T cells in placenta and skin: Their different functions may support the paradigm of microchimerism in systemic sclerosis

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This work is dedicated to the memory of E. Carwyle LeRoy who tragically passed away during his last trip to Italy. He strongly encouraged our work on gamma delta T cells, and gave us continuous and precious insights into the understanding of the disease’s pathogenesis.

ABSTRACT

Increased amounts of foetal cells persisting after pregnancy could be involved in the pathogenesis of systemic sclerosis (SSc) and other autoimmune diseases. Evidence suggests a specific role for a subset of T lymphocytes showing the γδ T cell receptor (TCR) at the fetal/maternal interface. γδ T cells significantly increase in the early pregnancy decidua and recognize trophoblast antigens, probably a highly evolutionarily conserved molecule such as Hsp60 or Hsp60-derived peptides, and are likely to suppress the maternal anti-foetal immune response via TGFβ production, thus contributing to pregnancy maintenance. The similarity between the presence of host γδ T cells in pregnancy decidua and in SSc skin suggests that the functional activities of these cells can be differentially modulated by several mechanisms including the nature of the antigen and the involved organs. To support pregnancy, the decidual microenvironment might induce a Th2 activity of host Vδ1+ T cells. On the contrary, either the presence of foetal cells in the skin of SSc patients or an as yet unidentified stimulus (i.e. infections), may trigger Vδ1+ T cells toward the Th1 phenotype with the subsequent activation of cytotoxicity and modulation of the cytotoxic α/β acquired T cell response.

On these grounds, understanding the mechanisms which prevent the maternal immune system from rejecting a semiallogenic foetus could be helpful to understand the development of some autoimmune diseases, and potentially to develop new targeted therapeutic strategies.

Like the mythologic chimera, the presence of genetically different cells in the same individual has been called chimerism. When low levels of donor cells are present the term “microchimerism” is applied. It is well known that donor-derived hematopoietic cells may be passively transsered to the recipient during solid organ transplantation and successively detected as resident cells many years afterwards. Under certain conditions, spontaneous microchimerism may even be essential for the development of immunological unresponsiveness to transplant organs.

During pregnancy, there is bidirectional traffic between the mother and foetus. Foetal stem cells carrying paternal human leukocyte antigens (HLA) traverse the placenta and may persist in the maternal circulation for decades. Similarly, maternal cells may pass into the foetal circulation and persist into adult life (1).

The recent findings that increased amounts of foetal cells which persist after pregnancy could be involved in systemic sclerosis (SSc) (2-4) and other autoimmune diseases (5-7) have raised the possibility that an allogenic process more than an autologous breakdown in self-tolerance may be involved in the pathogenesis of these disease (8).

Clinical and immunological features of SSc strikingly resemble chronic graft-vs-host-disease (GVHD), a known condition of chimerism that occurs in some patients after allogenic bone marrow transplantation (BMT), and that microchimerism could pathogenetically support these well-recognized similarities (9).

Recent studies suggest that pregnancy-associated microchimerism alone cannot explain the female predilection to SSc (10, 11). The microchimerism could be adverse within the context of other factors such as immunoactivity of both host and microchimeric cells, the transformati ve potential of the latter, the microenvironment, some infectious triggers and mainly the HLA gene relationship between donor and host which is of central importance in transplantation.
tion. It has been supposed that HLA-similar microchimeric cells could result in an impairment of host immunoregulatory pathways (12). Intriguingly, mothers with SSc had more often given birth to an HLA-DRB1 compatible child prior to disease onset than controls mothers (13). No association was observed for HLA-class I genes, suggesting that the DRB1 locus may be one of the factors influencing the regulation and/or pathogenicity of foetal microchimerism (13).

On these grounds, understanding the mechanisms which prevent the maternal immune system from rejecting a semi-allogenic foetus could be helpful to understand the development of some autoimmune diseases, and potentially to develop new targeted therapeutic strategies.

Pregnancy can result in a mutual state of tolerance between the mother and foetus. Although the foetus expresses paternally inherited antigens, it is not normally rejected. The foetus escapes the mother’s immune surveillance, and the mother becomes tolerant for her foetus. Thus, the uterine decidua seems to be an immunologically privileged site. The basis of this immunologic privilege is clearly not a simple anatomic barrier. It is well known that the barrier is likely to be functionally inhibitory for both macrophages and T cells, by producing inhibitory cytokines such as transforming growth factor-β. Some of these inhibitory decidual cells may be resident T cells.

