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Microchimerism in Endocrine Pathology

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Abstract

Chimerism in an individual refers to the coexistence of cells arising from two distinct organisms. It can arise *iatrogenically* via transplant or blood transfusion, and *physiologically* via twin to twin transfer, or from trafficking between mother and fetus during pregnancy. Many of the diseases associated with microchimerism affect the endocrine system (e.g., autoimmune thyroid disease and diabetes mellitus type 1). Microchimerism is relevant to endocrine pathology because (a) it is associated with pregnancy, a condition of complex endocrine physiology; (b) maternofetal and feto-maternal cellular migration must involve the placenta, itself an endocrine organ; and (c) in some species, chimerism results in states of intersexuality, a condition intimately involved with endocrine physiology. Studies of feto-maternal microchimerism in the thyroid have documented the presence of fetal cells in association with Hashimoto thyroiditis, Graves' disease, thyroid adenoma, and papillary thyroid carcinoma. Studies of materno-fetal microchimerism have documented the presence of maternal cells in juvenile diabetes and other pediatric conditions. Microchimerism plays a potential role in the repair of diseased thyroid and pancreatic tissues.

Keywords

microchimerism; endocrine pathology; thyroid; Hashimoto thyroiditis; diabetes mellitus; papillary carcinoma; stem cell

Introduction

Chimerism in an individual refers to the coexistence of cells arising from two distinct organisms. It can arise *iatrogenically*, via organ transplant or blood transfusion, and *physiologically* via twin to twin transfer, or from trafficking between mother and fetus during pregnancy. Fetal and maternal cells persist in the mother and child respectively, for many years after parturition [1].

Many theories have been proposed regarding the possible significance of feto-maternal microchimerism; it has been invoked as an etiologic factor in autoimmune diseases of the

skin and thyroid, and, conversely, as a source of stem cells that may help to heal those and other conditions. Fetal cell microchimerism has also been theorized to be a source of immune modulation that may serve to tolerize the mother to the fetus [2]. This possible tolerizing effect, as well as the post-partum survival of fetal cells in the mother, has been studied as a function of the extent of genetic variation (as determined by human leukocyte antigen (HLA) typing) between mother and fetus [3]. Assisted reproductive technologies, such as in vitro fertilization and egg-donor pregnancy, have entered the chimerism discussion as well, in part because of the increased frequency of twinning, and therefore the increased opportunities for chimerism that occur. Overall, an awareness of pregnancy-associated microchimerism presents an opportunity to reassess multiple issues related to endocrinology, immunology, and pathology.

With regard to endocrine pathology, microchimerism is particularly interesting because many of the diseases with which it has been associated affect the endocrine system (e.g., autoimmune thyroid disease [AITD] and diabetes mellitus type 1 [DM1]). Microchimerism is also relevant to endocrine pathology because (a) it is associated with pregnancy, a condition of complex endocrine physiology; (b) materno-fetal and feto-maternal cellular migration must involve the placenta, itself an endocrine organ [4]; and (c) in some species, chimerism results in states of intersexuality, a condition intimately involved with endocrine physiology. In this review, we will discuss the field of microchimerism in the context of endocrine pathology.

Feto-maternal Cell Microchimerism

Thyroid Disease

In the study of fetal cell microchimerism in humans, much work has focused on the thyroid gland. Srivatsa et al. performed fluorescent in situ hybridization (FISH) analysis for the X and Y chromosome on paraffin-embedded thyroid tissue of 29 women who had undergone thyroidectomy, as well as eight normal thyroids obtained from necropsy material [5]. The authors compared the presence of male cells, presumably of fetal origin, with the tissue histology, and also examined the pregnancy and medical histories of the women. The study found male cells in 12 of the 20 patients with a known history of male children, and four of the nine patients with no known history of male children. Of the women with male children, male cells were present most often in the thyroids of women with Hashimoto thyroiditis (83%; Fig. 1), and also, somewhat less frequently, in the thyroids of women with other, non-inflammatory diagnoses. In one patient, male cells had an epithelial phenotype. The authors suggested that fetal cells in the thyroid may play a role in a graft-versus-host type of reaction in the thyroid, or alternatively, that the fetal cells may be involved in tissue repair. This concept of repair was further supported by the work of Khosrotehrani et al., who detected male fetal cells in three thyroid specimens as part of a larger study [6]. They found that fetal cells in the damaged portion of the gland tended to have an epithelial phenotype (cytokeratin positive), while those in the healthy tissue tended to have a leukocyte phenotype (expressing the common leukocyte antigen, CD45).

