Function of fetal microchimerism during disease and tissue repair in parous women★

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Abstract

BACKGROUND: Fetal microchimerism is a kind of stem cells which comes from fetus in pluripara. The research on fetal microchimerism is a hotspot because it may affect the health condition of pluripara.

OBJECTIVE: To introduce the methods of how to detect fetal microchimerism, and the function of fetal microchimerism during disease and tissue repair of the mother.

METHODS: "Fetal microchimerism" was used as a key word, and papers published before 2011−05−20 were retrieved in PubMed. Repetitive papers were eliminated.

RESULTS AND CONCLUSION: Totally 655 papers were retrieved, and finally 26 were reviewed. There are several methods used for fetal microchimerism detecting, and fetal microchimerism may pay an important role in the pathomechanism of pluripara autoimmune diseases, cancer and tissue repair.

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INTRODUCTION

Microchimerism is the presence of a small number of cells that originate from another individual and are therefore genetically distinct from the cells of the host individual. In contrast to iatrogenic microchimerism after hematopoietic cell transplantation (HCT), organ transplantation or blood transfusion, physiologic cell-traffic occurs during pregnancy between mother and fetuses or between twins. Quantitative studies on bi-directional transfer of cells have revealed that the number of maternal–fetal transfers is lower than that of fetal–maternal transfers[1]. Stem cells migrating from the fetus to the mother are called fetal cell microchimerisem (FCMC). In 1979, Herzenberg declared that fetal genetic material routinely appeared in the peripheral blood of pregnant women[2]. Here we reviewed methods to detect fetal microchimerisem and the relationship between fetal microchimerism and diseases or tissue repair.

DATA AND METHODS

Information retrieval

Retriever: the first author.
Retrieval duration: from database establishment to May 2011.
Retrieval word: fetal microchimerism.
Database: PubMed (http://www.ncbi.nlm.nih.gov/PubMed).
Retrieved literature: A total of 655 papers were collected and involved fetal microchimerism and cancer, fetal microchimerism and tissue repair, fetal microchimerism and autoimmune diseases.

Inclusion and exclusion criteria

Inclusion criteria: Articles published recently in authoritative journals in the same field.
Exclusion criteria: repetitive studies and Meta-analysis.

Quality evaluation

Totally 655 English papers were collected. Following reading the titles and abstracts, unrelated articles were excluded. Articles published recently in authoritative journals in the same field were included, including experimental studies, clinical studies and reviews.

RESULTS

General condition of involved articles

A total of 26 articles were included finally, including 12 related to the distribution of fetal microchimerism in different organs, 6 related to the distribution of fetal microchimerism in cancer tissues, 5 related to fetal microchimerism and tissue repair, and 3 reviews.

When and where can fetal microchimerism be detected in a woman?

According to the study of Sato *et al*[3], fetal cells do not require a full-term pregnancy, which can be detected as early as gestational week 4, also after spontaneous abortions, termination of pregnancy. Cirello *et al*[4] detected fetal microchimerism in female patient's thyroid tissue, even 46 years after the delivery. On the contrary, Hamada *et al*[5] argued that fetal nucleated cells could no longer be detected in maternal peripheral blood at 3 months after parturition. Meanwhile Ariga *et al*[6] declared that cell-free fetal DNA disappeared from the maternal circulation immediately after birth, whereas cellular fetal DNA disappeared by approximately 1 month postpartum. Tan *et al*[7] detected fetal DNA in maternal mouse brains by Q-PCR, and they revealed that the number of fetal cells per 1 000 maternal cells at 4 weeks postpartum are over two times larger than that of parturition day. In one word, from the fourth pregnant week to decades after parturition, fetal microchimerism can be detected. In addition, according to our research on mice, the number of pregnancies seems to have a positive effect on the chance of detected fetal cells or fetal DNA. Beside in

the peripheral blood, fetal microchimerism has also been found in the hematopoietic tissues, breast, thyroid gland and visceral organs such as the liver, kidney, cervix, pancreatic gland, and even in the brain (in mice with excitotoxic lesions in lateral ventricle)[7-8]. Furthermore, fetal microchimerism is identified in the mesenchymal stem cell population from the bone marrow[9]. In mice, fetal cells are found to enter the maternal blood and brain, and some of these cells express immunocytochemical markers for neural cell types[7].

