Microchimerism and Endocrine Disorders

Laura Fugazzola, Valentina Cirello, and Paolo Beck-Peccoz

Department of Medical Sciences, University of Milan; and Endocrinology and Diabetology Unit, Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda, 20122 Milan, Italy

Context: The term "microchimerism" indicates the coexistence, in the same organism, of genetically distinct populations of cells derived from two different individuals. The passage of cells from the fetus to the mother is called fetal cell microchimerism, whereas that occurring from the mother to the fetus is named maternal cell microchimerism. Microchimeric cells can persist in blood and tissues for decades.

Evidence Acquisition: A literature search through the U.S. National Library of Medicine was used to identify and review studies on maternal and fetal microchimerism, focusing on endocrine diseases.

Evidence Synthesis: According to the majority of reports, fetal cell microchimerism seems to have a detrimental role in autoimmune diseases and a positive effect on tumor burden in most human cancers studied. In autoimmune thyroid diseases, fetal microchimeric cells (*fmcs*) have been found to be significantly more represented within the thyroid gland of women with Hashimoto's thyroiditis and Graves' disease compared to those without thyroid autoimmunity, suggesting a pathogenic role. In thyroid cancer tissues, *fmcs* have been found to be present at higher levels than in contralateral normal tissues and have been shown to differentiate into epithelial and hematopoietic cells. Microchimeric cells with hematopoietic differentiation could have a role in destroying the tumor, whereas epithelial cells are believed to participate in the repairing processes. At the peripheral level, circulating *fmcs* were less frequently detected in patients with thyroid cancer than in healthy individuals, consistent with data obtained for breast cancer and other solid and hematological malignancies, indicating a protective role against cancer development. Finally, type 1 diabetes has been mostly related to maternal cell microchimerism. Indeed, the levels of circulating maternal cells were higher in type 1 diabetes patients than in controls. At the pancreas level, female β-cells were identified and hypothesized to be targets of autoimmunity or to regenerate diseased tissues. **(*J Clin Endocrinol Metab* 97: 1452–1461, 2012)**

The term "microchimerism" indicates the coexistence, in the same organism, of genetically distinct populations of cells derived from two different individuals. It consists of the transfer of a low number of cells from one individual to another and can occur in cases of blood transfusion, organ transplantation, and primarily during pregnancy. In the latter case, a transplacental bidirectional trafficking of maternal, fetal, and placental cells between mother and fetus is observed starting from the fourth to the sixth week of gestation, likely due to the fetoplacental unit suppression of the maternal immune system (1). The passage of cells from the fetus to the mother is called fetal cell microchimerism (FCM), whereas that occurring from the mother to the fetus is named maternal cell microchimerism (MCM). Both fetal and maternal microchimeric cells can persist in blood and tissues for decades or for the entire life of an individual (2–4). Another source of naturally acquired microchimerism could be the passage from

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Abbreviations: AITD, Autoimmune thyroid disease; APC, antigen-presenting cell; FCM, fetal cell microchimerism; FISH, fluorescent *in situ* hybridization; *fmcs*, fetal microchimeric cells; HLA, human leukocyte antigen; MCM, maternal cell microchimerism; MHCII, major histocompatibility complex II; *mmcs*, maternal microchimeric cells; NIMA, noninherited maternal antigen; NK, natural killer; PAPC, pregnancy-associated progenitor cells; PTC, papillary thyroid cancer; RA, rheumatoid arthritis; *SRY*, sex-determining region Y; Tg, thyroglobulin.

the mother of cells derived from an older sibling. In this case, cells from the sibling could persist in the mother for years after birth and could then be transferred to the fetus in a following pregnancy. Another possibility is the direct passage from a twin or a vanished twin (5, 6). Indeed, twin-twin trafficking occurs in up to 8% of twin pairs and 21% of triplet pairs (7). Finally, microchimeric cells can derive from spontaneous or elective abortions (8, 9). Interestingly, it has been reported in both humans and mice that abortion results in a greater frequency of FCM than delivery at term (8, 10).

