Fetal microchimeric cells in autoimmune thyroid diseases
Harmful, beneficial or innocent for the thyroid gland?

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Autoimmune thyroid diseases (AITD) show a female predominance, with an increased incidence in the years following parturition. Fetal microchimerism has been suggested to play a role in the pathogenesis of AITD. However, only the presence of fetal microchimeric cells in blood and in the thyroid gland of these patients has been proven, but not an actual active role in AITD. Is fetal microchimerism harmful for the thyroid gland by initiating a Graft vs. Host reaction (GvHR) or being the target of a Host vs. Graft reaction (HvGR)? Is fetal microchimerism beneficial for the thyroid gland by being a part of tissue repair or are fetal cells just innocent bystanders in the process of autoimmunity? This review explores every hypothesis concerning the role of fetal microchimerism in AITD.

Autoimmune Thyroid Diseases

Autoimmune thyroid diseases (AITD) are the most prevalent autoimmune disorders affecting up to 5% of the general population.[1,2] The two most common forms of AITD are Graves disease (GD) and Hashimoto's thyroiditis (HT). Although HT and GD are multifactorial diseases where genes and environmental factors influence the onset and development of the disease,[3] fetal microchimeric cells have been proposed to play a functional role in the pathogenesis of HT and GD.[4-10]

Fetal Microchimerism

AITD has a marked female predilection with a female: male ratio of 10:1. Moreover, in women, the disease tends to be more prevalent between the ages of 30 and 50 y and is often detected in the years following parturition.[11-13] As studied by Jansson et

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al.,[14] almost 2 out of 3 women who develop GD, have a postpartum onset, suggesting an important role of immunomodulatory events following delivery. The presence of fetal microchimeric cells in the maternal thyroid gland, which could become activated in the postpartum period once the maternal immune suppression is lost, could indicate an important role of fetal cells in the pathogenesis of AITD.[15] Moreover, HT and GD are similar to Graft vs. Host disease occurring after hematopoietic cell transplantation, an iatrogenic form of chimerism.[16,17]

During pregnancy, fetal cells cross the placenta and enter into the maternal circulation.[18,19] The mother becomes microchimeric.[6-8] Once fetal cells take up residence in maternal tissues[20-22] such as the thyroid gland, they may survive without being destroyed due to maternal immune adaptations during pregnancy.[23] This immune deviation during pregnancy may remain for a few months after delivery,[24] allowing fetal cells to establish themselves and to survive the postpartum period.[25] Under normal circumstances, most fetal cells are lost during this time.[26] However, fetal cells have been detected 27 y postpartum,[27] which indicates incomplete elimination of fetal cells.[24] Circulating fetal microchimeric cells in maternal blood have been described in patients with autoimmune thyroid diseases,[4,9] systemic sclerosis[28-31] and multiple sclerosis.[32] Fetal microchimeric cells have also been found in thyroid glands from patients with GD[7,9] and HT,[6,7,10] in labial salivary glands and skin lesions of patients with systemic sclerosis,[22,33-36] in affected tissue in localized scleroderma,[37] in cervical tissue of patients with cervical cancer,[38] in liver of patients with primary biliary cirrhosis[39] and in synovial tissue of patients with rheumatoid arthritis.[40] A certain HLA compatibility between mother and fetus may have consequences for the type or number of fetal cells that persist in the mother.[41,42] Mothers and their offspring share one HLA haplotype and most often differ for their other haplotype because HLA genes are highly polymorphic. However, sometimes a mother and child have similar HLA alleles on their non-shared HLA-haplotype.[16,43] In addition, the immunogenetic susceptibility markers HLA DQA1*0501-DQB1*0201 and DQB1*0301, more

