Review Article

A Survey on the Role of Fetal Microchimerism in the Maternal Body

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Abstract

Microchimerism is explained as the simultaneous presence of a few foreign cells with different genetic origins of different individuals in a person. Transfer of these cells through blood transfusion, organ transplantation and particularly the mutual transfer of cells between the mother and fetus during pregnancy is possible. This article is an overview of the role of fetal cell microchimerism in maternal health and disease, especially autoimmune disorders and cancer. The original and related articles were found by search in PubMed, Scopus, Springer, Sciencedirect with an emphasis on literature published in the period 2000 to 2015. It was concluded that microchimeric cell can play different roles in maternal body, including natural microchimerism (bearing no biological role), utility (damaged tissue repair), and pathogenesis (causing autoimmune disease and cancer). Further studies and more in-depth knowledge about these cells may help explaining their new roles and using them in treatment or determining the prognosis of various diseases.

Keywords: Fetal microchimerism, Autoimmune diseases, Cancer.

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Introduction

Microchimerism is explained as the simultaneous presence of few foreign cells with different genetic origins of different individuals in a person. Transfer of these cells through blood transfusion, organ transplantation and particularly the mutual transfer of cells between the mother and fetus during pregnancy is possible. The initial appearance of fetal cells in the maternal blood occurs from 7-16 weeks up to 24 gestational weeks, where at the time of birth it increases and reaches the maximum value(1). In the maternal body, fetal cells can be present for up to 27 years after delivery, and the mother's cells will remain over 49 years in the child's body (2-4).

This article is an overview of the role of fetal cells microchimerism in maternal health and diseases, especially autoimmune and cancer. Most of the data have been collected from the available evidence found through search in PubMed, Scopus, Springer, Sciencedirect and some other databases with an emphasis on literature published in the period 2000 to 2015.

History of fetal microchimerism finding

For the first time, in the early 1970s fetal microchimerism was identified in the mother's peripheral blood and lymphocytes cultured as a natural event in pregnant women (5-7). The pathogenicity theory of these cells was first proposed by Nelson in 1996. He noted that transfer of the fetal cells to the maternal body following pregnancy may lead to maternal immune response to these foreign cells and brings about some reactions like graft-versus-host disease and autoimmune reaction (8). Based on the ability of these cells to differentiate into multiple cell lineages or very early stem cells progenitor, they have been

known as pregnancy-associated progenitor cells (PAPC) (9). The data retrieved from available research articles about these cells though 2000-2015, are outlined in Table 1.

Fetal cells microchimerism detection methods

Identification and study of fetal cells microchimerism are based on searching male cells and Y chromosome sequences in the maternal circulation. This detection is possible with amplification of SRY gene (sex-determining region Y) on the Y chromosome by using PCR method. This method is sensitive to detecting even one male cell per million female cells while it does not yield phenotypic information (10).

Special probes for chromosomes X and Y are used in another method named FISH method (fluorescent in situ hybridization). In this method, specific probes for chromosome X, (BAC probe pDMX1, locus DXZ1) bind to the digoxigenin and specific probes for chromosome Y (band region Yp11.1- q11.1, locus DYZ3) connect to Spectrum Orange fluorochrome (Vysis).

Immuno-FISH method (combining the two, FISH and immunohistochemistry methods) is another method which identifies these cells (11). To make sure about the results obtained from such methods, real time-PCR method has been used (12). In addition, fetal male and female offspring can be used for human leukocyte antigen (HLA) typing and identifying specific HLA in mother's polymorphisms (13).

How fetal microchimerism can be transferred to maternal body?

Early during pregnancy, the maternal lung tissue is the first choice for the traffic and implantation of embryonic cells. These cells path from the uterine veins to maternal large lower venous and pulmonary capillary bed which is around the small site and is receptive to these cells in the maternal lung (14-16). Interestingly, studies on the mice model have indicated that before the formation of the placenta, embryonic stem cells with the ability to differentiate into several cells, migrate to the maternal organs (17). After these transfections, they are implanted in mother's stem cell niches such as bone marrow and can be present and survive in reservoirs for several years (9, 18-20). Based on the result in mice model of chemical damage induction, following the tissue damage they migrate, differentiate and play an important role in the mother's body response to tissue repair (21, 22).