Women are physiologically more exposed than men to several sources of naturally acquired microchimerism. Indeed, an adult woman might have acquired microchimeric cells from her mother (MCM), either maternal cells or, less likely, fetal cells deriving from a previous sibling or abortion. Moreover, she might have acquired microchimeric cells from a twin sibling (trafficking of cells between individuals *in utero*) or a vanished twin. During her pregnancies, novel microchimeric cells might be acquired from fetuses or abortions. A dynamic interaction seems to exist between microchimeric cells of different origin (11). In particular, it has been observed that the number of fetal microchimeric cells (*fmcs*) does not increase with increasing parity, possibly indicating the occurrence of a competition between grafts, with the predominance of only one type of microchimeric cells. As a consequence, it could be speculated that the predominance of certain classes of microchimeric cells may lead to a protective, graft *vs*. tumor effect for the host, decreasing cancer risk, whereas another class of microchimerism may predispose to long-term alloimmune reactions resulting in an autoimmune disease. Differently, maternal microchimeric cells (*mmcs*) significantly decrease at each new pregnancy, likely as a consequence of the substitution of *mmcs* with *fmcs*. The shift from MCM to FCM may have a clinical relevance. Indeed, *mmcs* are partially genetically foreign to the fetus because they also express the noninherited maternal antigens (NIMA). Nevertheless, the deletion of maternal cells by NIMA-specific effector T cells is blocked by NIMA-specific regulatory T cells, induced by *mmcs* migrated to fetal lymph nodes (12, 13). Thus, the progressive reduction of *mmcs* in the host may have direct relevance to the tolerance of NIMA, possibly inducing a health disorder.

Although microchimerism has been extensively studied both in humans and in animal models in recent years, the exact role of this phenomenon in human health is not yet elucidated. Indeed, microchimeric cells could have a deleterious role, inducing autoimmune and neoplastic diseases, or alternatively a beneficial role including repair and regeneration of tissues and defense against cancers and infections. Finally, the occurrence of both effects or the total lack of actions cannot be excluded.

A search for original articles published up to november 2011 and focusing on fetal cell microchimerism was performed in PubMed. The search terms used were "microchimerism," "fetal cell," "microchimeric cell," "cancer," "immunoFISH," "autoimmunity," "immunohistochemistry," "CD45," "thyroid," "breast cancer," "pregnancy," "stem cell," "progenitor cell," "graft *vs*. host disease." All articles identified were English-language, full-text papers. The reference lists of identified articles were also checked for further papers.

Fetal Cell Microchimerism

Owing to the uniqueness of the Y chromosome, the easiest way to detect and to study FCM is to search for male microchimeric cells in women with a previous male pregnancy. Indeed, the amplification of the *SRY* (sex-determining region Y) gene on the Y chromosome is the most common method used, reaching a high sensitivity with the possibility to identify up to one male cell per million female cells. Another technique is the fluorescent *in situ* hybridization (FISH) analysis performed using two probes specific for the X and Y chromosomes (Fig. 1A). The detection of fetal cells derived from both female and male progeny can be achieved by the human leukocyte antigen (HLA) typing, based on the detection and quantification of noninherited, nonshared, maternal-specific HLA polymorphisms (14). By these techniques, FCM was found to be a common event in pregnancy, the number of *fmcs* progressively increasing during gestation, with a peak at delivery and a decrease in the postpartum period (1, 15).

Interestingly, it has recently been shown in a murine model that fetal cells with the potential to multilineage differentiation migrate to maternal organs before the formation of the placenta (16).

The exchanged cells are trophoblasts and mature cells of the immune system, such as T and B lymphocytes, monocytes/macrophages, and natural killer (NK) cells (17), but also hematopoietic stem cells-$CD34^+$ and progenitor cells-$CD34^+/CD38^+$ (18), mesenchymal stem cells (4), and endothelial progenitor cells (19). Concerning lymphocytes, *fmcs* have been found in the $CD4^+$ and $CD8^+$ T cell subsets (15). Due to the long lifespan of T cells, these microchimeric cells can persist in the mother for years. Differently, microchimeric cells positive for CD66b, and thus regarded as granulocytes, have an extremely short half-life, excluding their direct origin from the fetus and favoring their derivation from fetal hematopoietic stem cells or progenitor niches (20). In this context, it should be un-