How to detect fetal microchimerism?

PCR amplification based on male DNA

For the detection of fetal cells, almost studies have used specific probes to identify male DNA or male fetal cells. In 1989, Lo *et al*[10] were the first to show that the Y chromosome-specific sequences from a male fetus could be amplified from blood samples of pregnant women by PCR. PCR is very sensitive and usually allows for the detection of one male cell per 100 000 female cells, and quantitative real-time PCR even allows for the detection of one male cell per 1 000 000 female cells[11]. By the help from quantitative real-time PCR's high sensitivity, researchers can also address when fetal-cell DNA first appears in the peripheral blood of pregnant women, how long these fetal cells survive in their hosts, and the frequency of microchimerism in women with a male fetus.

Fluorescence in situ hybridization of Y chromosomes (FISH)

Relative to its advantage of high sensitivity, PCR's disadvantage is of false positive detection. Another approach to studying fetal microchimerism is to conduct FISH with probes that are specific to the Y and X chromosomes so as to identify male cells in the tissues (or in the blood) of women who have had sons. However, it is quicker and easier to detect male cells in the maternal blood or organs because of the universal nature of the Y chromosome, which the normal fertile women lack of. It is believed that male and female fetal cells cross the placenta in equal numbers. In addition, it is possible to detect female fetal cells in the mother by using family-specific polymorphisms or uniquely paternally inherited genes. To redeem the disadvantage of FISH in cell quantification, investigators now usually adopt both PCR and FISH to make their experimental results more reliable, informative, and comprehensive[12].

Green fluorescent protein (GFP)-based detection

It should be considered that male cells in a female could also derive from an older brother or male twins, especially in mice which are usually multiple births. To resolve this problem, investigators have crossed wild-type female mice with homozygous GFP transgenic male mice; however, cells with GFP detected in wild type female mice must come from hemizygous fetuses. By using GFP transgenic mice, investigators can simultaneously harvest accurate pregnancy histories and appropriate clinical tissues, more knowledge of fetomaternal trafficking and the role of microchimeric cells in the maternal tissues can be acquired. In fact, in our and other laboratories, by using GFP-based detection technology, fetal microchimerism has been found in the maternal mouse blood and tissues such as the brain, spinal cord, liver, kidney, spleen and so on.

How about the relationship between fetal microchimerism level and diseases?

The implications of persistent fetal cells in the maternal tissue lead to the generation of the "bad microchimerism" and "good microchimerism" hypotheses. The "bad microchimerism" hypothesis suggests that the persistence of fetal cells may contribute to postpartum autoimmune diseases. The "good microchimerism" hypothesis suggests that fetal microchimerism may be involved in tissue repair, and it may even contribut to neuron repair and cancer treatment.

Three overall mechanisms have been proposed by which fetal microchimerism might contribute to disease in the mother[13]. First, fetal microchimerism could function as an effector of alloimmune reactions. For example, in a study of women with scleroderma, male T cells that were alloreactive to maternal antigens were cloned from the peripheral blood and skin specimens[14]. Second, fetal microchimerism could serve as targets for effectors from the maternal immune system. Tissue differentiated fetal microchimerism has been identified in diseased tissues in thyroiditis and goiter, hepatitis, lupus, and other diseases[15]. Third, fetal cells could serve as an endogenous allogeneic source of progenitor cells to repair tissues that have been damaged by inflammation. Supporting the latter possibility, a murine model described trafficking of fetal microchimerism stem cells to damaged maternal tissues where they appeared to participate in the regenerative process[16].