Changes in the maternal immune system function during Pregnancy

Maternal immune tolerance to the fetus plays a decisive role in successful pregnancy outcome. Also, trophoblastic cells express fas ligand and eliminate maternal T cell clones that react with fetal antigens. With cytokines and indole amine 2, 3-dioxygenase secretion, they cause tryptophan metabolism in the mother's body and around the fetus. As good sex-steroid modulators and HLA-G, they inhibit natural-killer cells which are involved in cellular immunity, and modulate the maternal immune system during pregnancy (23). In addition, induction of T-regulatory cells and inhibition of Th1 and activation of Th2 in the mother's body, cause immune tolerance in the maternal immune system cells toward the fetus or her/his cells body and sustains the fetus for a successful pregnancy (24). In fact, the maternal immune system utilizes the following two mechanisms not to respond against these foreign cells. The first mechanism of immune tolerance has been described through maturation of these cells in the mother's thymus, where they encounter the mother's antigens (25). Second, the maternal native antigens after entering the fetus's body can induce differentiation of embryonic cells to T-regulatory elements. Following the migration to the mother's body, these cells may be influenced by the maternal immune system (26).

Fetal cells' microchimerism function in the maternal body

- *Autoimmune diseases*

Review of the related studies showed that embryonic stem cells in the maternal body are a mixture of paternal and maternal genes and the paternal genes are present in the mother's body as allo-antigens; thus, antibodies tend to act against them (27). In several studies, the incidence of these antibodies in autoimmune diseases (28-30), such as scleroderma (12), Rheumatoid arthritis (31-33), Lupus (34-36), Sjogren's syndrome (37, 38), Thyroiditis (39-43), Multiple and systemic sclerosis (44) have been investigated as compared to healthy individuals. Since most autoimmune diseases occur in reproductive age women, etiological hypothesis of embryonic microchimerism in these diseases has attracted much attention (45, 46).

Results of extensive studies on the role of fetal microchimerism in autoimmune thyroid disorders demonstrated that manifestation of thyroid autoimmune diseases in pregnant patients is moderated and during pregnancy they remit, whereas the condition is worsened after delivery and child birth (47). The hypothesis that fetal cells

may contribute to the pathogenesis of maternal thyroid autoimmune disease was highlighted through finding many of such cells in the mother's thyroid gland in cases with Hashimoto's thyroiditis and Graves' disease as compared to healthy women (23, 48, 49). Sometimes, the fetal immune precursor cells can be present in various organs and after proliferation, differentiation and activation, with production of cytokine and chemokine, they tend to play their part in the onset of autoimmune diseases and intensify the immune response (30, 50).

Also, maternal allo-reactive T-cells do not inhibit them and autoimmune diseases can be induced through the presence of these cells in mother's body (51). Evidence shows that maternal thyroid gland is an important organ for implantation of fetal cells and their constant presence for many years. The cells which are stranger to the maternal immune system may be activated and increase the incidence of numerous problems in the postpartum period, such as Graves' disease after delivery and absence of inhibitory fetal immune system (52). However, data of some studies have not shown a significant difference between the incidence of fetal microchimerism in autoimmune patient and healthy individuals and the data appear to be mixed and controversial (53-60).

- *Cancer*

The fetal microchimeric cells which are located around or within the tumor and characterized by the endothelial cell marker (CD31) expression, can be present in the blood or lymph vessels and play an important role in angiogenesis and gloomy prognosis of tumors (61). The role of fetal microchimerism in development of cancer was considered, according to reproduction ability which is similar to stem cells and manufactures diverse cells. Therefore, several studies about the relationship between such cells and non-autoimmune diseases such as hepatitis C (62), solid tumors (63), cervical cancer (64), breast cancer (65-67), and the papillary thyroid carcinoma have been performed (68, 69). Based on the Immuno-FISH analysis, most of these cells express the common leukocyte antigen (CD45). Therefore, their presence in the cervical area could change the maternal immune system and make the woman prone to infection and cancers (70).

