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MICROCHIMERISM – AN OVERVIEW

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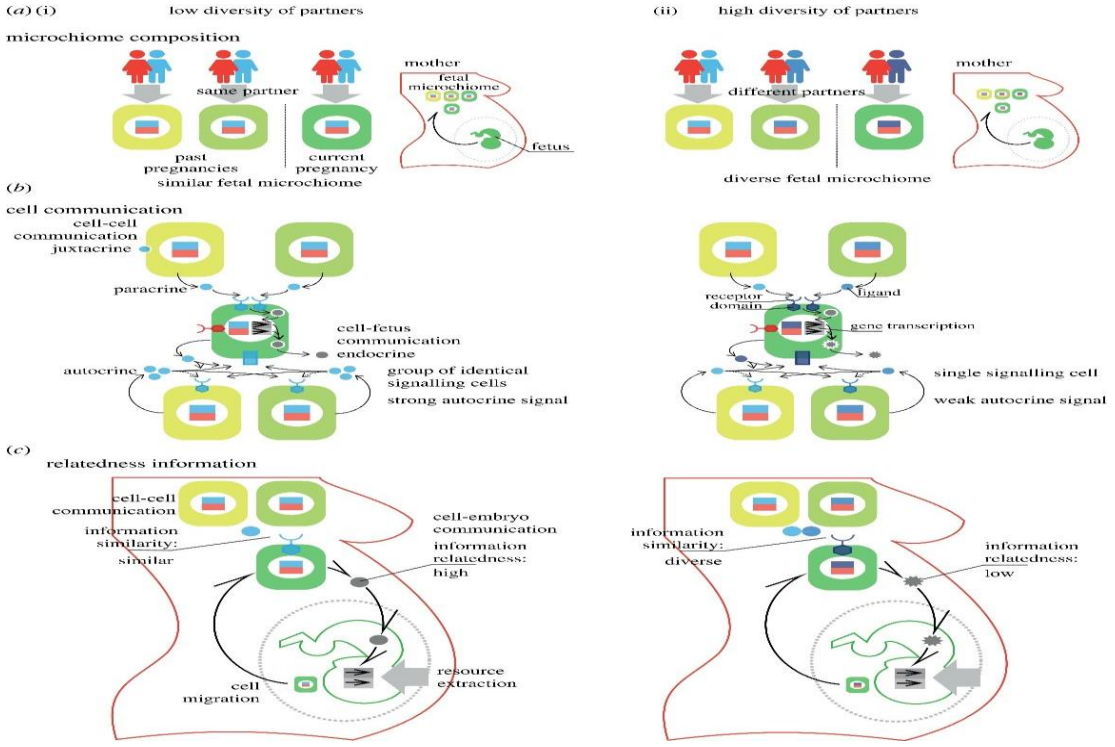
Abstract : Chimerism is the presence of more than one genetically distinct population of cells in a single organism that originated from more than one zygote and microchimerism occurs when the non-host cells represent only yug<5% of the cells of an individual and can be a consequence of pregnancy, organ transplantation, and transfusion. Most of the microchimerism was observed during pregnancy. Microchimerism can be divided into two types: the cells that are transferred from the fetus to the mother, called fetal microchimerism cells (FMC), and the cells that are transferred from the mother to the fetus, called maternal microchimerism cells. Both cells can remain in the blood and tissues for decades or even their whole life. In humans, FMC is the most common form of microchimerism. In this mini-review, we are going to discuss in detail microchimerism and pregnancy.

KEYWORDS: Feto-maternal microchimerism, pregnancy,semiallogenic,bone marrow transplants

1.INTRODUCTION

Microchimerism is the persistence of nonhost cells in a vulnerable host organism. Animal studies of EAE have shown that bone marrow transplants from resistant rats to susceptible affected rats can induce remission in affected animals.[1]Feto-maternal microchimerism (FMM) involves bidirectional cross-placental trafficking during pregnancy, leading to a micro-chimeric state that can persist for decades. During pregnancy, the pregnant woman exhibits a complex micro-chimeric phenotype, hosting cells from her current fetus, cells from previous pregnancies as well as cells from her mother.[2]Microchimerism in a pregnant woman not only involves cells from the current fetus but also that of any previous pregnancies as well as trafficking maternal cells the proband inherited from her mother.



