Editorial

Microchimeric cells: guardians or actors of immunity in scleroderma?

About 80% of all people with autoimmune diseases are women. Many suggestions have been proposed to interpret the reasons of such a gender difference: hormones, stronger immune response in women, different secretion of immuno-modulators according to sex...[1]. The recent knowledge that during pregnancy fetal cells pass through the placental barrier to reach the maternal circulation and inversely maternal cells reach the fetal circulation, more importantly that these cells and/or DNA could persist for decades in their respective hosts, gave new perspectives to interpret this gender gap. According to bi-directional traffic of cells during pregnancy, being a parous woman is a challenging status of being a chimera hosting unexpected semi-foreign fetus cells called fetal microchimeric cells as well as maternal microchimeric cells remaining after woman’s own intra-uterine life. Nevertheless immune balance has to be maintained.

Systemic sclerosis or scleroderma (SSc) is an autoimmune disease affecting mostly women in their post-partum years and having some clinical similarities with chronic graft versus host disease, a reaction affecting mostly women in their post-partum years and having some life. Nevertheless immune balance has to be maintained.

The recent knowledge that during pregnancy fetal cells persist in the host peripheral blood. Scaletti et al. [7] identified CD4+ auto-reactive T-cells by cloning T-cells from skin biopsies and peripheral blood of three women with SSc. Some of the autoreactive T cells exhibited a Y chromosome, presumed to origin from a male offspring, suggesting that these microchimeric cells are capable of an anti-host response. Another study found cellular Mc in SSc patients and controls, but the absolute amount of male DNA was higher in the patients, and the addition of an anti-CD28 costimulatory signal in vitro increased microchimeric cell levels in SSc PBMC but not in control PBMC [8]. These results support the hypothesis that fetal Mc cells have characteristics of T lymphocytes specific to maternal allogeneic antigens.

Finally, few authors analysed the immuno-phenotyping of Mc cells in SSc tissues. Among them, Johnson et al. [9] tested specimens obtained from autopsies of mothers with SSc or no autoimmune disease who have had sons. They analysed adrenal gland, heart, intestine, kidney, liver, lung, lymph node, pancreas, parathyroid, skin and spleen for male cells by fluorescence in situ hybridization (FISH). Male cells occurred in at least one site in each woman with SSc, most frequently in spleen, but never in pancreas, and not in non-autoimmune controls [9].

In this issue of *Rheumatology*, McNallan et al. report on the intriguing presence of microchimerism in skin tissues from localized scleroderma (LSc) and morphea patients. LSc is a connective tissue disorder limited to skin and subcutaneous tissue, which may share pathogenic processes with systemic sclerosis since abnormal collagen metabolism and autoimmunity are considered to be fundamental hallmarks of both.

From their considerable amount of microscopical analysis combining immunophenotyping and FISH methods on skin biopsies, they could conclude microchimeric cells might have had a real implication in the pathogenesis of LSc and morphea since tissues from LSc patients (affected or not) contain more chimeric cells per lymphocyte present than normal non-inflammatory control tissues. Secondly, chimeric cells have a distinct phenotype in affected tissues. The major distinctive population is primary organ derived: epithelial cells represent 42% of chimeric cells in affected tissues and are absent in unaffected tissues. Similarly, B lymphocyte chimeric cells follow the same pattern with 20% in affected tissues vs 3% in unaffected. Major Mc populations are also dendritic cells (DC), CD4 and CD8 T cells but their presence is rather linked to the disease than to the status of the skin. Amazingly none of the chimeric cells was found to be NK cell or macrophage.

The latter observation is surprising since several studies have shown that monocyte/macrophage cells infiltrate in clinically involved skin from patients with the systemic form of scleroderma and one could expect NK Mc cells. Moreover, our group has found male DNA (Lambert; 2000, unpublished work) in the NK subset from peripheral blood samples. One possible explanation is that what is seen in peripheral blood is not true in skin tissues.

Previous reports have mentioned microchimeric cells (either maternal or presumably fetal) in skin samples but very rare are the one in which phenotype was studied [10]. In McNallan et al.’s study, chimeric cells appear to be mainly epithelial cells rather than immune effector cells (i.e. CD8 etc.). This is not surprising...
since the epidermal layer of the skin is composed largely of specialized epithelial cells called keratinocytes. We could easily make the assumption that the epithelial cells they detect are indeed keratinocytes. Interestingly in a recent study in children presenting lesional skin with inflammatory conditions and more particularly in Pityriasis Lichenoides, maternally derived cells were mostly keratinocytes and not effecter cells [11]. Does this imply that multipotential stem microchimeric cells migrate to the host’s damaged tissue to repair? In this case, that would mean that we have a reservoir of multipotential stem microchimeric cells that would open the gate when ‘danger signals’ are sent.

Skin DC or Langerhans cells are antigen presenting cells of the epidermis originating from bone marrow progenitors. In the presence of antigens they become activated and migrate from the skin to the lymph nodes where they induce T cells responses, therefore, they function as sentinels of the epidermis and have an immunesurveillance function. The presence of Langerhans chimeric cells in LSc patients in McNallan et al.’s study again does not necessarily prove their participation in autoimmunity, but at the opposite, they could act as autoimmunity’s guardians. Moreover recent publications indicate that autoantigens in most autoimmune diseases act as dendritic cells chemoattractants in specific tissues [12, 13]. This could be the ‘danger signal’ discussed above.

Then why would the inflammation be maintained and autoimmune responses show up if we have natural guardians of autoimmunity? Among the hypotheses we could imagine that autoimmune responses subsequently develop only in subjects with impaired immunoregulatory function. The other, and non-exclusive, possibility is that microchimeric-tissue-transformed cells become the target of ‘auto’-immunity (because of its half foreign part) and participate in the process of inflammation.

Up to now, although many studies gave some pieces of the big puzzle ‘microchimerism and its role in autoimmunity’, there is no clear understanding whether microchimerism is an actor in the immune response or an inefficient guardian of autoimmunity. Immunophenotyping of chimeric cells is a necessary step to better understand the role of these cells. Future therapies will, depending on their role, respectively either eradicate or amplify microchimerism. This is also to note that a woman, principal target of autoimmunity, is hosting multiple sources of microchimerism and the good relationship between all those sources might be the sine qua non condition of a non ‘auto’-immune status. Therefore other microchimeric actors should also be analysed.

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