- *Tissue repair and protective role*

Results of the related studies suggest that fetal microchimeric cells are not only like carcinogens, but can also be involved in the response to carcinogens; with ability to differentiate to mature cells, they can repair the damaged tissues(70). Furthermore, studies on breast cancer patients and healthy subjects have shown that the circulation of these cells in patients is significantly lower than healthy individuals. This suggests that they could have a positive protective role and inhibit breast cancer in the mother's body (65, 71).

The hypothesis of protective role for these cells in lung cancer has been tested (72). In 2003, Whiteman *et al* suggested that the risk of epithelial ovarian cancer in older ages may be reduced (73). Data from a case-control study on tumor tissues and peripheral blood using a very sensitive method to find even a single male cell in 106 mother's cells showed the abundance of these cells among the circulating mononuclear cells of the women with papillary thyroid cancer who had been in the last delivery of male infants, as compared to healthy women. Suggesting their possible protective role against the development of thyroid neoplasms (74).

Characterizing fetal microchimerism

These cells may be found in normal and tumor thyroid tissues and express thyroglobulin or can stand in maternal thyroid gland and form the follicular cells (75). Male fetal cells which are found in cervical cancer have cytokeratin markers (CD45) and are able to differentiate into hematopoietic and epithelial cell lines. Meanwhile other fetal michrocimeric cells that lack these two markers in normal tissues can act as a precursor cell and differentiate into cell types (64). In addition, CD45+ male cells which are negative for MHC-II antigens cannot play a role as antigen processing cells (APC), but function as natural-killer cells (NK cells) and start cytotoxicity reactions against cancer cells in mother's body; finally, they have a protective role in maternal thyroid cancer(76).

Also the cells that are Tg +/MHCII- are able to take role in repairing damaged tissues. Based on these results, the lack of expression of MHC-II antigens causes targeting of RET/PTC oncogene and will specifically start tumor in thyroid follicular cells (68). The male fetus cells with CD45 +/MHCII- phenotype in the maternal body as tumor-associated macrophages often have an important role in tumor progression (77). Evaluation of the fetal cells in breast cancer has shown that these cells with epithelial and mesenchymal markers expression are involved in the tumor stroma formation (78, 79).

Since these cells are capable of producing several cell lines such as mesenchymal cells (80), epithelial cells (81, 82), skeletal muscle (83), cells

with an oligodendrocyte phenotype (84), and functional T and B cells (85-87) depending on cell marker expression in different tissues, they can have a role in repairing damaged tissue (88) or contribute to the process of angiogenesis, formation and survival of the tumoral cells (89, 90).

