INVITED COMMENTARY

Intrathyroidal microchimerism in Graves’ disease or Hashimoto’s thyroiditis: regulation of tolerance or alloimmunity by fetal–maternal immune interactions?

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Recent evidence suggests that uterine life sets the scene for many chronic diseases of adulthood, for which pregnancy has provided subtle but long lasting effects. Maternal diabetes mellitus (but not paternal) during pregnancy, for example, is a strong risk factor for insulin resistance and impaired glucose tolerance later in the life of the offspring (1). Such metabolic imprinting may also apply to obesity, hypertension and other components of the metabolic syndrome. Immunity is another example of early programming. The woman’s immune system during pregnancy undergoes alterations that help to tolerate the fetus during intrauterine life. These changes include an amelioration of pre-existent autoimmune disorders such as Graves’ disease and an exacerbation postpartum. Many autoimmune diseases remit during pregnancy and recur after childbirth, which is due to changes in both the humoral and cellular immune system. Murine in vivo experiments have demonstrated that pregnancy-specific factors such as glycoprotein 1a shift the T-lymphocyte repertoire from Thelper 1 to Thelper 2, and antigen presenting cells to an alternative mode of action resulting in anti-inflammatory action (2). Thymic education of the T-lymphocyte repertoire directs the tolerance level of an individual who can distinguish between self autoantigens in the context of a major histocompatibility complex (MHC) class II (extracellular) or class I (intracellular) molecule and foreign antigens. This distinction is vital in order to avoid potentially devastating disease and to combat infections, tumors and other pathogens. Such tolerance is achieved by deletion of autoreactive T lymphocyte clones and selection of others where signaling of autoimmunoregulator and antigen expression on thymic epithelium through lymphotoxin β receptor plays a crucial role (3). This selection occurs as early as during thymic development in utero.

Immune tolerance to the fetal implant allows the pregnant woman to accept circulating cells of the fetus. Such fetal cells comprise passenger leukocytes as well as mesenchymal stem cells that occur as early as the first trimester in the fetal blood (4).

Leakage of fetal cells into the maternal circulation occurs through the syncytiotrophoblast layer, the maternal–fetal synapse. In this environment, the maternal immune system recognises the fetal cell layer (which expresses HLA-G) and achieves a state of tolerance to the fetal discordant immunogenes such as HLA. Fetal cells are transferred to the mother during pregnancy and can be detected up to 38 years postpartum (5). Such fetal cells are detectable in peripheral blood collected by apheresis but also in organs and tissues affected by autoimmune disorders. Whether feto–maternal microchimerism is natural or potentially pathogenic is unclear at present. Whereas patients with scleroderma or Sjögren’s disease appear to have more detectable microchimerisms, other studies have shown no difference compared with normal controls where 16% of healthy females with sons have Y-chromosomal DNA detectable in blood in comparison with 22% to 26% in patients with scleroderma or connective tissue diseases (6).

Maternal cells traffic to the fetus during pregnancy and may persist into adult life (7). Persistent maternal cells carrying the surface markers CD34+, CD38+, CD3+, CD19+ and CD14+ have been reported in offspring 20 years after birth (5) and this phenomenon is significantly more frequent in juvenile inflammatory myopathy, where maternal microchimeras can be detected both in the circulation and in muscle tissue (8). Maternal microchimerism has been detected in a newborn thyroid autopsied at day 2 with multiple congenital abnormalities, but so far has not been reported in thyroid diseases (9). Juvenile thyroid autoimmunity would be a candidate for the study of possible maternal microchimerism.

We earlier showed that susceptibility to type 1 diabetes is not only conferred by inherited HLA genes but also that there is a significant difference between maternal not transmitted (not inherited) risk alleles influencing the predisposition in comparison with paternal influence (10). Such a difference had earlier been noticed in rheumatoid arthritis, where not inherited DR4 of mothers increased the risk in offspring (11). Although this observation has not been confirmed in other family data sets (12–14), it shows a potential mechanism of susceptibility acting in a subgroup of patients.

As early as 1945 it was shown that Rh− children of Rh+ mothers developed Rh antibodies less often,
indicating that the pre- or postnatal exposure may induce life-long tolerance (15, 16). Furthermore, polytransfused individuals less often develop HLA antibodies to those antigens they had encountered from maternal not inherited specificities. Also, transplant immunology has revealed that kidneys matched for maternally exposed but not inherited HLA specificities improves transplant survival in comparison with those of paternal origin (17). Therefore, the maternal–fetal immune interaction has a profound influence on the immune system both of mothers and offspring and helps to create immune tolerance relevant to organ transplantation but may also lead to graft-versus-host disease. It is therefore conceivable that such an interaction would also have an impact on thyroid autoimmunity.

The thyroid is a common target for autoimmunity that occurs from childhood to senescence. The high female preponderance and the high prevalence in women after childbirth suggest that pregnancy-related factors have a strong influence on thyroid autoimmune disorders such as postpartum thyroiditis, Graves’ disease and Hashimoto’s thyroiditis. These could be due to hormonal or X-chromosomal factors since Turner’s syndrome patients with an isochromosome X are more often affected by thyroid autoimmunity (18). Whether X-linked genes confer susceptibility to thyroid autoimmunity or trans-acting factors is still under investigation (19). Microchimerism could also play a role in this context. The discovery of Y-chromosomal DNA in blood or tissue samples of a woman has been taken as evidence for male cells in a female organism. Out of 50 donor apheresis samples of women that had been growth factor mobilised and CD34 enriched, a considerable proportion (34% and 48%) had Y-chromosomal DNA as quantitated by real-time PCR at the specific sequence DYS14 (20). Therefore, fetal microchimerism might contribute to graft-versus-host disease or autoimmunity, since the highest level of male DNA was detected in a woman with systemic sclerosis.

Sources of microchimerism are prior pregnancies including missed abortions, blood transfusions, bone marrow or organ transplants and unrecognised twins. The relevant microchimeric cells to autoimmunity are fetal pluripotent stem cells or T-lymphocyte progeny. The methods of detection include immuno-cytchemistry with cell-lineage-specific markers, single cell preparation and molecular PCR-based analysis to identify Y-chromosomal DNA in a female or HLA disparity at one locus. Whereas the PCR-based methods of Y-chromosomal detection merely demonstrate the presence of male cells, other methodologies such as immunocytochemistry, fluorescence in situ hybridisation and HLA typing identify the location, the cellular progeny and the immunogenetic properties of microchimers in a variety of tissues (21, 22).

Microchimerism in the thyroid has been shown for both goitrous and autoimmune thyroid disease (23–25). However, the prevalence of microchimerism in autoimmune thyroid disease has been higher than in non-autoimmune. Taken together, these observations raise the question whether the sequence of events in thyroid autoimmunity is at least partly due to alloimmunity rather than autoimmunity, which may start as early as pregnancy. This would imply that we need to develop strategies of protective immune regulation starting as early as during gestation. Further research is warranted to identify the mechanisms by which fetal microchimeric cells, long after pregnancy and childbirth, contribute to Graves’ disease and other thyroid autoimmunity.

References
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