The idea of fetal cells as modulators of the immune system was further explored using a polymerase chain reaction (PCR)-based technique to amplify the Y-chromosome-specific

SRY gene. Using this technique, Klintschar et al. examined the thyroids of 42 women (17 with Hashimoto thyroiditis and 25 with nodular goiter) [7]. The study found Y-chromosome DNA sequences in the thyroids of eight of the 17 patients with Hashimoto thyroiditis, but only one of the 25 women with goiter. The authors proposed that the fetal cells elicit an intrathyroidal graft-versus-host reaction that leads to the thyroiditis. Later, Klintschar et al. expanded the inquiry with a quantitative PCR-based approach, amplifying the *DYS14* region of the Y chromosome, a technique that allows greater sensitivity because of multiple repeats [8]. This study identified male DNA in eight of 21 women with Hashimoto thyroiditis, one of 18 women with multinodular goiter, and zero of 17 normal thyroid glands. The authors noted that male cells have been consistently shown to be present in a significant proportion (but not 100%) of patients with Hashimoto thyroiditis.

Ando et al. used a PCR-based technique to detect *SRY* sequence in thyroids from women with Graves' disease and thyroid adenomas. Examining 26 paraffin-embedded thyroid tissues, the authors identified *SRY* in 4/20 women with Graves' disease and 0/6 women with adenomas [9]. However, examining fresh-frozen thyroid tissues, they identified *SRY* in six of seven patients with Graves' disease and one of four patients with thyroid adenoma. They concluded that paraffin-embedded tissue is subject to DNA fragmentation and that fetal microchimeric cells in the thyroid may play an immunological role in autoimmune thyroid disease.

Renne et al. examined the thyroid glands of 49 women with reproductive histories positive for sons, using FISH analysis for X and Y chromosomes [10]. The authors found that of the 25 women with Hashimoto thyroiditis, 60% were positive for male cells in the thyroid. Of the 15 patients with Graves' disease, 40% were positive for male cells in the thyroid, and of the nine patients with thyroid adenomas, 22% were positive for male cells. The authors concluded that fetal microchimerism is found more frequently in autoimmune diseases of the thyroid than in non-autoimmune diseases and suggested that the fetal cells may be involved in immune modulation.

Imaizumi et al. used a murine model of experimental autoimmune thyroiditis, in which thyroiditis was induced by immunization with thyroglobulin [11]. Using PCR and ELISA techniques to amplify and detect *SRY*, the authors identified male DNA in 12 of 26 thyroglobulin-immunized pregnant mice and two of ten non-immunized pregnant mice. They found that the fetal cells that accumulated in the thyroid were of T-cell and dendritic cell lineage. They concluded that fetal T cells and dendritic cells migrated to the inflamed thyroid and potentially modulated the immune response. Thus, multiple human and animal studies have demonstrated the presence of microchimeric fetal cells in the thyroids of patients with AITD (Table 1).

A variety of arguments have been made against the importance of microchimerism in AITD. Prummel et al. wrote that there are many possible causes of AITD, which can be sub-grouped into genetic versus environmental causes [12]. Environmental variables include fetal growth, iodine intake, selenium intake, hormonal influences, parity, oral contraceptives, and fetal microchimerism, as well as stress, seasonal influences, allergy, smoking, medications, irradiation, and infections. The authors concluded that 21% of the