Table 1. Studies describing fetal microchimerism in AITD

Author	(Autoimmune) Thyroid Disease or Healthy	Biological material	Technique	% of women positive for fetal cells (n/total)	Number of fetal cells/number of maternal cells
Lepez et al.[4]	HT	Blood	FISH and repeated FISH	100% (7/7)	7–11/1,000,000
	GD			100% (4/4)	14–29/1,000,000
	Healthy			90% (9/10)	0–5/1,000,000
Renne et al.[7]	HT	Paraffin-embedded thyroid tissue	FISH	60% (15/25)	1–6/section, CD45+ (no thyrocytes)
	GD			40% (6/15)	ND
	Thyroid adenoma			22% (2/9)	ND
Klintschar et al.[6]	HT	Paraffin-embedded thyroid tissue	qualitative PCR SRY and Amelogenin	47% (8/17)	ND
	Nodular goiter			4% (1/25)	ND
Klintschar et al.[10]	HT	Paraffin-embedded thyroid tissue	qualitative PCR of DYS14 of Y chromosome	38% (8/21)	15–4900/100,000
	Multinodular goiter			5% (1/18)	182/100,000
	Healthy			0% (0/17)	ND
Ando et al.[9]	GD	Paraffin-embedded thyroid tissue	PCR-ELISA SRY	20% (4/20)	ND
	Thyroid adenoma			0% (0/6)	ND
	GD	Fresh-frozen thyroid tissue		85% (6/7)	14–295/100,000
	Thyroid adenoma			25% (1/4)	17/100,000
	GD	Blood		47% (8/17)	1–10/100,000
	Healthy			28% (4/14)	1–87/100,000
	Polycystic ovary syndrome never pregnant			0% (0/16)	0/100,000
Srivatsa et al.[8]	Various thyroid disorders, without documented male children	Paraffin-embedded thyroid tissue	FISH	44% (4/9)	1–165/section, individual or in cluster
	Various thyroid disorders, with male children			63% (12/20)	
	Healthy controls			0% (0/8)	ND

ND, not determined.

frequently observed in patients with thyroid autoimmunity, are also more common in patients of mother-child pairs with fetal microchimerism.[44]

During pregnancy, fetal trophoblasts, nucleated erythrocytes, T and B lymphocytes, monocytes, natural killer (NK) cells and hematopoietic progenitor cells (CD34+ or CD34+CD38+ cells) have been detected in the maternal circulation.[27,45] Fetal cells in pregnant mice express both progenitor and differentiated cell markers.[46] To persist after delivery, fetal microchimeric cells must have the ability for long-term engraftment in the maternal host and therefore must share properties with stem cells, such as unlimited self-renewal ability and plasticity for multilineage differentiation.[47] These cells were termed pregnancy-associated progenitor cells (PAPCs).[20] Many authors described the transfer of fetal hematopoietic progenitor cells,[27,48] fetal mesenchymal stem cells[49,50] or endothelial progenitor cells[51] to the mother. They can represent a long-term reservoir of stem cells with multilineage potential.[47,52]

Fetal microchimerism in AITD. Fetal cells have shown to be more common in thyroid glands[6-10] and in blood[4,9] of patients with AITD compared with healthy controls or patients with an benign adenoma or nodular goiter. Results of these studies are shown in **Table 1**. However, as shown by Ando et al.,[9] data

obtained on paraffin-embedded tissue are difficult to compare with data obtained on fresh-frozen material as paraffin-embedded tissue is subject to DNA-fragmentation. Moreover, techniques used to study fetal microchimerism, Fluorescence in situ Hybridization (FISH), qualitative and quantitative PCR, have different sensitivities influencing the results of the studies.[5,9]

In patients without history of male full-term pregnancy, male microchimerism has been found in blood and in the thyroid gland.[9,53] Abortion or undetected miscarriage can however also lead to microchimerism as transfer of microchimeric cells starts at the fourth week of pregnancy.[54] Studies investigating the occurrence of unrecognized miscarriages have reported that the rate of pregnancy loss prior to the first missed period is approximately 22–30%.[55] Moreover, other sources of microchimerism, natural and iatrogenic, have been described. Not only do fetal cells cross the placenta and enter into the maternal circulation during pregnancy, but due to a bidirectional transfer between the mother and the fetus, maternal cells can also enter the fetal circulation. The latter has been described in tissues of patients with different diseases such as type 1 diabetes.[56-58] Other naturally acquired sources of microchimerism include by fetofetal transfer from an undetected vanishing twin,[59] or possibly from an older sibling. Iatrogenic sources of microchimerism include

blood transfusion and organ transplantation.[60] Results of studies describing fetal microchimerism in AITD must therefore be interpreted carefully.

