

Sjögren's syndrome

Microchimerism in Sjögren's syndrome

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The evidence of microchimerism both lends support to and raises doubts about its specific role in SS

The advent of molecular biology techniques has led to the recognition that cells travel in both directions between mother and fetus. Fetal stem cells traverse the placenta and may persist in the maternal circulation for decades. Similarly, maternal cells may pass into the fetal circulation and persist into adult life.¹ The persistence of genetically different cells in the same person has been called chimerism. When low levels of donor cells are present the term microchimerism is applied.

Clinical and immunological features of different autoimmune diseases strikingly resemble chronic graft versus host disease, which occurs in some patients after allogeneic bone marrow transplantation, a known condition of chimerism.² The recent finding that increased amounts of fetal cells, which persisted after pregnancy, can be detected in autoimmune diseases³⁻⁸ has raised the possibility that an allogeneic process rather than an autologous breakdown in self tolerance may be involved in the pathogenesis of these diseases.⁹

Microchimerism has recently been investigated in Sjögren's syndrome (SS),¹⁰⁻¹⁵ a disease in which some histological patterns mirror the lesions seen in chronic graft versus host disease. In this issue of the *Annals* Kuroki and coworkers present their data concerning the presence of maternal fetal microchimeric cells in the salivary glands and lung tissue from 56 female patients with SS, 36 with primary SS, and 20 with SS associated with another autoimmune disease.¹⁶ Using both nested polymerase chain reaction (PCR) and fluorescence in situ hybridisation (FISH) techniques, they showed that male DNA were present in 10/28 (36%) labial salivary gland (LSG) specimens and in 2/9 (22%) lung specimens obtained from patients with SS with at least one son, but not in their peripheral blood mononuclear cells (PBMC). No differences were found between the patients with primary and secondary SS. Furthermore, the male chromosome specific sequence was not detected in the samples (LSG and bronchoalveolar lavage fluid) obtained from controls. On these grounds, they

suggest that microchimeric cells have a role in the pathogenesis of SS.

In a recent paper reported by a French group which studied LSG biopsy specimens from 16 female patients with primary SS and 11 from patients with systemic sclerosis (SSc), a disease in which microchimerism can be detected, male DNA was not detected in any of 16 LSG specimens of primary SS¹¹; on the contrary, five (45%) of the 11 SSc specimens, regardless of the presence of secondary SS, were positive for microchimeric cells. In this study the sensitivity of PCR was high, because DNA from three male cells that was added to DNA extracted from a normal female LSG specimen was always detected. Thus, the authors conclude that the pathogenesis of the lesions in the target organs of primary SS may be unrelated to the presence of microchimeric cells.

"Mothers with SSc often have an HLA-DRB1 compatible child before disease onset"

Some other papers have been recently published whose goal was the identification of microchimeric cells in SS. Endo and coworkers, studying the PBMC of both patients with SS and those with SSc, by nested PCR, found no difference between controls and patients in either disease¹⁰; in addition, in salivary glands male DNA was detected in 11/20 women with SS, and fetal cells were clearly detected, by in situ hybridisation, in 3/8 patients with SS. These results are in contrast with the data for PBMC reported in this issue but agree with the results reported by Miyashita and coworkers, who did not find any difference between patients with SS and controls, and found a higher percentage of patients displaying male DNA positive cells, probably owing to the specific primers they used.¹⁵ On the contrary, no male DNA was found in the PBMC of patients with SS, by nested PCR and by combined in situ hybridisation and PCR, by Toda and coworkers.¹⁴

Thus, the studies on microchimerism in SS provide variable results. There are

both clinical and technical issues to keep in mind in evaluating these studies. Different groups of patients, both primary and secondary SS, are often included together in the studies. Furthermore, clinical data are not always available. Classification criteria may be different and several studies neither consider the disease activity of each patient nor mention the treatment. Some studies do not provide data on pregnancy history, and others do not correlate this information with microchimerism results. All these studies aim at obtaining evidence about the presence of microchimeric cells, but the results may be different in different target organs, or may vary depending on whether a target organ derives from early or late disease, and finally, the results may not be directly comparable—for example, deriving from PBMC and affected tissues. Technical variables are of equal significance. The studies assess fetal microchimerism by testing male DNA, but the specific Y chromosome sequence is variable. In fact, some Y chromosome sequences show cross reactivity with autosomal sequences. Multiple copy sequences are more sensitive than single copy sequences, although the latter can be easily adapted to quantitative assays. Nested PCR for extracted DNA is a highly sensitive technique and may explain some differences in the results, although it raises concern about contamination, especially for paraffin embedded samples, because paraffin baths are not systematically changed between different samples and previous nuclear material might have contaminated the solutions. Thus, studies of affected tissues may be more informative if techniques such as in situ hybridisation or FISH are used and expert readers are employed.¹⁷

The evidence for two way traffic in the placenta raises an important question about the immunological interplay between cells from both the child and mother, leading to the possible pathological consequences. Recent studies suggest that microchimerism associated with pregnancy cannot alone explain the female predilection to SSc,^{18,19} and maybe to other autoimmune diseases. The microchimerism might be adverse owing to other factors, such as immunoreactivity of both host and microchimeric cells, the transformative potential of the latter, the microenvironment, some infectious triggers, and mainly, the HLA gene relationship of donor and host, which is of central importance in transplantation. It has been suggested that a high HLA similarity between microchimeric and host cells, deceiving the host immunoregulatory pathways, might result in an impairment of the immune response against non-self components.²⁰ Intriguingly, mothers with SSc had more often given birth to an HLA-DRB1 compatible child before disease onset than

had control mothers. No association was seen for HLA class I genes, suggesting that the DRB1 locus may be one of the factors influencing the regulation and/or pathogenicity of fetal microchimerism.²¹

Presently, the evidence of microchimerism, due to persistent fetal or maternal cells in SS and in other autoimmune diseases, both lends support and raises doubts about its specific role. The presence of microchimerism in healthy subjects suggests that all this information should be viewed with caution. Paradoxically, microchimerism may be either an incidental biproduct of pregnancy without biological implications or may have some beneficial effects (the improvement, during pregnancy, seen in mothers with rheumatoid arthritis in association with fetomaternal HLA disparity),²² although the increased risk of SSc in women who have previously given birth to an HLA-DRB1 compatible child strongly argues against this interpretation. Furthermore, the unexpected cellular transformative potential which has been recently seen in several cell lines²³ might lead to very different interpretations of the data. In fact, microchimeric cells, in target tissues, might transform themselves into differentiated cells, functioning as either a target or a trigger for autoimmune diseases, or alternatively, have a restorative function in the tissue, possibly benefiting the host.

Finally, further studies are needed to elucidate the role of microchimerism in health and disease. Understanding the mechanisms which prevent the maternal immune system from rejecting a semi-allogeneic fetus would probably be helpful in understanding the development of some autoimmune diseases, and potentially helpful for developing new targeted therapeutic strategies.

ACKNOWLEDGEMENTS

The authors thank Dr EL Nelson for her continuous advice and helpful suggestions.

Ann Rheum Dis 2002;**61**:1039–1040

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