Year	Sample origin	Problem	Gene /Test	Technique	Result	Reference	
						First author, et al	Ref .no
2000	H-Blood	SSc	SRY gene	FACS, Nested PCR, HLA typing	The first description of an association between persistent FM in maternal T lymphocytes and specific HLA class II alleles	Lambert NC	28
2000	H- Blood, Liver T	PBC, SSc	Y Ch	PCR	FM does not seem to play a major role in most cases of PBC. However, the association with anticentromere antibodies suggests a possible role in the subgroup of patients with scleroderma	Corpechot C	55
2000	H-Blood	PBC	Y Ch (SY154,SRY)	PCR	FM but also fragments of fetal DNA are present in maternal circulation. Overall, our data do not support the hypothesis that fetal microchimerism plays a significant role in the onset or progression of PBC	Invernizzi P	54
2001	H- Blood	NON	Y Ch	Real-time PCR	Fetal genetic material can be detected throughout pregnancy, and its quantity is a function of gestational age and of whether the plasma or cellular compartment is examined.	Ariga H	1
2001	H-Thyroid T	Hth	SRY gene	PCR	FM might play a role in the development of Hashimoto's disease	Klintschar M	39
2001	H-Thyroid T	Vthd	X ,Y Ch	FISH	Relation between FM and thyroid disease. FM might be capable of differentiation into mature thyroid follicles in their mothers with favorable environmental factors	Srivatsa B	48
2001	H-Blood	Sjs	SRY gene	Nested PCR	Does not exclude the possibility that FM may play a part in the pathogenesis of Sjs	Mijares-Boeckh-T	38
2001	Mice T	AIT	interleukin-4	*Cytokine assays*	Pregnancy loss was increased in experimental autoimmune thyroiditis in a manner that was dependent on paternal antigens	Imaizumi M	40
2001	H-fetalblood, liver, BM	-	MSCs phenotype	*FACS,ICC*	population of MSCs was isolated from fetal blood, liver, and bone marrow in the first-trimester of pregnancy	Campagnoli C	80
2002	H-PBMCs	SSc	Y Ch (DYS14)	Real-time PCR	Quantitative differences in the circulation of women with SSc are due to cells and not to free DNA	Lambert NC	12
2002	H-Blood, Thyroid T	AIT	SRY gene	Q PCR-ELISA	Inflamed thyroid gland was capable of accumulating fetal cells, including T cells and dendritic cells	Imaizumi M	41
2002	H-Thyroid T	Gd	SRY gene	ELISA-PCR	Intrathyroidal FM was common and profound in female patients with Gd	Ando T	23
2002	H-Blood	Sjs	SRY gene	PCR	anti-maternal GVHD may be involved in the development of Sjs	Endo Y	37
2002	H-?	SSc	SRY gene	ELISA-PCR	FM is a common event in both healthy controls and patients with connective tissue diseases, and is unlikely to represent per se a risk factor for these diseases	Gannage´ M	53
2002	H-Liver T	hepatitis C	X ,Y Ch	FISH-PCR	long-lived FM crossed the placental interface, remained in maternal circulation or elsewhere, and, ultimately, migrated to areas of the affected liver	Johnson KL	62
2003	H-Cervical T	CC	X ,Y Ch	FISH	CC might be associated with FM, possibly from fetomaternal cell trafficking	Cha D	64
2003	H-child T	trisomy 21, congenital ichthyosis	X ,Y Ch	FISH	Maternal cells enter the fetal circulation and are capable of migration to fetal and neonatal organs. This is of importance with regard to potential consequences of umbilical cord blood transplantation and postnatal development of autoimmune disease	Srivatsa B	3
2003	H-NLS heart T	NLCHB	X ,Y Ch	FISH, Immuno FISH	Differentiated tissue-specific maternal microchimerism can occur in neonates. Thus, semiallogeneic maternal cells could be the target of an immune response.	Stevens AM	11
2003	H-Blood	SLE	SRY gene	PCR	FM does not interfere with the disease course of SLE, although further analysis on larger groups will be necessary to confirm these observations.	Mosca M	34