Fetal microchimerism: harmful, beneficial or innocent for the thyroid gland? The consequences of long-term persistence of fetal microchimerism are difficult to assess to date. As fetal microchimerism in peripheral blood is an almost universal finding during normal pregnancy[61] and during the postpartum period,[4,42] the presence of fetal cells in the circulation does not indicate an aberrant immune response by the mother. An actual active role of fetal cells in autoimmune diseases has not yet been proven, only the presence of these cells in tissues affected by the disease. The mechanism that attracts fetal cells to migrate into the maternal thyroid gland has not yet been studied. Cytokines, chemokines, and adherent factors may be involved.[26]

There are a number of potential mechanisms by which fetal immune and non-immune cells may influence the autoimmune status of the mother. Harmful, beneficial as well as innocent effects have been assigned to the long-term persistence of fetal microchimeric cells.[62] In a harmful way, fetal cells can cause autoimmune thyroid disease by initiating a Graft vs. Host Reaction (GvHR), or the maternal host can initiate a Host vs. Graft Reaction (HvGR) against intrathyroidal fetal cells. In a beneficial way, fetal cells can offer help in tissue repair. Another hypothesis suggests that fetal cells are just present in the thyroid gland as innocent bystanders.

Harmful

It is possible that fetal cells themselves play an active role in determining the maternal immune repertoire. Postpartum, fetal immune cells can interact with maternal cells and may initiate the onset of postpartum AITD.[15,63] Presence of fetal cells in the thyroid gland,[6-10] where the autoimmune reaction is taking place, supports this hypothesis.

Fetal cells could act as effector cells initiating a GvHR (hypothesis 1) or could be target of an HvGR (hypothesis 2). After delivery, when placental immune suppression is lost, fetal immune cells may become activated and initiate an autoimmune reaction based on HLA discrepancies. The activation of fetal immature T cells, monocytes, macrophages and NK cells and the production of inflammatory cytokines and chemokines are believed to initiate the autoimmune disease (hypothesis 1).[30,34] Alternatively, fetal cells could be recognized as partially allo-immune and give rise to an autoimmune reaction by a direct response of the maternal cells to the fetal cells or by molecular mimicry between fetal antigens and intrathyroidal maternal antigens (hypothesis 2).[17,64,65]

Hypothesis 1: microchimerism induces a graft vs. host reaction (GvHR). During pregnancy, circulating fetal cells do not initiate disease, which indicates the success of placental immune suppression. After pregnancy, once maternal tolerance against fetal cells is lost,[15] fetal cells could become activated due to an unknown factor. Triggers can be viral or bacterial agents, drugs or abnormal tissue proteins.[66] Accumulating evidence suggests that these activated fetal microchimeric cells initiate a local immune GvHR. Similarities between autoimmune diseases and Graft vs. Host Disease (GvHD) suggest a functional role for fetal microchimerism to initiate a GvHR resulting in AITD.

To be able to initiate a GvHR, three conditions must be fulfilled.[67] First of all, fetal cells have to be present at the site of the immune reaction. As fetal cells have already been detected in blood[4,9] and thyroid glands of patients with AITD,[6-10] this condition is fulfilled. Second, the microchimeric cells must be immunologically competent T or B cells. In blood of patients with HT, mainly fetal CD8+ cytotoxic T cells were detected.[4] In our opinion, these fetal cytotoxic T cells could cause cell death leading to hypothyroidism.[68] In patients with GD, the majority of fetal cells was found in the B cell fraction.[4] These B cells could possibly be activated by fetal CD4+ T cells, also detected in the blood of these patients. From our point of view, it can be presumed that fetal thyroid-reactive T cells could cause activation of thyrotropin receptor-reactive B cells, secreting TSHR-stimulating antibodies causing hyperthyroidism.[68] Thyroid auto-antibodies have already been described in blood.[69] These mechanisms are illustrated in **Figure 1**, upper left.

Even fetal progenitor cells have been shown in maternal blood and tissues subject to autoimmunity.[20,27,70] It is possible that these progenitor cells develop in the maternal thymus and bone marrow into respectively functional T and B cells, as shown in mice,[71] and migrate into the maternal thyroid gland where they start an immune reaction. However, some level of histocompatibility is necessary to survive positive and negative selection in the thymus and periphery. In systemic sclerosis (SSc), HLA compatibility between mother and fetus has already been shown,[42] as well as fetal CD3+ T cells[34] and CD4+ T cells.[28] It is possible that a mother is heterozygote for certain HLA loci and fetal cells homozygote, upon which fetal cells will be tolerated by the mother, while the fetus may recognize the non-shared haplotype and starts an immune reaction against maternal cells.