susceptibility to AITD can be attributed to environmental factors. Walsh et al. performed an epidemiological study of 1,045 women who had participated in a 1981 community health survey in Western Australia [13]. For these women, the authors obtained measurements of thyroid-stimulating hormone (TSH), thyroid peroxidase antibody (TPO-Ab), and thyroglobulin antibody (Tg-Ab) using a chemiluminescence analyzer and looked for an association between these laboratory values and the patient's medical histories as reported in the survey, specifically with regard to thyroid disease and parity. The authors determined that previously pregnant women are not at increased risk of positive thyroid antibodies, or raised or reduced TSH, and concluded that parity is not a risk factor for thyroid autoimmunity or thyroid dysfunction. The authors wrote that the data, therefore, do not support a pathogenic role for fetal microchimerism in AITD. As part of a Danish population study on iodine intake and thyroid disease, Bulow Pederson et al. measured TPO-Ab and Tg-Ab levels and surveyed the medical and obstetric histories of 3,283 women [14]. Women who had been treated for thyroid disease, or who had been pregnant in the past 12 months, were excluded from analysis. The authors found no association between levels of circulating thyroid antibodies and number of pregnancies, and concluded that these data argue against the hypothesis that microchimerism is a trigger of thyroid autoimmunity.

Cancer

Cirello et al. expanded the search for microchimeric fetal cells to neoplastic thyroid tissue (Fig. 2). This group studied thyroid tissues from 63 women with papillary thyroid cancer (PTC). Using PCR for *SRY*, they identified male DNA in 47.5% of tumor tissues, but in only 25% of contralateral thyroid tissue not involved by tumor [15]. Using FISH analysis with probes specific to the X and Y chromosome in a selected subset of male-cell-positive cases, these authors found higher numbers of male cells in the tumor-involved tissue than in the contralateral tissue. Combining FISH with immunohistochemistry (IHC) in the same subset, they found that many of the male cells in both tumor and non-tumor tissue expressed thyroglobulin (Tg). They found a smaller number of cells expressing CD45 in tumor tissue only. The authors concluded that fetal cell microchimerism is present in many women with PTC. They hypothesized that the Tg-positive cells could have a repair function, while the CD45-positive cells could be directed against tumor cells.

In addition to the thyroid, several other human endocrine tissues have been evaluated for the presence of fetal microchimerism. Cha et al. studied the cervical tissue of eight women who had undergone hysterectomy for cervical cancer by performing FISH for X and Y chromosomes, and IHC for keratin and CD45 [16]. The authors found several male cells, some of which were keratin-positive, and others of which were CD45+, with no double-positive cells. They suggested that fetal progenitor cells may differentiate in the maternal host and that they might alter immune function, possibly making cervical tissue more susceptible to infection by human papilloma virus. Dubernard et al. studied ten pregnant women carrying male fetuses and having pregnancy-associated breast cancer, as well as four female controls with benign breast lesions [17]. This group performed FISH for the X and Y chromosomes, and IHC for keratin, vimentin, CD45, and CD34. They found male cells in 9/10 carcinomas versus 0/4 benign lesions. Of all the male cells found, 22% were positive for vimentin, 16% positive for keratin, 5% positive for CD34, and none positive for CD45.

They concluded that malignancies that occur during pregnancy frequently appear to recruit fetally derived cells and that the fetal cells mainly have a stromal origin.