2003	H	Ovarian C	Case-control study	OR, CI	ovarian cancer risk is reduced by pregnancy at older ages	Whiteman DC	73
2004	H-Thyroid T	Hth, Gd, NA, DFA	X ,Y Ch	FISH, HLA typing	FM is observed in thyroids of mothers with sons, and this is found more frequently in thyroid autoimmune diseases	Renne´ C	24
2004	H-BM, ribs	NON	X ,Y Ch	FISH	fetal stem cells transferred into maternal blood engraft in marrow, where they remain throughout life	O'Donoghue K	20
2004	H-Tissue sections	NON	X ,Y Ch	FISH	FM, bearing epithelial, leukocyte, or hepatocyte markers, in a variety of maternal tissue specimens suggests the presence of fetal cells that may have multilineage capacity	Khosrotehrani K	51
2004	H- Blood	SSc	HLA-SP, FP	Real-time PCR, HLA typing	MMc is not uncommon in the peripheral blood of healthy adults, is increased in frequency in patients with SSc, and may be present in bone marrow and disease-affected tissues	Pang JM	13
2004	Mice variety maternal organs	-	GFP transgene, fetal DNA	FISH	FM are engrafted to maternal hematopoietic system without apparent injury and they also contribute to the repairing process of maternal liver and kidney	Wang Y	21
2005	H-Serum	thyroid disease	TSH, TPO-Ab, Tg-Ab	ELISA	Parity is not a risk factor for thyroid autoimmunity or thyroid dysfunction. These data do not support a key pathogenic role for fetal microchimerism in chronic autoimmune thyroid disease	Walsh JP	56
2005	Mice- Blood, BrainT	-	GFP transgene, SRY gene	Real-time PCR, FISH	Identification of FM in maternal brain, FM cross both the placental and blood-brain barriers and to target injured brain may improve selection procedures for isolation of progenitor or stem cells for brain repair by intravenous infusion	Tan XW	19
2006	H-Serum	randomly selected	TPO-Ab, Tg-Ab	RIA technique (DYNO test)	No association between previous pregnancy, parity and thyroid antibodies, which argues against the role of FM as a trigger of thyroid autoimmunity. Exogenous oestrogens may reduce aspects of autoimmunity	Bu¨ low Pedersen I	57
2006	H-Thyroid T	Hth, MNG	Y Ch (DYS14)	Real-time PCR	The percentage of FM varies to a great extent in Hashimoto's thyroiditis,and this phenomenon can occur in nodular goiter in rare instances	Klintschar M	42
2006	H- fetal blood, liver, BM	-	MSCs phenotype	IHC,ICC,WB	hfMSCs readily undergo muscle differentiation in response to galectin-1 through a stepwise progression similar to that which occurs during embryonic myogenesis	Chan J	83
2006	H-skin biopsy	VLS	Y Ch	PCR, FISH	persistent male FM are not involved in the pathogenesis of lichen sclerosus of the vulva	Bauer M	58
2007	Mice - variety maternal organs	-	GFP transgene	Real-time PCR immune FISH	FM presence in liver and spleen. Furthermore, real-time PCR amplification is more sensitive than immunofluorescence for the detection of FM	Khosrotehrani K	22
2007	H-Blood	Breast C	Y Ch (DYS14)	Real-time PCR	allogeneic FM may contribute to reduction in risk of breast cancer	Gadi VK	65
2007	Mice -T	-	X ,Y Ch	Real-time PCR FISH	fetal endothelial progenitor cells are acquired by the mother and participate in maternal angiogenesis during pregnancy	Nguyen Huu S	89
2008	H-Blood	female C patients	Y Ch	PCR	Maternal tolerance might be exploited in female patients with malignant disease to deliver immune cellular therapy from their sons	Gilmore GL	70
2008	H-lung/ thymus T	lung c	SRY gene	Nested PCR	FM were identified in pathological post-reproductive tissues, where they were more likely to be located in diseased tissues at several-fold higher frequency than normal tissues. FM are present at sites of tissue injury and may be stem cells, either recruited from marrow or having proliferated locally	O'Donoghue K	72
2008	H-serum	AIT	anti-TPO, thyrotropin	RIA technique	Association between parity and AIT and conclude that parity appears to be a potential risk factor for AIT	Friedrich N	43
2008	murine Breast T	Breast C murine model	X ,Y Ch	FISH	FM expressing cytokeratin-are always present in murine breast C associated with gestation. Interestingly, high-grade tumors contain more fetal cells	Dubernard G	78
2008	H-Thyroid T	PTC	SRY gene	PCR, FISH, Immuno-FISH	FM negative for either CD45 or Tg could have ''progenitor-like'' properties able to transdifferentiate in different cellular types.Protective role of microchimerism in thyroid cancer	Cirello V	68