Third, microchimeric cells must recognize the cells of the host as foreign. In patients with SSc, in contrast to controls, CD28 stimulation of peripheral blood mononuclear cells caused an increase in the amount of fetal cells.[29] T cell clones have been isolated from female patients with SSc which turned out to be self-reactive and appeared to be male in origin. These clones produced higher concentrations of IL-4 than control clones did.[36] These results suggest that the fetal cells were immunologically active and able to proliferate, and that one of the immune targets of these fetal immune cells were maternal antigens. This has to be confirmed for AITD.

An argument against this hypothesis is the low concentration of the fetal cells in the maternal circulation,[4,6] and that only a part of all patients with AITD show microchimerism in their thyroid gland.[6-10] In patients who appear to be negative however, it is possible that fetal microchimeric cells are not detectable by the methods used, that microchimeric cells originate from another (natural or iatrogenic) source or that the clinical context of the studied samples is not properly described. It is also possible that only female fetal cells, provoking the immune reaction, are present.[6] Our study of microchimerism in blood of patients with
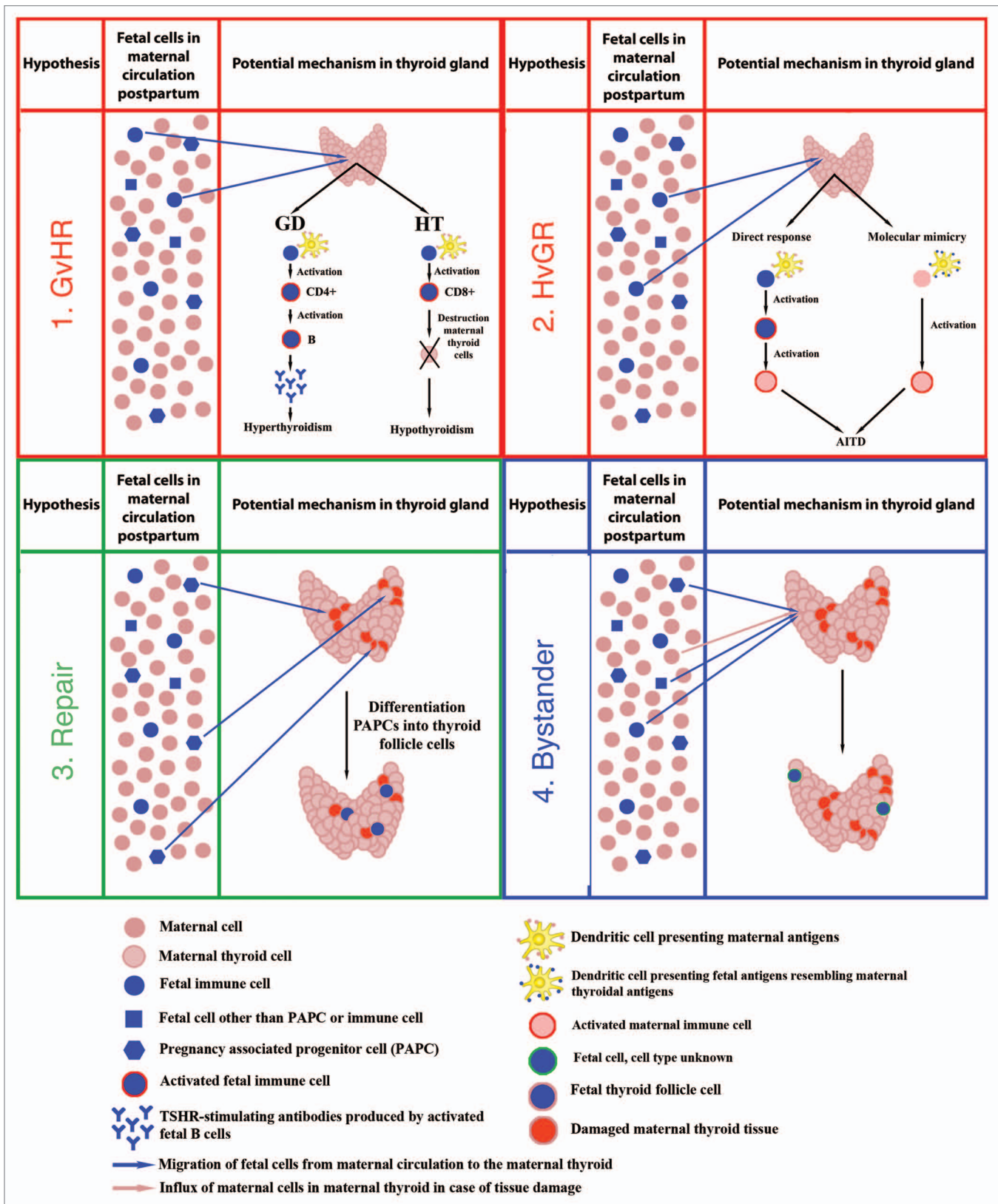
Figure 1. Potential mechanisms of harmful (red), beneficial (green) and innocent (blue) microchimerism in the thyroid gland.