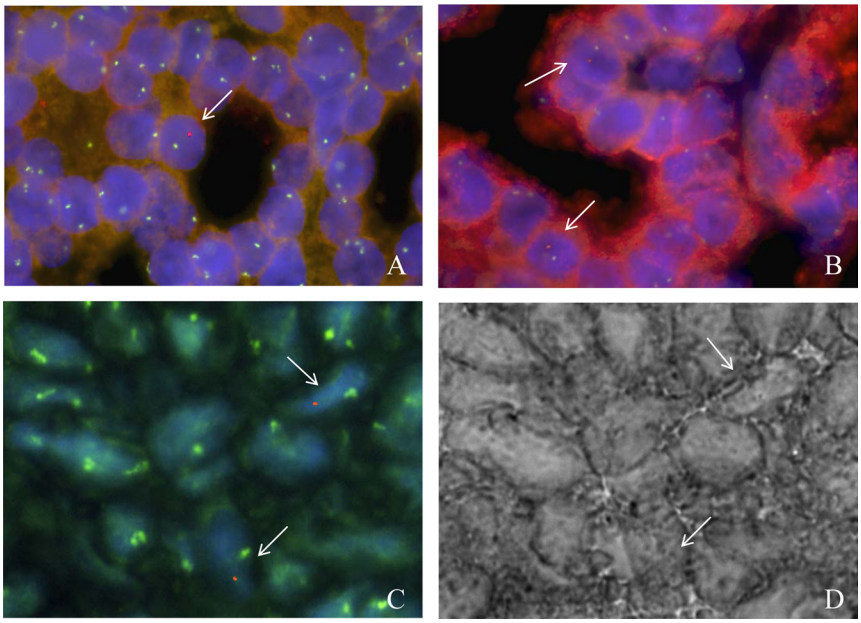

FIG. 1. A, Papillary thyroid tumor section at fluorescence microscopy at FISH analysis, which leads to the morphological definition and spatial localization of microchimeric cells. X (*green signal*) and Y (*red signal*) chromosomes are identified by specific probes in the nuclei of male cells (*arrow*). B, Papillary thyroid tumor section at fluorescence microscopy in immuno-FISH experiments using immunohistochemistry with anti-Tg antibody and FISH (probes specific for X- and Y-chromosomes). Male cells (Y-chromosome in *red* and X-chromosome in *green*) surrounded by female cells can be observed (indicated by *arrows*). The Tg expression is indicated by the fluorescent red staining within the cytoplasm (magnification, ×100). C, Papillary thyroid tumor section at fluorescence microscopy in immuno-FISH experiments using immunohistochemistry with anti-CD45 antibody and FISH (probes specific for X- and Y-chromosomes). Male (*arrows*) and female cells of hematopoietic origin can be observed. D, The same male cells as *panel C* visualized by light microscopy (*arrows*). The darker staining on cell surface surrounding the male nucleus indicates CD45 expression, consistent with a leukocyte phenotype.

derlined that, although the specific nature of microchimeric cells is still unknown, their ability to differentiate into several lineages indicates that they could actually be very early stem or progenitor cells. Indeed, they have been called "pregnancy-associated progenitor cells" (PAPC), and they are believed to harbor features in the middle between embryonic and adult stem cells (21). Likely, PAPC can survive by homing in maternal stem cell niches, such as the bone marrow, and representing a long-term reservoir of stem cells with multilineage potential. In the case of tissue injury, PAPC are believed to migrate to the damaged organ and differentiate as part of the maternal repair response. In this context, some murine models have been developed by inducing the chemical damage of maternal organs. The finding of fetal cells in the maternal pancreas, liver, kidney, myocardium, or brain resembling their maternal counterparts, such as acinar cells in the pancreas, hepatocytes in the liver, and tubular cells in the kidney, indicates that FCM may contribute to tissue repair and regeneration (10, 16, 21–24). The maternal lung was found to be one of the preferential sites of trafficking and homing of PAPC, likely due to the passive flowing through the uterine vein into the inferior vena cava up to the pulmonary capillary bed and to a receptive microenvironment for retention and engraftment of these cells (25, 26). Nevertheless, besides this passive mechanism of cell accumulation, the finding of a nonrandom distribution of a mixed population of differentiated and progenitor *fmcs* in maternal organs indicates the existence of an active mechanism of fetal cell recruitment. Two mechanisms have been proposed to explain the immunological tolerance allowing the persistence of *fmcs* in maternal blood without inducing a graft *vs.* host reaction. The first is that fetal T cells could possibly mature in the maternal thymus, where those directed toward maternal antigens could be deleted (18). The second is that maternal antigens, once passed into the fetus, could induce differentiation of fetal cells into specific T-regulatory elements able to migrate to the mother, where they can influence the maternal immune system (27). In this context, it was hypothesized that T cells alloreactive to maternal antigens might occasionally not be suppressed, thus inducing maternal autoimmune diseases (3).