2008	Mice-Blood,T	-	organ imaging	PCR, Flow cytometry	Flow cytometry allows for both quantitative and qualitative evaluations of fetal cells at very high sensitivity in a plethora of maternal organs	Fujiki Y	10
2008	H-Blood	Breast C	Y Ch (DYS14)	PCR	Some parous women are not afforded protection from breast cancer by pregnancy might in part be explained by differences in FM	Gadi VK	71
2008	Mice- T	AID	egfp	*FC,MACS, Real-time PCR*	during gestation mothers acquire fetal lymphoid progenitors that develop into functional T cells	Khosrotehrani K	85
2008	H-T	-	centromeric repeat probe DYZ1	*FISH,IHC,*	FM are present at sites of maternal tissue injury during pregnancy, and may participate in tissue repair	Santos MA	88
2008	Mice- T	Skin C	Y Ch	*FISH,IHC*	long-term engrafted fetal cells home to early stage skin tumours where they participate in formation of the stroma	Nguyen Huu S	90
2009	MMTV-H-Ras transgenic mice	Breast C	Y Ch	FISH	FM expressing cytokeratin-are always present in murine breast C associated with gestation. Interestingly, high-grade tumors contain more fetal cells	Dubernard G	66
2009	H- IVS	NON	X ,Y Ch	FISH	Most CD34+cells in maternal placental blood at term are fetal in origin from endothelial and not hematopoietic lineages	Parant O	82
2009	H , mice - Tumors	Melanoma	X ,Y Ch	FISH	Frequently harbor fetal cells that have an endothelial phenotype	Nguyen Huu S	61
2009	H-child T	Cohb, Thr, Hep	X ,Y Ch	FISH	Maternal cells are present in multiple tissue types and occur independently of inflammation or tissue injury. Loss of tolerance to maternal parenchymal cells could lead to organ specific “auto” inflammatory disease and elimination of maternal cells in areas of inflammation	Stevens AM	4
2009	H- PBMC	RA	HLADRB1,DQB 1 typing	HLA-specific qPCR	the first to indicate that FM can contribute to the risk of an autoimmune disease by providing HLA susceptibility alleles	Rak JM	31
2009	H- fetalblood	-	Olig-2	Cell culture, RT pcr	hfMSC can differentiate into cells with an oligodendrocyte phenotype both in vitro and in vivo	Kennea N	84
2010	H- Blood	NON	Y Ch (DYS14)	HLA typing, qPCR	FMc in PBMC increased as gestation progressed and was found within CD4+ and CD8+ subsets in some women in the latter half of gestation. A number of factors could influence cellular FMc levels including subclinical fetal-maternal interface changes related to parturition	Adams Waldorf KM	86
2010	H-Breast T	Breast C	Y Ch (DYS14)	qPCR	Protective association of FM against breast cancer observed previously in the peripheral blood is also reflected in breast tissue	Gadi VK	67
2010	H-Blood	NON	Y Ch (DYS14)	FACS, qPCR	Microchimeric CD66+ cells could have an impact on innate and adaptive immune responses	SunkuCuddapah CS	87
2010	H-Blood	NON	HLA polymorphisms	HLA genotyping, qPCR	Was not a significant association in FMc prevalence or concentration with parity	Gammill HS	59
2010	H- PBMC	PTC	SRY gene	PCR,FISH	FM could reside in maternal niches and could be recruited to diseased areas, where they could differentiate to regenerate damaged tissues	Cirello V	69
2010	Mice- Blood, Organ T	-	fetal DNA	qRT-PCR	Chemically-induced miscarriage significantly increases FM trafficking in murine maternal lung compared to controls, suggest a relationship between fetal loss and microchimerism	Johnson KL	15
2010	Mice variety maternal organs	-	GFP transgene, fetal DNA	PCR, FISH	FM did not pass through the placental barrier, FM entered maternal circulation early after implantation, and sustained their population long after delivery	Sunami R	17
2010	Mice variety maternal organs	-	GFP transgene, fetal DNA	PCR, FISH	most FM with multilineage potential in maternal tissues migrate to the maternal body early after implantation, and thereafter sustain their population over the long term after delivery	Sunami R	18