Materno-fetal Cell Microchimerism

General Studies

Several authors have documented the presence of maternal cells in the fetus or child (materno-fetal cell microchimerism) and have proposed theories regarding its possible significance. Srivatsa et al. performed FISH for X and Y chromosomes on various tissues of four non-transfused newborn males [18]. They found female cells, ranging from three to 45 per slide, to be present in the male newborns' organs. They were most prevalent in a case of trisomy 21 with *hydrops fetalis*. Because of the connection between Down syndrome and autoimmune diseases, the authors suggested that maternal microchimerism may play a role in autoimmune disease of the child. Gotherstrom et al. performed a case study of a second trimester fetus with malformations and analyzed post-termination fetal tissue for the presence of maternal CD3, CD19, CD34, and CD45-positive cells by magnetic activated cell sorting and PCR amplification [19]. This group detected maternal cells in the fetal liver, lung, heart, thymus, spleen, adrenal, and kidney, as well as the placenta, but not in the pancreas or gonadal tissues. They concluded that maternal cells were widely distributed in a second trimester malformed fetus. Jonsson et al. assessed 11 terminated fetuses (five normal and six with trisomy 21 or malformations) by PCR for the presence of maternal HLA sequences in fetal DNA derived from tissue and determined that maternal microchimerism was widespread in all organs [20]. They concluded that exposure of the fetus to maternal cells might be part of the development of immune tolerance. Stevens et al. studied tissues of seven male infants by FISH and IHC. They found maternal cells present in all seven infants, comprising 0.017% to 1.9% of parenchymal cells in various organs [21]. IHC showed that these cells differentiated into hepatocytes, renal tubular cells, and beta islet cells. The authors concluded that differentiated maternal cells are present in multiple fetal tissues and hypothesized that loss of tolerance to these cells by the infant's immune system could lead to organ-specific inflammatory disease.

Endocrine Pathology

Much of the investigation of the role of materno-fetal cell microchimerism in autoimmune endocrine disease has focused on the pancreas. Nelson et al. used a PCR-based protocol to assess for the presence of maternal microchimerism in the peripheral blood of 172 individuals, including 94 with DM1, 54 unaffected siblings, and 24 unrelated healthy subjects [22]. In a separate analysis of pancreatic autopsy material from four males with DM1, they performed FISH for X and Y chromosomes and IHC for insulin and CD45. The first study found significantly higher levels of maternal microchimerism in patients with DM1 than in the other populations studied. The second study found that female cells in the pancreases of males with DM1 are often positive for insulin by IHC. The authors concluded that maternal cells could contribute to endocrine function in offspring.

Animal models have been used to further investigate the potential role of chimeric stem cells. Two studies in particular provide collateral support for the idea that stem cells that

cross the placenta can have beneficial effects in target tissues such as the pancreas. Chen et al. assessed the rat for vascular endothelial growth factor receptor-I (VEGF-R1), vascular endothelial growth factor A (VEGF-A), integrins, and multipotent mesenchymal stromal cells (MMSCs) [23]. They found that when MMSCs are transferred to rat maternal venous blood, they traffic through the placenta, engraft in various fetal organs, and persist in offspring for at least 12 weeks. The authors concluded that materno-fetal microchimerism arises by trafficking of MMSCs via VEGF-A and integrin-dependent pathways across the placenta to the fetus. This study supports the idea that stem cells can cross the rat placenta and home to various organs. Verda et al. studied the effect of injection of embryonic stem cells (ESC) into non-obese diabetic mice [24]. In ten mice, the stem cells were injected into the bone marrow, and in eight, they were injected intravenously; additionally, there were nine control mice. After injection, the team evaluated the mice for histology of the islets of Langerhans, clinical hyperglycemia, and responsiveness to glutamic acid decarboxylase isoform 65. They found that nine of ten mice from the bone marrow-injected group, five of eight mice from the intravenously injected group, and one of nine controls did not become hyperglycemic. They also found that all mice with greater than 5% donor microchimerism did not have diabetes or insulinitis. They concluded that ESC-derived hematopoietic stem cells can induce an islet cell tolerizing graft-versus-autoimmunity effect without graft-versus-host disease. This study provides support for the idea that stem cells homing to the murine pancreas can have beneficial effects.

Effect of Chimerism on Sexual Development and Endocrine Function

The ability of maternal, and other, stem cells to differentiate into endocrine tissues raises the question of what may happen when the stem cell donor is of different sex than the recipient. This situation occurs in the case of sons who are chimeric with their mothers' cells, in twins who incorporate stem cells from an opposite sex twin, and in recipients of therapeutic stem cell transplants from opposite sex donors. The potential effects range from minimal, as in the case of confined blood chimerism, to moderate endocrine disturbance, to major developmental effects, as in hermaphroditism. An appreciation of the potential chimeric effects of stem cells has occurred coincidentally with the rise of in vitro fertilization (IVF). In IVF, the practice of transferring multiple embryos has led to an increase in the rate of twinning and possibly to an increase in twin-related complications, such as chimerism [25].