Maternal Cell Microchimerism

The presence of maternally derived cells in the offspring is called MCM. This phenomenon was first described about 50 yr ago when routine karyotyping of newborn male infants demonstrated the presence of sex chromosome mosaicism (28, 29), and it was subsequently found to be a rather common occurrence (30). It is unknown when maternal cells pass through the placenta during gestation, although cells of maternal origin have been detected at a very early stage (31, 32) and can persist in adulthood up to 40 yr of age (33). Interestingly, it was shown that maternal cells cross the placenta and migrate to fetal lymph nodes where they seem to be able to suppress fetal immunity against the mother, blocking the reaction toward NIMA (12).

The detection of *mmcs* cannot be based on the amplification of a unique gene, as occurring for the detection of male *fmcs*. Indeed, *mmcs* have been detected in tissues of sons by FISH using X- and Y-specific probes (34) and in

the DNA obtained from cord blood, peripheral blood mononuclear cells, or whole blood both in female and male children using a panel of quantitative PCR assays targeting nonshared HLA polymorphisms (14). It is also possible to detect maternal nucleated cells and plasma DNA using a quantitative assay of two polymorphic NIMA, the deletion of the glutathione S-transferase M1 gene and the insertion/deletion of intron 16 of the angiotensin-converting enzyme gene (31). Due to the need for these complex techniques and to the lower number of *mmcs* detected in the progeny with respect to *fmcs* in the mother (31), MCM has been poorly studied both at peripheral and tissue levels of healthy or affected individuals. Particularly, MCM has been detected in lymphoid (lymphocytes) and myeloid (monocyte/macrophages and NK cells) compartments of peripheral blood of healthy adults (35). MCM was also reported with widely variable frequency in healthy tissues (liver, spleen, thymus, thyroid, heart, pancreas, lung, adrenal gland, and kidney) obtained from abortions, biopsies, and autopsy material of normal or malformed fetuses (32, 36, 37), in mesenteric lymph nodes from normal fetuses (12), and in lymphoid organs (tonsils and/or adenoids) of relatively healthy children (38). In thymus, liver, and spleen, maternal cells resulted positive for CD3 (T-cell), CD19 (B-cell), CD34 (hematopoietic progenitor cells), and CD45 (leukocytes) antigens, indicating an engraftment capacity (37). Transplacentally acquired maternal T lymphocytes have also been reported in the peripheral blood of a significant proportion of children with severe combined immune deficiency syndrome (39, 40). Moreover, *mmcs* have been detected in the tissues of children who died from congenital heart block due to neonatal lupus syndrome (6, 41) or those affected with cutaneous inflammatory diseases (42) or with type 1 diabetes (T1D) (34), suggesting a possible involvement of these microchimeric cells in the process of tissue repair and regeneration.

Microchimerism in Human Diseases

Autoimmunity

A possible role for FCM in triggering an autoimmune process has been repeatedly proposed, based on the evidence that autoimmune diseases have a higher prevalence in females, with peak incidence in women of childbearing age. The first studies on microchimerism were performed at the peripheral blood level and focused on several autoimmune diseases, such as systemic sclerosis, primary biliary cirrhosis, Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis (RA), thyroiditis (17, 43–63), and multiple sclerosis (64). Circulating *fmcs* were found to be more abundant in these patients compared with healthy individuals, and in some cases *fmcs* were documented in tissues such as in skin lesions of patients with systemic sclerosis (47) and in rheumatoid nodules, indicating a potential role in their formation (65). Although these data could indicate a detrimental role for FCM in autoimmune diseases, other studies documented the lack of a significant difference in *fmcs* prevalence between patients with systemic autoimmune diseases and healthy individuals or reported controversial results (49–53, 56, 58). The causative mechanism proposed is based on the finding that, after transfer to the mother, the progenitor cells of the fetal immune system can persist and move to different organs where they could proliferate, differentiate, and activate. Activated fetal T cells, monocytes, macrophages, and NK cells, together with the locally produced cytokines and chemokines, could be involved in the initiation of autoimmune diseases (allo-autoimmunity) (43, 44). Alternatively, these cells might be recognized as partially alloimmune, thus giving rise to an immune reaction (auto-alloimmunity). Moreover, it was suggested that FCM might contribute to the risk of an autoimmune disease by providing HLA susceptibility alleles, as demonstrated for RA and systemic sclerosis (45, 46). In particular, RA-affected women without HLA risk alleles could develop the disease due to the naturally acquired fetal susceptibility alleles, whereas the absence of the disease in women carrying HLA risk alleles could be due to the acquisition of protective alleles from the fetus (66).