FETAL LOSS:

The presence of fetal cells in the maternal circulation during and after pregnancy has been acknowledged for many years. Most, if not all, pregnant women have fetal cells in their circulation. Microchimeric fetal cells are semiallogenic to the maternal immune system, and women who have had an HLA-compatible fetus may have more persistent microchimeric cells than if the fetus was not compatible. To this hypothesis, microchimeric cells were cleared more rapidly in an animal model if they were from an allogenic, rather than a syngenic, fetus.[4] In the case of humans, however, Evans et al were unable to demonstrate the importance of compatibility between mother and fetus in the development of microchimerism. However, without considering the compatibility between mother and fetus, Lambert et al demonstrated that some HLA haplotypes, such as HLA–DQA10501, are more strongly associated with fetal cell microchimerism. this study is based on the hypothesis that persistent, semiallogenic fetal cells trigger a maternal immune reaction resulting in what appears to be an autoimmune disorder.[5] However, since microchimeric cells were found in tissues from patients with non-autoimmune diseases, it is possible that these cells participate in response to tissue injury, or that they are unrelated to the disease process and are therefore a consequence rather than a cause of the disease. that the fetal cells originated from a fetus electively terminated 20 years earlier.[6] In addition, terminations of pregnancy result in large fetomaternal transfusions, which suggests that factors that increase fetomaternal cell trafficking may also influence the persistence of microchimeric cells.

BREASTFEEDING -RELATED MATERNAL MICROCHIMERISM

In addition to pregnancy-related MMc, compelling evidence points to the existence of a postnatal MMc present in the infant, which is related to breastfeeding. Experiments in rodents and non-human primates, and limited human-based observations, support the idea that cells from breast milk may traffic from the mother to the infant's tissues through the gut mucosae. This phenomenon is likely to occur mainly during the early stages of lactation when breast milk cells are abundant and the infant's gut permeability is highest.[7] The precise nature of the maternal cells present in breast milk that are involved in microchimerism is presently unknown but may include stem cells and progenitor cells as well as mature immune cells. Colostrum (the form of milk produced in the first days of lactation) contains high numbers of maternal cells of various types including epithelial cells, T and B lymphocytes, natural killer (NK) cells, dendritic cells, macrophages, and others. In the weeks after birth, the immune cell concentration of breast milk decreases rapidly. Breast milk lymphocytes consist mainly of an extra-lymphoid memory cell population.[8]

Most CD4+ and CD8+ T cells are effector memory cells. Up to 6% of breast milk cells are progenitor or stem cells of hemopoietic, mesenchymal, and neuroepithelial lineages.[9] Some of these cells express markers that suggest a mesenchymal stem cell phenotype (CD90, CD44, CD271 and CD146), some express markers of embryonic stem cells (TRA-1-60, octamer-binding protein 4 (OCT4), NANOG and SOX2) and some express markers of luminal mammary epithelial cells (cytokeratin 18).[10]Given their potential, breast milk stem cells are good candidates for long-term MMc in the infant intestinal tissues. Indeed, it is likely that infants may become tolerant to stem cells of maternal origin as these cells do not express MHC antigens.[11]

A recent study from the group of Sing Sing Way established the cross-generational reproductive benefit conferred by maternal microchimerism, which involved the persistence of non-inherited maternal antigen-specific regulatory T cells of fetal origin in the genital tract of female offspring. [12 In] This study, there was a direct quantitative relationship between MMc and cross-generational reproductive fitness. We can therefore hypothesize that, if tolerance and reproductive fitness (and potentially other consequences such as tissue healing and immune modulation) are quantitative functions of pregnancy-related MMc, breastfeeding-related MMc may increase these beneficial functions in the child in an additive or synergistic fashion.

