglets [110,111]. Traditionally, it was generally accepted that milk cells were made up of various end-differentiated maternal cell lineages such as mononuclear phagocytes, polymorphonuclear leukocytes, lymphocytes, colostral corpuscles, and ductal/luminal epithelial cells. This idea was reflected in almost all studies on milk cells [30,109,107,112,113,114,115,116]. Recently, various stem/progenitor cells in human and non-human mammal breastmilk were also thought to come from maternal mammary stem cells [117,118,119], which was supported by the fact that similar stem/progenitor cell properties were described in human breast epithelial cell lines [120,121,122,123]. Therefore, previous studies on the cell transmission to offspring through breastfeeding, did not further investigate the origins of milk cells, and relevant laboratory techniques for distinguishing milk cells from different individuals have not yet been developed. However, in the recently proposed FBBIC Cycle theory, milk cells are hypothesized to be heterogeneous and derived from both maternal and fetal sources [82]. According to this new understanding, the co-existence of partial milk cells within the body of a suckling infant may be the result of MICT, FICT and FBBIC Cycle.

Clinical significance

In the 1980s, some researchers found that breastfed patients who were the recipients of maternal-donor related renal transplant had better graft function rates than their non-breastfed counterparts, [124,125] in which the tolerance to noninherited maternal antigens (NIMAs) through the exposure to maternal cells via prenatal MFCT and postnatal MICT via breastfeeding was believed to be one of tolerogenic mechanisms. [89,92,126]

However, compared to MFCT, the real significance of MICT in the genesis of tolerance to NIMAs needs further evaluation. Breastfeeding-mediated postnatal MICT may play a role in strengthening the tolerance to NIMAs, similar to the strengthening provided by immunization to a vaccine.

V. Migration of Breastmilk and Breastfeeding-Mediated Fetal Cells into the Infantile Body (FICT)

Inter-sibling or allogeneic fetal cell transmission is defined as the migration of a small amount of foreign fetal cells into the tissues or circulation of infants during lactation via breastfeeding, in which the "fetus" that the fetal cells are derived from and the "infant" who harbors the fetal cells are not the same individual and the fetal cells are not from the maternal host source.

It is easy to understand that the following three conditions are most likely to allow FICT to occur in a suckling infant: (i) the infant is breastfed by an allogeneic lactating mother; (ii) the infant is fed with donor breast milk from a Human Milk Bank; and (iii) the infant is breastfed by his or her own multiparous mother. In the first two conditions, the fetal cells obtained by the breastfed infant are allogeneic. In the third condition, the fetal cells left in the breast milk are derived from his or her siblings in previous pregnancies or abortions.

Theoretically, FIMC and the FBBIC Cycle may even occur simultaneously in infants who are breastfed by their own multiparous mothers. In other words, when breastfed by his or her own multiparous mother, a suckling baby may regain following two kinds of fetal cells: one is his or her own fetal cells defined under the FBBIC Cycle, and the other is fetal cells left by his or her siblings in previous pregnancies. The possibility that FICT of some embryonic/fetal stem cells derived from maternal siblings and grandmothers cannot be ruled out.

Embryonic stem cells are cells that come from an organism at its earliest stages of development [127] and can infinitely renew themselves and transform into multicellular lineages in the bodies of macroorganisms, such as humans and non-human mammals [22,127].

Therefore, embryonic/fetal cells, including stem cells, in breast milk may theoretically come from the following possible sources: (i) the embryo/fetus of the extant pregnancy, (ii) embryonic/fetal siblings in an extant multiple pregnancy, (iii) the embryo/fetus of previously aborted or successful pregnancies, (iv) the embryo/fetus of maternal siblings, (v) mother herself, and (vi) grandmother.

To the best of my knowledge, it is the first time that the theoretical possibility of FICT (inter-sibling or allogeneic fetal cells transmission) has been proposed. FICT involves the migration of a small amount of foreign fetal cells into the tissues or circulation of infants during lactation via breastfeeding, in which the "fetus" that the fetal cells are derived from and the "infant" who harbors the fetal cells are not the same individual. In addition, the fetal cells are not from the maternal host source. FICT is most likely to occur in infants who are breastfed by an allogeneic lactating mother, fed with donor breastmilk from a human milk bank, or breastfed by their own multiparous mother. Theoretically, FICT and FBBIC (fetal-maternal microchimerism by breastfeeding-induced cell cycle) may even occur simultaneously in infants who are breastfed by their own multiparous mothers. FICT may play a role in the tolerogenic mechanisms of

transplantation immunology, as discussed in the article entitled "A noninherited-paternal-antigens-centric model for the birth order and sibship size effect in transplantation immunology" in this issue.