Because semiallogeneic maternal cells could trigger an autoimmune disease or be the target of an immune response, a possible role of MCM in the pathogenesis of several autoimmune diseases has been suggested. Indeed, *mmcs* have been found to be present at higher levels with respect to controls in several skin and muscle diseases, such as scleroderma (14, 33), juvenile idiopathic inflammatory myopathies (67), juvenile dermatomyositis (68, 69), and pityriasis lichenoides (42). The presence of *mmcs* was also demonstrated in liver biopsies of patients with biliary atresia (70–72), and the hypothesis that maternal immunological insults could be pathogenic was based on the finding of a high number of $CD8^+$ T cells in the livers of these patients (73). Moreover, it was proposed that the RA risk-associated HLA alleles of the mother could be passed to the children as NIMA, therefore inducing the disease even in the sons who do not carry RA susceptibility alleles (74).

Cancer

FCM has been detected in parous females with different cancers, both hematological malignancies and solid tumors (breast, lung, thyroid, colon, uterine, ovarian, cer-

vical cancers, and melanomas), at lower frequency than in healthy women. Interestingly, in patients with solid tumors, FCM has been documented less frequently than in those with hematological malignancies (75). The possible role of *fmcs* in solid tumors was first studied in cervical cancer (76). Immuno-FISH analyses showed that the majority of these cells expressed the CD45 leukocyte common antigen, whereas a lower number of cells were cytokeratin-positive. The persistence of these cells was thought either to have a role in carcinogenesis, inducing an alteration of the immune system in women or making the cervix more susceptible to infections, or to be involved in a response to carcinogenesis, being fetal precursors able to differentiate and to repopulate or to repair the damaged tissue. More recently, studies on FCM in breast cancer demonstrated that circulating *fmcs* were significantly less represented in patients compared with healthy controls, suggesting that they could provide a protective advantage against breast cancer (77, 78). Moreover, studies at the tissue level showed the presence of *fmcs* in the tumor stroma of patients with breast cancer developed during or shortly after pregnancy, but not in benign mammary lesions. These microchimeric cells expressed mainly mesenchymal or, to a lesser degree, epithelial or endothelial markers and were hypothesized to have a repairing function (79). This protective role was hypothesized also for *fmcs* in lung cancer, where they were found to be clustered in diseased tissues at higher frequency than in normal specimens (80). More recently, data have been obtained in melanomas that were found to harbor *fmcs* in a proportion higher than benign nevi in humans and to be exclusively present in melanomas and not in normal skin in mice (81, 82). Interestingly, the *fmcs*, mostly expressing the endothelial cell marker CD31, were located within or around the tumor and appeared to be able to form either blood vessels or lymphatics, suggesting that the fetal contribution to lymphangiogenesis may worsen the prognosis of the maternal tumor. Moreover, the finding of *fmcs* in the majority of chemically induced lesions in mice indicated the selective recruitment of fetal cells in tumoral areas as an early step in skin carcinogenesis.

Scanty data are available on MCM and cancer. In particular, two cases have been reported of fetuses developing the same neoplasm of the mothers, likely due to the transplacental passage of maternal neoplastic cells (82, 83).

Microchimerism in Endocrine Diseases

Microchimerism has been studied in some endocrine diseases. The first reports focused on FMC in autoimmune thyroid disorders. Studies that followed were devoted to the study of FCM in both benign and malignant thyroid nodular diseases. Finally, maternal microchimeric cells were found and believed to be implicated in the type 1 diabetes mellitus of the child (Fig. 2).

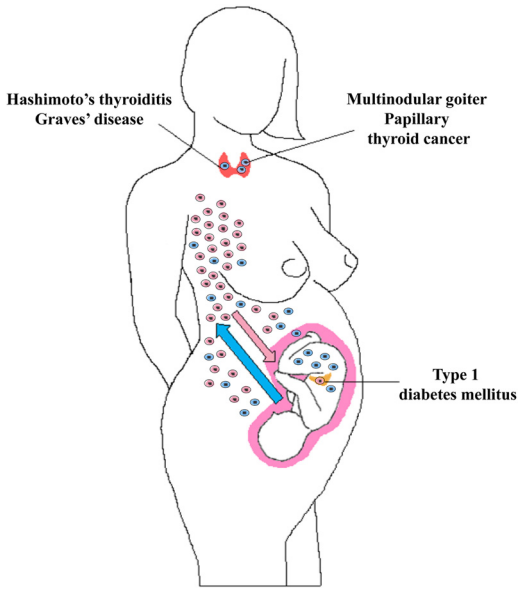

FIG. 2. The endocrine diseases for whom data on microchimerism have been reported to date. Fetal microchimerism has been studied in both AITD and non-AITD, whereas maternal microchimerism has been involved in T1D.