Walker et al. presented a case report of monochorionic dizygous (MCDZ) twins after IVF [26]. As in other MCDZ cases, these twins exhibited confined blood chimerism. Williams et al. reported on another case of confined blood chimerism in MCDZ twins conceived by IVF and suggested that the blood chimerism could be due to either placental vascular anastomoses or to trophoblast mixture during early blastocyst development [27]. Strain et al. described a 46,XX/46,XY hermaphrodite conceived by IVF and showed that the child resulted from the amalgamation of two fertilized ova [25]. Ekelund et al. reported a case of dizygotic, monochorionic twins conceived by intracytoplasmic sperm injection [28]. Amniocentesis revealed that the fetal karyotypes were 46,XX, and 46,XY. Post-natally, karyotyping revealed blood chimerism. These authors concluded that blood chimerism in twins may be more common than previously thought, possibly due to the existence of undiagnosed dizygotic monochorionic pregnancies.

Le Blanc et al. studied stem cell engraftment in a female fetus with a severe, non-lethal type of osteogenesis imperfecta [29]. The authors performed in utero transplantation of mesenchymal stem cells (MSC) cultured from the liver of an aborted male fetus. A bone biopsy performed on the recipient at 9 months of age was analyzed by IHC for bone markers (osteocalcin, bone sialoprotein [BSP], and osteopontin), as well as FISH. Using centromeric probes for X and Y, the authors found that 0.3% of the cells staining for osteopontin or osteocalcin were male. Using a male whole-genome probe, they found that 6.8% to 16.6% of the cells that stained with BSP were male. The authors concluded that fetal MSC from an allogeneic donor are capable of engrafting and differentiating in an immunocompetent recipient. These studies bring attention to the question of how sexual differentiation may be influenced by chimerism of non-sex-matched individuals, especially when the chimerism or transfusion occurs during fetal life.

Conclusions

The existence and persistence of materno-fetal and feto-maternal microchimerism have been demonstrated in multiple studies that involve endocrine tissues. Hypotheses have been generated regarding the distribution and function of microchimeric cells. It is notable that so many studies have documented a disproportionate amount of fetal cell microchimerism occurring in the thyroid. Is this because a significant amount of maternal cardiac output passes through the thyroid, or is it because the thyroid has a microenvironment that is particularly hospitable to fetal cells, or some other reason? Similarly, if maternal cells are so prevalent in fetal and neonatal tissues, including the pancreas, what functional implications does this have? What is the long-term clinical significance of an opposite sex stem cell transplant performed in a fetus or neonate? Until further work is performed to answer these questions conclusively endocrine pathologists need to be aware of these phenomena.

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Fig. 1.
Section from a patient with Hashimoto thyroiditis. Multiple studies have shown an association between feto-maternal microchimerism and Hashimoto thyroiditis [5, 7, 8, 10]

Fig. 2. Section from an individual with papillary thyroid carcinoma. In a recent study, more fetomaternal microchimerism was identified in tissue affected by papillary thyroid cancer than in contralateral, uninvolved thyroid tissue [15]

Table 1

Selected clinical scenarios associated with microchimerism

Type of microchimerism	Tissue(s)	Clinical scenario	References
Feto-maternal	Thyroid	Hashimoto thyroiditis	[5, 7, 8, 10]
	Thyroid	Graves' disease	[9, 10]
	Thyroid	Thyroid adenoma	[9, 10]
	Thyroid (murine)	Experimental autoimmune thyroiditis	[11]
	Thyroid	Papillary thyroid cancer	[15]
	Cervix	Cervical cancer	[16]
	Breast	Pregnancy-associated breast cancer	[17]
Materno-fetal	Various	4 male newborn infants	[18]
	Various	1 malformed fetus	[9]
	Various	11 terminated fetuses	[20]
	Various	7 male infants	[21]
	Pancreas	4 males with DM1	[22]
	Peripheral blood	172 individuals, including 94 with DM1	[22]

DM1 diabetes mellitus, type 1