The transfer of viable maternal immune and stem cells from breast milk to an infant may contribute to optimizing neonatal and infant immune system maturation, tissue repair, and immune tolerance and thereby complement pregnancy-related MMc

MICROCHIMERISM IN OTHER HUMAN DISEASES:

Microchimerism has also been associated with nonautoimmune human diseases. Examples are polymorphic eruptions of pregnancy (PEP), pre-eclampsia, infectious hepatitis, non-autoimmune thyroid disorders, blood cancers, and cervical cancer. PEP is a cutaneous eruption that occurs during the third trimester of pregnancy and disappears after pregnancy. In one study, male DNA was detected in the skin lesions of the women with PEP who were carrying male fetuses and not in women without PEP. These findings suggested that fetal cells migrate to the skin during gestation and might be involved in cutaneous disorders of pregnancy. Pre-eclampsia is another human pregnancy-related disorder of unknown etiology and is one of the leading causes of maternal and fetal mortality and morbidity in the developed world. In several recent studies, fetal cells and cell-free fetal DNA from pregnant women with pre-eclampsia have been investigated (reviewed in Ref.).[13] It had been shown that a substantial proportion of erythroblast cells present in the blood of women with pre-eclampsia were of fetal origin and that a significant increase in cross-placental traffic of fetal cells occurred in women with pre-eclampsia compared to controls. In addition to the disturbed cellular transfer, an increase in cell-free fetal DNA levels in pregnancies complicated by pre-eclampsia was also reported. Fetal cells were also detected in a woman with infective hepatitis and a woman with multinodular goiter.[14] In both cases, there was no history of blood transfusion or organ transplantation and they did not have twin siblings suggesting fetal origin of the microchimeric cells. Transfers of maternal malignant cells to offspring have been reported in cancers. Similarly, a recent report documented the presence of male cells in the cervical tissues of women with cervical cancer, which is the third most common

type of cancer in women.[15] The source of the male cells was not confirmed which raises the possibility that sexual partners may also transfer cells that can become incorporated into host tissues under certain circumstances.

PCR-BASED MICROCHIMERISM DETECTION METHODOLOGY:

ARTIFICIAL MIXED MICROCHIMERISM SYNTHESIS:

To allow the determination of efficiency, sensitivity, and specificity, we used different sources of control DNA receiving either a donor or a recipient label. Mixed chimeras were prepared by mixing 10-fold serial dilutions of donor-labeled DNA that ranged from 500 ng to 0.5 pg in a constant amount of recipient-labeled DNA of 200 to 500 ng. Patients. To assure the validity of all the techniques used, 20 healthy control subjects were enrolled to create a battery of artificially controlled microchimeras. Also, to validate results in a clinical setting, 119 transplanted recipients (single kidney [n ¼ 84], heart [n ¼ 27], or liver [n ¼ 8]) were included for longitudinal microchimerism detection at 0, 2 (M2), 6 (M6), 12 (M12), and 18 (M18) months, forming the prospective cohort. The time 0 analysis corresponded to blood extraction before transplantation to examine the presence of pre-transplant microchimerism (from any source) and to allow comparison with M2 to M18 analysis. Also, 33 transplanted recipients (single kidney [n⅛5], double kidney [n ¼ 10], or liver [n ¼ 8]) were included for only one single transversal microchimerism determination, forming the retrospective cohort. All recipients received cadaver donor organs and were transplanted at the Hospital Universitari de Bellvitge (Barcelona, Spain) between March 2001 and January 2006.[16]

BLOOD SAMPLES AND DNA EXTRACTION FOR MICROCHIMERISM STUDY:

Peripheral blood samples were collected in K3EDTA and analyzed in three different fractions: whole peripheral blood (PB), mononuclear cells (MNC), and granulocytic cells (GC). The separation of these last two fractions allowed an increase in donor-cell detection sensitivity. All MNC and GC fractions were isolated by Ficoll–Hypaque (lymphocyte isolation solution; Beckman Coulter, Germany) gradient density separation. Genomic DNA was extracted from each fraction using the QIAamp Blood Kit (Qiagen, Hilden, Germany), following the manufacturer's recommendations. Theoretical Number of PCR Replicates: Not all PCR replicates were found to be positive for positive control DNA at extreme dilutions, thus revealing the initial rate of PCR success for this extreme dilution. We found that specific detection of this DNA was statistically measurable by the probability of a positive PCR event in all PCR performed for the same positive control sample. To determine the number of PCR replicates that would be needed to find at least one single positive PCR event using a positive control sample, the binomial distribution probability test was applied. This statistical test was used to determine the theoretical number of PCR replicates to be achieved (with an acceptable statistical probability of detection) for a specific initial rate of PCR success on a potential positive sample.[17]

Short Tandem Repeat (STR) Analysis:

A panel of six Cy5-labeled STR markers (TPOX, HUMH01, CSFP01, LPL, FVW, and F13A) was used for microchimerism detection. A previous informative marker screening step was required for each donor-recipient pair using multiplexed PCR for TPOX-HUMTH01-CSFP01 and also for LPL- FVW-F13A. PCR was carried out in a PTC-100 thermocycler (MJ Research, Inc., Reno, NV). PCR products were run in a 6% denaturing polyacrylamide gel usinAlfExpress II (Amersham Pharmacia, Uppsala, Sweden) automated DNA sequencer and analyzed with AlfWin Fragment Analyzer software (Amersham Pharmacia).[18]

Variable Number of Tandem Repeat (VNTR) Analysis:

A panel of six Cy5-labeled VNTR markers was also used for microchimerism detection with a previous informative screening step, but for this analysis, multiplexed PCR reaction could not be achieved because of loss of efficiency. PCR products were run in a 12% nondenaturing polyacrylamide gel using the same automated DNA sequencer described above.[19]

Human Leukocyte Antigen (HLA) Class I and Class ll Polymorphism Analysis:

HLA-A and -B typing and donor detection were performed by reference strand conformation analysis (RSCA). Class II typing for HLA-DRB1 and microchimerism-specific detection were both performed using Olerup primers by sequence-specific primer (SSP)-PCR. All HLA disparities were graded from 0 to 6 (out of 6), showing full match to full mismatch, respectively. Like VNTR analysis, all Cy5-labeled PCR products resulting from the HLA study were analyzed in AlfExpress II automated sequencer. For real-time HLA-DRB1 SSP-quantitative PCR (Q-PCR), the same primers were adopted (without Cy5-added modification). All Q-PCR was performed in a LightCycler v2.0 (Roche, Germany) real-time thermocycler, and results were analyzed with the LC Software v4.0 (Roche Germany), allowing the use of nonlinear inflection-reproducible standard curve points at extreme dilution points.[20]

SEX MISMATCH ANALYSIS:

SRY male-specific primers were used for microchimerism determination in a transplanted female receiving an organ from a male. To ensure the absence of previous microchimerism interference, an initial pre-transplant analysis step of women was required. Gender-specific PCR amplification and analysis were carried out by real-time PCR.

CONCLUSION

While feto-maternal exchange in pregnancy was previously viewed as a rare and innocuous event, a vast body of work in the interim has shown that it is a common feature of mammalian pregnancy being readily discernible from mouse to man. The effects of this exchange are far-reaching and can persist into adulthood and possibly even old age. In this review we have highlighted the potential anomaly regarding FMM occurring in pre-eclampsia and how this could contribute to the etiology of this enigmatic disorder, but also to the development of autoimmune diseases years post-partum. Should an imbalance between trafficking maternal cells and newly acquired fetal microchimerism prove to be a pivotal trigger driving these developments, then it is highly likely that an altering of the microchimeric milieu could be used to modulate or steer the maternal immune system away from this destructive direction. Evidence that such a mechanism may be viable is provided by reports indicating that the incidence of pre-eclampsia is reduced in women who have received blood transfusions, an event known to lead to a microchimeric state.

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