AITD however, showed fetal cells in all patients with an AITD. Taken together, these data suggest a potential role of fetal cells in the pathogenesis of AITD.[4,6]

Hypothesis 2: microchimerism induces a host vs. graft reaction (HvGR). Alternatively, fetal cells could initiate AITD by being the target of a HvGR.[17] Fetal microchimeric cells have to be recognized by the mother as foreign. Because fetal cells contain paternal genes, the cells are semi-foreign to the mother. After delivery, once the immune tolerance mechanisms of the mother are no longer present, maternal cells may react against the paternal antigens of the intrathyroidal microchimeric cells.[6,8,10] Maternal cells could induce an immune reaction by a direct response to microchimeric cells or by cross-reactivity due to molecular mimicry,[72] both illustrated in **Figure 1**, upper right.

In case of a direct response to microchimeric cells, fetal cells can initiate a GvHR against maternal antigens upon which intrathyroidal maternal autoreactive T cells become activated which eventually leads to the maternal cells causing damage to the tissue. Another possibility is that fetal antigen presenting cells present maternal antigens to maternal immune cells resulting in an immune reaction from the mother against her own cells.[25] In molecular mimicry, maternal cells start an immune reaction against fetal antigens, but due to similarities between fetal antigens and maternal thyroidal self-antigens, autoimmunity to the thyroid occurs.[72]

Evidence for this HvGR hypothesis is shown in morphea, or localized scleroderma, where fetal microchimeric cells were mainly displaying an antigen-presenting role as B cells and dendritic cells.[37] In addition to this study, the maternal immune system is directly responsive to fetal cells since the level of microchimeric cells seems dependent on the level of fetal-maternal compatibility, at least in animal models.[73]

Beneficial

An argument against a harmful role of microchimeric cells is the fact that fetal cells have also been detected in healthy women without signs of autoimmunity.[7,8,43] Male cells have been detected in thyroid, lung, lymph node and skin in women with sons and in kidney, liver and heart in women with and without sons.[74] In the latter part, an unrecognized miscarriage of a male fetus could have been occurred. Presence of fetal microchimeric cells in affected and healthy women suggests that these cells do not play a direct role in triggering maternal autoimmune disorders. Instead of causing an autoimmune reaction, they could be a part of tissue repair.

Hypothesis 3: microchimeric cells repair injured tissue. Beneficial microchimerism has mainly been described in cases of tissue repair in cancer.[38,75,76] The first study on fetal microchimerism in cancer was performed by Cha et al.[38] In this study, male cells were detected in cervical tissue of patients with cervical cancer. However, Gadi et al.[77] were the first to make an association between the presence of fetal microchimerism and the influence of pregnancy in breast cancer. As breast cancer was less prevalent in parous women compared with nulliparous

women, fetal microchimeric cells may reduce the risk of developing breast cancer. Also, fetal microchimerism was less present in peripheral blood of women with breast cancer than in healthy women.[77] According to Dubernard et al.,[78] fetal cells are recruited from the peripheral blood into the damaged tissue to repair it if malignancies are developed during pregnancy. Fetal microchimerism has also been investigated in thyroid cancer, cervical cancer, lung cancer and melanoma.[8,38,75,76,79,80] The proposed role of fetal microchimerism in cancer has been a beneficial one, although a role in disease progression has also been considered as contributing to lymphangiogenesis or tumor growth.[80] In mice, fetal progenitor cells participate in inflammation and angiogenesis during wound healing.[81]