Thyroid Disorders

Autoimmunity

FCM has been extensively studied in autoimmune thyroid diseases (AITD). Indeed, autoimmune thyroiditis appears to be modulated by pregnancy, with a trend to improve during pregnancy and to worsen after childbirth (85). The hypothesis that FCM could play a role in the pathogenesis of AITD was further supported by the finding of a significantly higher degree of microchimeric cells within the thyroid gland of women with Hashimoto's thyroiditis and Graves' disease, compared with women without thyroid autoimmunity (59, 60–62, 86). In particular, the first evidence of the presence of FCM in AITD derived from a study on Hashimoto's thyroiditis patients, using a PCR-based semiquantitative technique for *SRY* gene detection. Male DNA, of presumed fetal origin, was found in eight of 17 patients and in one of 25 nodular goiter controls. This strong evidence of an etiological role of microchimerism in the pathogenesis of Hashimoto's thyroiditis (59) was further confirmed using a quantitative real-time PCR, which allowed quantification of the microchimeric cells in numbers between 15 and 4,900/100,000 cells (60). Further insights came from studies performed using a FISH approach with a Y-chromosome-specific probe. In

specimens obtained from women who had a previous male pregnancy before being submitted to thyroidectomy for a variety of thyroid diseases, male cells were found to be sparsely spread throughout thyroid samples, rather than accumulating within a lymphocytic infiltrate. Fetal cells were found more frequently in patients with Hashimoto's thyroiditis (60%) and in those with Graves' disease (40%) than in follicular adenoma cases (22.2%) (62). Consistent data have been obtained by PCR-ELISA assay for the detection of the *SRY* gene in Graves' disease cases, which were found to harbor FMC in a percentage significantly higher than control adenomas. It was also shown that male cells can be detected in the peripheral blood of either Graves' disease patients or healthy women, demonstrating that circulating microchimeric cells are a common finding in women of reproductive age (61). Additional data have been obtained in a murine model of experimental autoimmune thyroiditis (87), where fetal immune cells (T cell and dendritic cell lineages) were found to accumulate in maternal thyroids.

Interestingly, the AITD susceptibility markers, HLA DQA1*0501-DQB1*0201 and DQB1*0301, are more common in mother-child pairs positive for FCM. This finding raises the unanswered question of whether these histocompatibility alleles predispose only to thyroid autoimmunity or to FCM as the first step and to autoimmunity as a secondary event (62). Moreover, it cannot be excluded that the higher prevalence of FCM in autoimmune patients with respect to controls could also be due to an abnormal passage of fetal cells to the mother due to a placental leakiness related to a preexisting subclinical autoimmune disease (59).

If fetal microchimerism has a role in the pathogenesis of AITD, one would expect thyroid autoantibodies to be higher in women with previous pregnancies compared with nonparous women, but to date only one case-control study indicated parity as a potential risk factor for AITD (88). By contrast, three large epidemiological community-based studies failed to demonstrate an association between pregnancy, parity, abortion, and the presence of thyroid autoantibodies or thyroid dysfunction, indicating that FCM could be a marginal phenomenon (89–91). Nevertheless, HLA genetic compatibility between fetal and maternal cells might be a more crucial risk factor than the number of pregnancies in the initiation of the autoimmune reaction by *fmcs* (62).