VI. Fetus-to-Infant His/Her Own Cells Transmission Cycle or Fetus-Breastmilk-Breastfeeding-Infant-Cells Cycle (FBBIC Cycle)

Recently, a model called *Fetus-Breastmilk-Breastfeeding-Infant-Cells Cycle* (FBBIC Cycle) was proposed to reveal an unrecognized mechanism [82], in which, "fetus" and "infant" are the same individual and the absorbed fetal cells from breastmilk were derived from the suckling infant's own host cells. Therefore, the FBBIC Cycle reflects the fetus-to-infant his/her own cell external transmission via breastmilk and breastfeeding.

If an infant has never been breastfed by his or her own mothers' breastmilk, his or her FBBIC Cycle may be missed [82]. In fact, among the six different eukaryotic cell transmissions, only the FBBIC Cycle can account for why the following three physiological events are naturally connected: (i) embryonic/fetal growth and development, (ii) production of breastmilk and (iii) breastfeeding offspring.

Pregnancy-Associated Maternal Immune Protection Blank (MIPB)

In humans, the gestational course from a fertilized egg to a matured fetus normally takes 37-40 weeks. In clinical medicine, pregnancies of less than 37 weeks or longer than 42 weeks are usually considered a pathological condition. During gestation, the maternal body is constantly exposed to novel external foreign antigens, including those in foods and air. It is well known that the establishment of immune to a specific antigenic stimulation usually needs 4 weeks.

During gestation, newly formed maternal immunity cannot be transferred to her offspring in the extant pregnancy through DNA inheritance. However, such newly acquired maternal immune protection can be transferred to her offspring mainly through trans-placental IgG and possibly gestational MFCT. Therefore, the gestational period represents a relative maternal immune protection blank (MIPB) for novel external foreign antigens for the offspring, during which, there is a 4-week absolute MIPB for gestational offspring.

How does offspring overcome this deficiency? FBBIC Cycle may be one of mechanisms for answering this question. During gestation, fetal cells migrate into the maternal blood circulation and other tissues/organs, where they have an opportunity to encounter the novel foreign antigens that the pregnant maternal body is exposed to.
Normal pregnancy has been shown to be a systemic Th2 characterized immune response in the maternal body since 1993 [128].

Moreover, studies on human breastmilk have already shown that there is certain amount of microorganisms in normal breastmilk, including bacterial [129-132], fungal [146], and viral species [133-138], and therefore, any exposure to novel bacterial, viral,

and fungal agents or other foreign antigens during gestation may affect both maternal immune cells and those microchimeric fetal cells. Because some fetal cells are embryonic stem cells, and have the ability to differentiate into various cell lineages, including immune cells (such as T memory cells, for example). If these fetal cells return to the body of the suckling infant via breastfeeding, it is certain that the acquired cellular immunity during gestation in the maternal body will be transferred to postnatal suckling neonates.

It already has been proposed that fetal cell-derived maternal alloantigens-tolerogenic fetal T regulatory cells (MATF-TRCs) [35,37] and paternal alloantigens-tolerogenic fetal T regulatory cells (PATF-TRCs) [82] may be involved in suppressing postnatal antimaternal or antipaternal immune reaction to a maternal or paternal graft [82].

Concluding Remarks

Eukaryotic cell transmission among fetuses, mothers, and infants during pregnancy is a complex process that covers both gestation and lactation. To date, six pregnancy-associated cell transmission models have been proposed, of which the FBBIC Cycle is the only model that can provide the most benefits to offspring's prenatal and postnatal life in physiology and immunology, and explain the necessity and continuity of gestation to lactation in pregnancy [82]. Prenatal FFCT and postnatal FICT may involve in the paternal alloantigens-tolerogenic mechanism of offspring. A thorough theoretical exploration of the relationship between fetuses, infants, mothers, and fathers is a current major concern in fimpology, which will undoubtedly contribute to the interpretation of prenatal genetic diagnosis, the development of molecular diagnostic techniques, and the clarification of tolerogenic mechanisms in transplantation immunology.

Abbreviations:

FMCT: the gestation-associated fetus-to-maternal cell transmission;
MFCT: the gestation-associated maternal-to-fetal cell transmission;
FFCT: the gestation-associated fetus-to-fetus cell transmission;
MICT: the breastmilk and breastfeeding-mediated maternal-to-infant cell transmission;
FICT: the breastmilk and breastfeeding-mediated fetus-to-infant allogenic or semi-allogenic cell transmission;
FBBIC Cycle: the fetus-to-infant his/her own fetal cell external transmission via breastfeeding.
FMMC: fetal-maternal microchimerism;
MFMC: maternal-to-fetal microchimerism;
FFMC: fetofetal microchimerism;
MIMC: maternal-infantile microchimerism;
FIMC: fetoinfantile microchimerism;
NIPAs: noninherited paternal antigens;
NIMAs: noninherited maternal antigens;

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