If fetal cells do have a function in tissue regeneration, two conditions must be fulfilled: they have to migrate to the damaged area and they have to show plasticity. During pregnancy, fetal progenitor cells have been detected in maternal blood and tissues.[23,27] They are capable of engrafting into maternal bone marrow.[50] After pregnancy, fetal microchimeric cells expressing tissue specific markers have been found in maternal tissues, both healthy and affected.[74] In humans, fetal hepatocytes,[20,82,83] cardiomyocytes,[21] endothelial cells, bone and cartilage[40] and intestinal epithelium[20] have been detected. In animal models, fetal hepatocytes,[84] kidney tubular epithelium,[84] neurons[85] and glia,[86] and cardiomyocytes[87] have been detected. These data suggest that fetal progenitor cells are capable of differentiating into tissue specific mature cells within injured maternal organs.[20,88] The diversity of cell types into which microchimeric cells can apparently differentiate, suggests that a very early stem cell type is involved, the pregnancy-associated progenitor cells (PAPCs).[20,47]

In patients with multinodular goiter, fetal epithelial cells were detected. 14% to 60% of these cells stained positively with cytokeratin, a marker of epithelial differentiation.[20] Fetal microchimeric cells were also observed in thyroid glands of patients with various thyroid disorders, such as adenoma and thyroid carcinoma, but were absent in necropsy specimens from normal thyroid glands. Fetal cells were detected both individually and in clusters. In one patient with a progressively enlarging goiter, fully differentiated male thyroid follicles closely attached to and indistinguishable from the rest of the thyroid were observed.[8] In some patients with papillary thyroid cancer, fetal microchimeric cells were detected in tumor tissue as single cells or in clusters.[75] Presence of microchimeric progenitor cells in the adult thyroid gland could be a potential source for tissue regeneration,[64,89] as shown in **Figure 1**, lower left. In women with papillary thyroid cancer, the prevalence of male DNA was reduced in peripheral blood compared with healthy women.[89] As in other cancers, the specific homing to the injured tissue may explain their reduced number in maternal peripheral blood.

Adapting the phenotype of the cells in the maternal tissue is however not sufficient to dedicate a role in tissue repair as its function has not yet been proven. Moreover, it can be hypothesized that after successful repair by chimeric cells, a HvGR to these microchimeric cells could still be induced at a later time, if an altered immunological response occurs.[72]

Innocent

Hypothesis 4: microchimeric cells as 'innocent bystanders'. A fourth hypothesis suggests that fetal microchimeric cells are innocent bystanders and do not participate in triggering or exacerbating AITD.[3]

It seems that a disease activity threshold is necessary for the significant detection of fetal microchimeric cells, suggesting that their presence is a consequence and not a cause of the disease.[47,52] It is possible that the microchimeric cells are equally distributed throughout the body. If tissue damage occurs, fetal cells will be attracted due to inflammatory infiltrates and the level of microchimerism in the diseased tissue will be higher compared with that of the healthy tissue, which would imply that there is no relation to the pathogenesis of the disease itself.[72] The relationship between inflammation and the presence of microchimerism could be indicative of this theory.[90] Fetal intrathyroidal cells, even immune cells, could therefore be a reflection of an ongoing local immune reaction without active participation.[91] Due to damage to the blood vessels, fetal cells could leak out into the damaged tissue without having an active role in tissue damage or repair.[54] This has been shown in **Figure 1**, lower right. Because pregnancy is very common and autoimmune diseases are quite rare, it is likely that only certain subsets of microchimeric cells have pathogenic potential, while most of them are only innocent bystanders.

An argument in favor of this hypothesis is the fact that three large epidemiological community-based studies failed to demonstrate an association between pregnancy, parity, abortion, and the presence of thyroid autoantibodies or thyroid dysfunction.[92-94]

Fetal cells would only be a remnant of pregnancy. In contrast, one case-control study indicated parity as a potential risk for AITD by showing higher thyroid autoantibody levels in women with previous pregnancies compared with non parous women.[95] However, HLA 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 fetal microchimeric cells.[7]

Conclusion

Microchimerism might have harmful, beneficial or innocent effects for the host depending on a number of factors including the origin of the microchimeric cells, type of cells acquired, tissue environment or type of malignancy. HLA haplotype and degree of differences between mother and child have the potential to affect the balance of beneficial vs. harmful consequences of microchimerism for the recipient.[96] In our opinion, the more fetal cells show similarities with the maternal cells, the more likely they have the potential to start a GvHR once they have been activated by yet undetermined mechanisms.

Whether the higher prevalence of microchimerism in thyroid autoimmunity is mere coincidence or is a marker for immune-mediated disease requires further investigation. Further research to characterize the fetal cells detected in blood and tissues is mandatory.

Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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