2010	H-cord blood	-	CD4+, CD34+	MLR, FC	FM T cells are distinct populations that arise from different populations of HSC present at different stages of development, fetus for variable degrees of immune responsiveness at birth	Mold JE	26
2011	H-Blood	MS	Y Ch	qPCR	The association between FM and MS warrants further study to define this relationship	Bloch EM	44
2012	H-Blood	RN	Y Ch (DYS14)	HLA-specific qPCR	FM was frequently found in RNs of RA patients.	Chan WF	32
2012	Mouse Lung T	NON	Egfp	qRT-PCR	FM in the murine maternal lung are a mixed population(trophoblasts, mesenchymal stem cells, and cells of the immune system	Pritchard S	16
2012	Non transgenic Goats- Blood	NON	MaSp1,MaSp2 ,Hbgene	PCR,Western blot	Fetal-maternal and fetal-fetal transfers of DNA do not occur frequently in the goat and that ectopic expression of this mammary-specific transgene is not occurring in the tissues available	Steinkraus	60
2012	H-Brain T	AD, NO neurologi c disease	Y Ch (DYS14)	Real-time PCR(TaqMan)	Lower prevalence& concentration of FM in the brains of women with Alzheimer's disease than the brains of women without neurologic disease. FM is frequent and widely distributed in the H female brain.	Chan WFN	94
2013	H-Blood	back, wrist neck pain	SRY gene	Real-time PCR(TaqMan)	Define the cause of the clinical signs of joint inflammation reaction, which was characterized as GVHD	Reda SY	95
2013	H-Buffy coat cells	Breast C	Y Ch (DYS14)	PCR	In situ breast cancer are deficient in carriage of male microchimerism of presumed pregnancy origin at rates comparable to those observed in women with invasive breast cancer	Eun JK	96
2015	H-Renal biopsies	LN	SRY gene	Real-time PCR	High prevalence of FM in renal biopsy from women with LN, FM role in the etiology of LN. evidence that FM could have a beneficial effect in this disease	Florim GMS	97

Table 1. A summary of the most relevant research articles on fetal microchimerism published 2000-2015. AIT: Autoimmune thyroiditis, AID: autoimmune diseases, AD: Alzheimer disease, BM: Bone marrow, Ch: chromosome, CC: Cervical cancer, C: carcinoma, Cohb: congenital heart block, CI: confidence interval, DFA: Diffuse follicular adenoma, Egfp: Enhanced green fluorescent protein transgene, EAT: experimental autoimmune thyroiditis, FM: Fetal microchimerism, FP: fluorogenic probe, FC: Flow cytometry, Gd: Graves' disease, GVHD: Graft-versus-host disease, GFP: green fluorescent protein, H: Human, HLA: Human leukocyte antigen, Hth: Hashimoto's thyroiditis, Hep:hepatitis, HSC: hematopoietic stem cells, IVS: placental maternal blood from the intervillous space, ICC: Immunocytochemistry, IHC:Immunohistochemistry, LN: Lupus nephritis, MNG: multinodular goiter, MM: Maternal Microchimerism, MS: multiple sclerosis, MSCs: mesenchymal stem/progenitor cells, MACS: Magnetic cell sorting, MLR: mixed lymphocyte reaction, NA: Nodular adenoma, NON: Women with health history under male fetus deliver, NLS: neonatal lupus syndrome, NLCHB: neonatal lupus congenital heart block, OR: odds ratio, PBC: primary biliary cirrhosis, PBMCs: peripheral blood mononuclear cells, PTC: papillary thyroid cancer, RA: Rheumatoid arthritis, RN: rheumatoid nodule, Sjs: Sjögren' syndrome, SLE: systemic lupus erythematosus, SSc: scleroderma, SRY: sex-determining region Y, SP: specific primer, Thr:thrombocytopenia, T: Tissue, TPO-Ab: thyroid peroxidase antibody, Tg-Ab: thyroglobulin antibody, Vthd: Various thyroid disorders, VLS: vulval lichen sclerosus, WB: Western Blot.

Conclusion

An overview of the results and data obtained from related studies over recent 10-15 years demonstrates different roles for fetal microchimeric cell in the maternal body, including natural microchimerism (no biological role), utility (damaged tissue repair) and pathogenesis (causing autoimmune disease and cancer) (91-97).

Several studies have indicated that the isolation of fetal stem cells from maternal blood and their proliferation can be used in transplantation (98, 99). According to the available evidence, such cells can be obtained from the umbilical cord (100), amniotic fluid (101) and the placenta tissue (102).

Many investigations on identifying the role of these fetal michrocimeric cells in the mother's body and their phenotypes and genotypes have recently been carried out. Their novel roles in the treatment and determining the prognosis of various diseases are yet to be further explained.

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