Furthermore, extravillous (foetal) trophoblast cells lack polymorphic class I and II antigens, failing to express paternal HLA molecules and thus preventing the allostimulation of maternal cytotoxic cells (14). The extravillous part specifically expresses a non-polymorphic class I-like molecule, HLA-G, but no class II HLA molecules. The expression of the HLA-G gene during pregnancy may prevent foetal rejection by inactivating decidual (maternal) cytotoxic and natural killer (NK) cells, the predominant effector cells found in the uterus, through interaction with killer inhibitory receptors (15, 16).

In this light, increasing evidence suggests a specific role for a subset of T lymphocytes showing the γδ T cell receptor (TCR) at the foetal/maternal interface (17). Their specific location in hollow organs like the uterus suggests both their sentinel function and regulatory activities. They functionally show MHC-restricted and MHC-unrestricted cytotoxic activity (displaying both cytotoxic and NK activities), react to Heat shock proteins (Hsp) and generally are divided in two major subsets, the majority expressing the Vδ2 chain and the minority expressing the Vδ1 chain. Their activation does not require a professional antigen processing system and leads to the subsequently acquired αβ T cell response (18). γδ T cells significantly increase in the early pregnancy decidua and almost all of them express a selective V gene subset expansion displaying the Vδ6 chain of their TCR (19). They recognize trophoblast antigens, probably a highly evolutionary conserved molecule such as Hsp60 or Hsp60-derived peptides and are likely to suppress the maternal anti-foetal immune response via TGFβ production with a shift to Th2 cytokines pattern (TGFβ, IL4, IL10) of the decidual T cells, thus contributing to pregnancy maintenance (20). Furthermore, a recent report has suggested a regulatory role for γδ T cells in abortion, via the release of Th1 abortogenic cytokines (21), showing their ability to modulate their own cytokines production. Several lines of evidence in recent years reported by us and other groups suggest that γδ T cells are increased, activated and recruited via adhesion molecules in the involved tissues of SSc (22, 23). These lymphocytes may specifically kill endothelial cells (24), which seem to be the main target in the early phases of both GVHD and SSc (25). The similarity between the presence of host γδ T cells in pregnancy decidua and in SSc skin suggests that the natural activities of these cells can be differentially modulated by several mechanisms including the nature of the antigen and the involved organs. To support pregnancy the decidual microenvironment might induce a Th2 activity of host Vδ1+ T cells, leading to a transient state of tolerance toward the alloantigens expressed on foetal cells via Th2 cytokine production (20). On the contrary, either the presence of foetal cells in the skin of SSc patients or an as yet unidentified stimulus (i.e. infections), may trigger Vδ1+ T cells toward Th1 phenotype with subsequent activation of cytotoxicity and modulation of cytotoxic αβ acquired T cell response. In fact, a Th1 polarization of γδ T cells and an increase of their cytotoxic activity can be observed during SSc (26), in the context of a generally considered Th2 disease (27), suggesting that these cells may play an autonomous role.

Foetal cells could also potentially differentiate to allogenic immunocompetent cells (included γδ T cells), thus participating in the pathogenesis of SSc damage, mirroring the acute phase of GVHD in which both recipient and donor γδ T cells directly recognize and eliminate cells which have been damaged by cytokines released from infiltrating activated semiallogenic donor T cells. The downmodulation of these γδ T cells by specific MoAb strongly decreased the tissue damage (28). To confirm this hypothesis it has been recently observed that patients with dc-SSc have significantly more CD4+ microchimeric T cells than the controls, supporting the hypothesis that microchimeric CD4+ T cells may be involved in the pathogenesis of SSc (29).

An increased percentage of γδ T cells can be observed in the dermis of c-GVHD patients, particularly in the perivascular zone, when compared to healthy controls and BMT recipients without GVHD (30), similar to that which is observed in the skin of SSc patients (23). In a similar fashion, Vδ1+ lymphocytes in SSc patients could selectively recognize HSP60 expressed on the damaged endothelium by donor cells and directly kill these cells, thus initiating the process that will lead to disease evolution and consequent fibrosis.

The presence of microchimerism in healthy subjects suggests that all of these results must be interpreted with caution. Obviously, further studies are needed to clarify the exact role of microchimerism in autoimmune diseases. Paradoxically, microchimerism could
be either an incidental bioproduct of pregnancy without biological implications or could have some beneficial effects (explaining for example the improvement observed during pregnancy in mothers with rheumatoid arthritis in association with foeto-maternal HLA-disparity) (31), although the increased risk of SSc observed with the prior birth of an HLA-DRB1-compatible child and the possibility that foetal cells can transform themselves in differentiated cells, thus functioning as either a target or a trigger for autoimmune diseases (32) strongly argue against this interpretation.

Finally, these observations provide new perspectives on the role that γδ T cells and microchimerism might play in the pathogenesis of SSc and other autoimmune diseases, suggesting a potential new area for therapeutic interventions.

References