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Fetal microchimeric cells in blood and thyroid glands of women with an autoimmune thyroid disease

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Persistence of fetal microchimeric cells may result in the development of autoimmune thyroid diseases (AITD) such as Hashimoto thyroiditis (HT) or Graves disease (GD). In women, HT and GD show an increased incidence in the years following parturition. Although fetal cells have already been shown to be more common in the thyroid glands of patients with an AITD compared with controls, these cells haven't been described in blood of these patients. Our study detected fetal cells in blood of all patients with an AITD. Moreover, fetal cells were immune cells potentially capable of initiating a graft vs. host reaction and suggest a potential role of these cells in the pathogenesis of AITD. Our study indicates the value and need for further research in this field.

Keywords: fetal microchimerism, Hashimoto thyroiditis, Graves disease, autoimmune thyroid disease, FISH, real-time PCR

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During pregnancy, fetal cells cross the placenta into the maternal circulation[1,2] and can persist in the postpartum period in tissues such as the thyroid gland.[3] The mother becomes microchimeric.[4-6] The persistence of these fetal cells may result in the development of autoimmune thyroid diseases (AITD)[7,8] such as Hashimoto thyroiditis (HT) and Graves disease (GD). In women, HT and GD are more prevalent between the ages of 30 and 50 y and are often detected in the years following parturition.[9-11] Moreover, HT and GD are similar to graft vs. host disease occurring after hematopoietic cell transplantation, an iatrogenic form of chimerism.[8,12]

The presence of fetal cells can be investigated by real-time PCR or fluorescence in situ hybridization (FISH) using male-specific markers in women who had given birth to a son. While real-time PCR only indicates the presence of fetal cells and estimates the amount of fetal cells,[7] FISH gives an exact number.[5,6] Therefore, data obtained by real-time PCR are hard to compare with those obtained by FISH, as shown by Renne et al.[5] Using real-time PCR, the authors detected fetal microchimerism in 38% of the patients with HT, compared with 83% using FISH. The differences might be explained by different sensitivities of both techniques.[12] With real-time PCR, a single male cell can be detected within a background of 100,000 female cells[13] compared with one male cell within 2,000,000 female cells with FISH.[14] Therefore, our study used the latter technique to detect fetal cells in blood of women with an AITD.

Fetal microchimerism has already been shown to be more common in the thyroid glands of patients with AITD compared with controls.[4-6,15,16] Using real-time PCR, Klintshar et al. detected fetal cells in 47% of the thyroid glands of patients with AITD compared with 4% of women with nodular goiter.[4] Later, the authors 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.[15] This study identified male DNA in 38% of women with HT, in 5% of women with multinodular goiter and 0% of women with normal thyroid glands. In 20% of patients with GD, fetal cells were detected in paraffin-embedded thyroid tissue compared with 0% in women with adenoma.[16] However, examining fresh-frozen thyroid tissues, fetal microchimeric cells were detected in 85% of patients with GD

compared with 25% of patients with adenoma, showing that paraffin-embedded tissue is subject to DNA fragmentation. Using FISH, Renne et al.[5] found that 60% of women with HT, 40% of women with GD and 22% of patients with thyroid adenoma were positive for male fetal cells in the thyroid. Using the same technique, Srivatsa et al.[6] detected fetal cells in 72% of women with an AITD compared with 0% in healthy controls.

In contrast to thyroid tissue, fetal cells were detected in the blood of all patients with an AITD in our study.[14] The highest number of fetal cells was observed in patients with GD (14 to 29 fetal cells per million maternal cells), followed by HT (7 to 11) compared with the low number of fetal cells detected in healthy volunteers (0 to 5). This indicates a higher degree of microchimerism in AITD compared with healthy controls ($p < 0.05$). Moreover, significantly more fetal cells were detected in patients with GD compared with patients with HT ($p = 0.0061$).[14]

The etiologic consequences of fetal microchimerism are difficult to assess to date. Up to now, only the presence of fetal engrafted cells in AITD is proven, but not an actual active role of microchimerism in the autoimmune process. An argument against an active role is that only a part of all patients with AITD show microchimerism in their thyroid.[4-6,15,16] Nevertheless, in patients who appear to be negative, it is possible that fetal microchimerism is not detectable by the methods used or the fact that only female fetal cells are present.[4] In our study however, fetal cells were detected in all patients with an AITD. Taken together, these data suggest a potential role of these cells in the pathogenesis of AITD.[13,17]

If fetal cells indeed play a role in AITD, it is expected that fetal cells are pluripotent stem cells or immune cells. Male fetal CD34+ and CD38+ progenitor cells, capable of differentiating into immune competent cells,[3] but also mature fetal T, B and NK cells[18] have been isolated from the blood of women with scleroderma, an autoimmune disease of the skin. Cha et al.[19] suggested that fetal progenitor cells may differentiate in the maternal host and might alter immune function. Fetal immune cells may be reactive to maternal antigens[20] and, therefore, have the capacity to trigger graft vs. host reactions. It is possible that fetal cells also elicit an intrathyroidal graft vs. host reaction that leads to AITD.[5] Ando et al.[16] and Davies et al.[21] propose that after delivery, when placental tolerogenic mechanisms are lost, intrathyroidal fetal immune cells are activated and initiate a graft vs. host reaction against maternal antigens resulting in the activation of maternal autoreactive T cells which could eventually modulate AITD in the postpartum.

Our study focused on the presence of fetal B and T cells in blood of women with an AITD because these subsets are more likely to initiate or be involved in immune response. In patients with HT, mainly fetal CD8+ cytotoxic T cells were found.[14] One might speculate that these cytotoxic T cells could cause cell death leading to hypothyroidism.[22] In patients with GD, the majority of fetal cells was found in the B cell fraction.[14] These B cells could possibly be activated by fetal CD4+ T cells, also detected in the blood of these patients. Other cell types, not isolated during selection of T and B cells, were also found and are likely to be natural killer (NK) cells or hematopoietic progenitor cells capable of differentiating into immune competent cells.[18] One might speculate that thyroid-reactive T cells could cause activation of thyrotropin receptor (TSHR)-reactive B cells, secreting TSHR-stimulating antibodies causing hyperthyroidism.[22] These thyroid antibodies have already been described in blood.[23] Our study indicates the value and need for further research in this field.

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