Goiter and thyroid cancer

FMC have also been reported in non-AITD (*i.e.* benign adenoma, multinodular goiter, and thyroid cancer), and less frequently in normal thyroid glands. In particular, in nodular goiters, male cells were found either isolated or in clusters and appeared to be fully differentiated and to form part of thyroid follicles, indistinguishable from the rest of the maternal thyroid. This finding indicates that *fmcs* could resemble the host cell phenotype, probably due to the acquisition, migration, and differentiation of fetal stem cells (86). Our group has been involved in the study of FCM in thyroid cancer. First, in a series of 40 women affected with papillary thyroid cancer (PTC) and with a previous male pregnancy, the presence of FCM was investigated at the tissue level. Male cells were detected by FISH in a high proportion of tumors (47.5%), whereas they were always absent in tumor tissue from patients with only female offspring or nulliparous. Moreover, *fmcs* were significantly more represented in neoplastic thyroid tissue (about 10 per million maternal cells) than in normal sections (0–3 per million), consistent with findings obtained in other solid tumors (76, 79). Based on these initial data, a possible role in the protection toward the tumor was hypothesized, and further studies on the immunophenotypization of male cells were carried out. The immunophenotyping showed the presence of male cells expressing thyroglobulin (Tg) both in tumor and normal tissues. Interestingly, male cells positive for Tg are interposed between maternal follicular cells to form thyroid follicles (Fig. 1B). Differently, male microchimeric cells stained with the CD45 antigen were detected at a lower percentage and only in tumor sections (Fig. 1, C and D). These findings are in accordance with previous data on cervical cancer, showing the presence of fetal cells positive for CD45 and for cytokeratin and suggesting that fetal male cells are able to differentiate toward hematopoietic and epithelial phenotypes. Microchimeric cells negative for both markers were found more frequently in normal tissues than in tumors and were regarded as harboring "progenitor-like" properties able to transdifferentiate in different cellular types. Further studies were aimed to immunophenotype Tg and CD45-positive cells to identify their function by using the staining with major histocompatibility complex II (MHCII), which is a marker of antigen-presenting cells (APC). Interestingly, the aberrant expression of MHCII antigen has been shown to be triggered by oncogenes, such as *ret*/PTC, being specific of tumoral follicular cells that could thus be regarded as APC. Tg^+ male cells resulted negative for MHCII antigens, arguing against a transformed phenotype, whereas Tg^+ female cells were, as expected, $MHCII^+$. On the other hand, $CD45^+$ male cells were negative for MHCII staining, not supporting a role as APC, which can be hypothesized instead for $CD45^+$ female cells that resulted as $MHCII^+$. Consistent with these findings, we hypothesized that $Tg^+/MHCII^-$ male cells could have a role in tissue repair and that $CD45^+/MHCII^-$ male cells could be NK cells with a role in the initiation of a cytotoxic reaction toward mater-

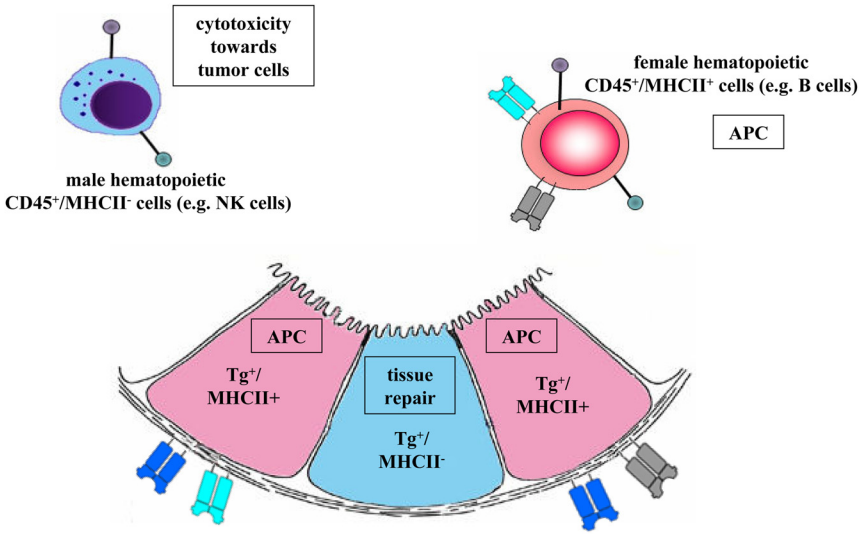

FIG. 3. PTC: immuno-FISH experiments using specific X and Y probes and antibodies against Tg, CD45, and MHCII led to the identification of epithelial and hematopoietic cells with a supposed different role (reported into *squares*). Female $Tg^+/MHCII^+$ follicular cells are neoplastic cells with a role as APC. Male microchimeric cells interposed between female cells are Tg^+ but $MHCII^-$ and are supposed to have a function in tissue repair. A role as APC can also be hypothesized for female $CD45^+/MHCII^+$ cells, whereas microchimeric male $CD45^+/MHCII^-$ cells could be NK cells with a cytotoxic effect toward neoplastic cells.

nal malignant cells, on the whole indicating a protective role of microchimerism in thyroid cancer (92) (Fig. 3). Nevertheless, $CD45^+/MHCII^-$ male cells could also be regarded as macrophages, with a possible role in tumor development as already reported for tumor-associated macrophages (93).