Fetal microchimerism in autoimmune diseases

Some autoimmune diseases such as Sjogren's syndrome, systemic lupus erythematosus, autoimmune thyroid disease and scleroderma are most striking sex difference. One feature of autoimmune diseases is the predominance in the female sex, and over 80% of patients with autoimmune disease are women[17]. Besides sex hormone, it has been hypothesized that autoimmune disease pathogenesis may be secondary in affected women to the presence of allogenic fetal cells decades after pregnancy. Microchimeric cells were first found in peripheral blood mononuclear cells from patients with scleroderma, and it was suggested that nonautologous cells may be mediating a graft versus host disease like reaction in these patients[18]. In detail, Bloch *et al*[19] found that 21 out of 51 multiple sclerosis-positive subjects (41%) were classified as positive for fetal microchimerism. Cumulatively, available data on the role of fetal microchimerism in autoimmune diseases are still controversial and studies have also shown that naturally acquired fetal microchimerism and maternal microchimerism are common in healthy individuals. The majority of studies have examined fetal microchimerism in autoimmune diseases, for the incidence of most autoimmune diseases is increased in women and is often particularly increased in post-reproductive years.

Fetal microchimerism in women with cancer

In the last five years, the research focus on fetal microchimerism has been extended from autoimmune diseases to malignant tumors. In thyroid tissue, the number of microchimeric cells in tumors and neoplastic is more than that in normal samples. The presence of male DNA was detected in the tumor tissue in the 19 of 40 women with papillary thyroid

carcinoma who had at least one male pregnancy before the diagnosis of tumor. It is worth to note that only 2 of 19 tumors positive for fetal cell microchimerism had an associated autoimmune thyroiditis at histology[4]. On the contrary, fetal microchimerism is lesser in breast cancer tissue than in normal breast tissue. Gadi *et al*[20] reported that healthy women or unselected women with carcinoma *in situ* or invasive breast cancer were evaluated for fetal microchimerism using Y-chromosome specific real-time quantitative PCR. Male genomic DNA, presumably from sons, was detected in 14% of the breast cancer cohort compared to 43% in the control cohort (cancer patients and control women were similar for reproductive histories). In analyses restricted to breast cancer cases, it also appeared that women with more aggressive breast cancer features were less likely to harbor fetal microchimerism than those who had more prognostically favorable tumor characteristics. Recently, fetal microchimerism has been studied in breast carcinomas occurring during or after gestation in a transgenic murine model. Fetal cells expressed cytokeratin, and were specifically found in tumor areas rather than in healthy tissues. Just like in humanbeings, higher numbers of fetal cells were found in high grade tumors[21]. Cha *et al*[22] described the presence of fetal cells in cervical cancer tissue. Six of eight cancer patients harbored male microchimerism in the cancer tissue with a similar proportion of cells expressing either hematopoietic lineage or epithelial markers. The number of microchimeric cells has been found to be independent on the number of male pregnancies and on the interval between pregnancy and disease, confirming that fetal cells are present in the maternal blood for decades after delivery.

Although the published data suggest a protective association of fetal microchimerism in the peripheral blood, other mechanisms by which fetal-derived cells participate in cancer are feasible. According to the study of Gadi *et al*[20], women with breast cancer compared to healthy women may harbor differently functioning fetal microchimerism. In my hypothesis, most fetal microchimerism were killed by maternal autoimmunity when they passed through placental barrier, otherwise supernumerary fetal microchimerism could differentiate into cancer cells years later, that is the reason why we can find more of then in thyroid cancer tissues. Maybe women with autoimmune disease, which is an immunological rejection to fetal microchimerism, will have less chance to suffer cancer.

