

Interdisciplinary Research in Chimerism

Autoimmunity, Reproduction, Cancer, Infectious Disease and Transplantation

Note: For a lay description of our work and this field please see "Your cells are my cells." JL Nelson. [*Scientific American* 298:72-79, 2008.](#)

Overview

Some cells are known to traffic from a mother into the fetus and from the fetus into the mother during pregnancy. Surprisingly, a small number of these cells persist in their respective hosts decades later. This phenomenon is referred to as *microchimerism*.

The shared goal of our interdisciplinary research team is to identify the good and bad consequences of microchimerism for human health and to utilize this knowledge to develop novel strategies for treatment and prevention of human diseases.

In addition to the long-term effects of microchimerism, we are studying immune system effects of maternal-fetal exchange during the course of pregnancy. We are doing this work for a number of reasons.

First, the autoimmune diseases rheumatoid arthritis and multiple sclerosis improve during pregnancy. Second, some complications of pregnancy are thought to have an immune basis. Third, studying pregnancy could lead to insights that are helpful for improving transplantation success because, although a fetus is genetically half foreign (genes inherited from the father), the mother does not reject and instead nourishes the growing fetus.

Autoimmune Disease

In 1996 we proposed that fetal microchimerism might in part explain the female predilection to autoimmune disease. In work that was reported in 1998 we discovered elevated levels of fetal microchimerism in the blood of women with scleroderma compared to healthy women.

This was the first study to look at microchimerism in an autoimmune disease. Subsequent studies found fetal microchimerism in internal organs and in skin affected by scleroderma. Ongoing studies in our research group investigate microchimerism in the autoimmune diseases rheumatoid arthritis, scleroderma, type 1 diabetes and primary biliary cirrhosis.

In 1999 we found that maternal microchimerism persists into adult life in individuals who have normal immune systems. Presumably this is due to engraftment with maternal stem cells. Stem cells can become multiple different types of cells. We therefore asked whether maternal cells can become part of the cells that make up tissues.

We found maternal cells in the hearts of infants who died from heart block due to neonatal lupus and most of the maternal cells were cardiac myocytes (heart muscle cells). Our theory is that the maternal cells are the target of an immune attack.

In other studies we found elevated levels of maternal microchimerism in patients with insulin-dependent (type 1) diabetes. In the pancreas we identified maternal cells that produce insulin (islet beta cells). In type 1 diabetes, for a number of reasons, we believe these cells are helping to repair damaged tissues.

Microchimerism has been studied by our group and by others in a number of different autoimmune diseases including systemic and neonatal lupus, myositis, multiple sclerosis, scleroderma, thyroiditis, primary biliary cirrhosis, Sjögren's syndrome and rheumatoid arthritis.

Women with rheumatoid arthritis often have their disease improve or even disappear during pregnancy. A beneficial role of fetal microchimerism is suggested by our finding that elevated levels of fetal microchimerism significantly correlated with pregnancy-induced amelioration of rheumatoid arthritis.

Reproduction

We are investigating microchimerism in complications of pregnancy, especially preeclampsia, a disorder characterized by high blood pressure in women in their third trimester of pregnancy, and in recurrent pregnancy loss. As noted above, we are studying the role of fetal microchimerism in women with rheumatoid arthritis who become pregnant because pregnancy often induces remission or improvement of rheumatoid arthritis.

Cancer

In hematopoietic cell (bone marrow or stem cell) transplantation donor cells provide an advantage against recurrent leukemia and other malignancies. By analogy, we asked whether fetal microchimerism might contribute to the protection from breast

cancer observed in women who have had children.

Supporting this possibility we found a significant decrease of fetal microchimerism among women with breast cancer compared to healthy women. Conversely the question of whether microchimeric cells sometimes "go bad" and result in malignancy is of interest as suggested in some anecdotal reports.

Infectious Disease

The T lymphocyte is a key determinant of immune reactions between a person's own cells and foreign cells. Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are characterized by critical deficiencies in CD4+ T lymphocytes. We are studying maternal microchimerism in patients with HIV and are looking at whether maternal microchimerism levels correlate with whether there is progression or non-progression to AIDS.

Transplantation

Transplantation results in chimerism (called "iatrogenic chimerism"). In hematopoietic cell transplantation, graft-vs.-host disease occurs more often if the donor is a woman with prior pregnancies. We tested female apheresis products and found they contained male microchimerism, consistent with the interpretation that fetal microchimerism contributes to graft-vs.-host disease.

In kidney, pancreas and islet transplantation we have tested serial serum samples and found that donor-specific microchimerism detection may become a useful non-invasive test for early rejection. Several other groups are now therapeutically exploiting the principles of naturally-acquired microchimerism in their selection of donors for transplantation.

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