Data on tumor tissues were subsequently extended at the peripheral blood level, using a highly sensitive technique able to identify one male cell per 10^6 female cells, in a case-control study including a group of women affected with PTC with at least one previous male pregnancy and in a matched group of healthy females. The frequency of *fmcs* in the circulating mononuclear cells was found to be significantly lower in the group of PTC women than in healthy controls (94). These results were consistent with findings in other neoplasms (75, 77, 78) and suggested that *fmcs* could have a protective role against the development of thyroid neoplasia. Moreover, when we extended the study at the tissue level, we found that the majority of patients were either negative in the blood and positive in the tissue or positive in the blood level and negative at the tissue level. This finding further supported the hypothesis that *fmcs* could engraft in maternal lymphoid organs and bone marrow niches and could migrate through the circulation to reach diseased or injured areas where they could differentiate to repair and regenerate damaged tissues.

Diabetes

As reported above, AITD studies focused on FCM, whereas T1D has been mostly related to MCM. In particular, using a panel of quantitative real-time PCR assays targeting NIMA, the prevalence of circulating maternal cells was found to be significantly higher in T1D patients (51%) than in unaffected siblings (33%) and in unrelated healthy subjects (17%). Interestingly, the increased *mmcs* levels in T1D patients were not associated with the susceptibility haplotypes DQB1*0201-DRB1*03 and DQB1*0302-DRB1*04, thus excluding that maternal cells could be a source of susceptibility HLA genotypes. However, it was observed that patients who inherited from the mother the T1D-associated DQB1*0302-DRB1*04 haplotype had MCM more frequently than those inheriting the haplotype from the father (70 *vs.* 14%). Finally, no correlations were found between the levels of microchimeric cells and the gender, age, and time from disease onset (34).

More insights into the possible role of *mmcs* in this disease have been obtained by immuno-FISH and confocal imaging studying pancreatic tissues from male patients and normal controls. Maternal cells were found to be arranged in small groups or clusters close to or within islets, suggesting their active replication, and were found to produce insulin. In particular, *mmcs* were present at higher levels in insulin-positive islets, whereas no microchimeric cells positive for CD45 were found in pancreatic tissue (34, 95). Female islet β-cells corresponded to the 0.39–0.96% of the total number of islet β-cells in T1D patients, whereas they were extremely rare in pancreases from non-T1D cases. The precise role of female islet cells in diabetic male patients has not yet been elucidated, but it has been hypothesized that they could be targets of autoimmunity. In this case, the role of MCM would be detrimental. Alternatively, *mmcs* could contribute to the beneficial regeneration of the β islets of the host.

Conclusion and Perspectives

The literature data herein reviewed indicate that microchimerism is an interesting and emerging phenomenon. There is some evidence that microchimeric cells, both of maternal and fetal origin, are present in normal subjects and in autoimmune and nonautoimmune diseases. In Hashimoto's thyroiditis and Graves' disease, FCM could have a role in triggering the autoimmune process, as pos-

tulated for several autoimmune disorders. In thyroid cancer, *fmcs* have been found to be able to differentiate in epithelial cells expressing Tg and in hematopoietic cells. The high plasticity of microchimeric cells has been observed in other human cancers and strengthens the hypothesis that they could actually be progenitor elements, engrafting the maternal bone marrow during pregnancy and moving to the diseased areas to destroy tumoral cells and to repair thyroid follicles. Finally, the elevated levels of circulating *mmcs* in patients and the finding of chimeric islet indicate that MCM could be involved in the pathogenesis of T1D or in the restoration of the function of the injured pancreas. Further studies are mandatory to go thoroughly into the phenotype of the microchimeric cells, either maternal or fetal, to get more insights about their role in human health. More importantly, a possibility exists for exploiting acquired microchimeric cells to a therapeutic benefit, based on their transdifferentiation properties toward different cellular lineages and their regeneration ability.

Acknowledgments

Address all correspondence and requests for reprints to: Laura Fugazzola, M.D., Department of Medical Sciences, University of Milan, Endocrine Unit-Padiglione Granelli, Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda, Via Francesco Sforza, 35, 20122 Milan, Italy. E-mail: l.fugazzola@ policlinico.mi.it, or laura.fugazzola@unimi.it.

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