Fetal microchimerism in tissue repair

Due to difficulties in obtaining sufficient amounts of human tissue, as well as accurate pregnancy histories, animal models are excellent alternatives to investigate fetal–maternal microchimerism. Jimenez *et al*[23] could demonstrate the long-term persistence of male $CD34^+$ cells in the maternal tissue of Rhesus monkeys. Other studies examining fetal-maternal microchimerism were performed with mice and rats tissue damage models. Christner *et al*[24] reported the number of fetal microchimeric cells was associated with dermal fibrosis in mice following injection of vinyl chloride. In GFP transgenic rats, microchimeric cells were found in gentamicin-injured maternal liver and kidney, but not in non-injured maternal organs, suggesting that they have been recruited from the circulation or from the bone marrow to diseased organs in order to contribute to the repairing process[25]. When Robert[26] were analyzing surgical specimens from a 48-year-old woman who had a progressively enlarging nodular goiter for 10 years, they found that a section of her thyroid was composed of entirely male cells. These cells had the appearance of normal thyroid follicular cells and surrounded colloid. In 2005, Tan *et al*[7] further demonstrated that fetal cells could pass through the blood brain barrier and respond to brain tissue injuries, and adopt locations, morphologies, and expression of immunocytochemical markers indicative of perivascular macrophage-, neuron-, astrocyte-, and oligodendrocyte-like cell types. These studies addressed fetal microchimerism associated with maternal tissue damage, and the results indicated that fetal cells were engrafted into the maternal immune system and contributed secondarily to reparative or regenerative processes in different tissues.

DISCUSSION

We wish to determine if fetal cells create functional improvement in response to maternal injury especially if fetal cells create functional improvement in response to nervous injury, and if they have function of repair we need to know how to improve it. We want to know how we can change the number of fetal cells grafting into mother in our will, such as make it more during injury repairer and fewer during postpartum autoimmune diseases. We need to isolate and culture the fetal stem cells and promote their differentiation in our desire. We also need to determine if fetal stem cells in the adult have a competitive advantage over endogenous adult stem cells during injury repair. If we can prove this to be true, this would provide an intriguing explanation as to why women live longer than men. In addition, after years of date accumulation, the detection of fetal microchimerisim may reveal a woman's childbearing history objectively, and it will become a witness in forensic medicine to identify a woman who is involved in forensic issue.

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胎儿微嵌合体在经产妇疾病及组织损伤修复中的作用*

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摘要

背景：胎儿微嵌合体是指存在于经产妇体内、来自胎儿的干细胞，其对母体健康的影响日益受到重视。

目的：介绍胎儿微嵌合体的检测手段、胎儿微嵌合体在母体疾病及组织损伤修复中的作用，引起临床对胎儿微嵌合体研究的重视。

方法：以“fetal microchimerism”为检索词，应用计算机检索 Pubmed 数据库 2011-05-20 之前的相关文章。纳入与胎儿微嵌合体研究相关的文献，排除重复性研究。

结果与结论：共检索到 655 篇文献，排除无关重复的文献，保留 26 篇文献进行综述。目前研究证实多种检测胎儿微嵌合体的手段可供研究者选择，胎儿微嵌合体在引起母体发生自身免疫性疾病、提高母体对于肿瘤等侵害因素的抵御能力、促进损伤修复等方面具有一定作用。

关键词：胎儿微嵌合体；组织修复；自身免疫性疾病；癌；干细胞；妊娠
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此问题的已知信息：关于胎儿微嵌合体与母体免疫性疾病的关系已有多篇报道，亦有少量中文文献涉及此领域。关于胎儿微嵌合体与肿瘤、胎儿微嵌合体与组织修复已有文献报道。

本综述增加的新信息：文章对现有文献进行了综合归纳，结合自身研究成果介绍了胎儿微嵌合体在组织损伤修复尤其是中枢神经损伤修复中的应用及前景。

临床应用的意义：胎儿微嵌合体作为经产妇体内天然存在的干细胞，具有不存在伦理制约、无引起肿瘤发生的潜在危险等特点。本综述有利于提高临床对于胎儿微嵌合体的重视程度，针对胎儿微嵌合体的深入研究有望成为重要的组织工程手段，取代干细胞移植用于损伤修复。