See related article on pg 345

COMMENTARY

Microchimerism and Skin Disease: True-True Unrelated?

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Microchimerism, the stable presence of foreign cells in an individual, may result from trafficking during pregnancy or from organ or hematopoietic transplantation, and has been hypothesized to cause autoimmunity and certain skin diseases. Yet microchimeric cells are found in normal individuals and may be important to tissue repair. Thus microchimerism may be common, and finding microchimeric cells in diseased as well as normal tissue may be a "true-true unrelated" situation.

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Microchimerism and Cell Trafficking During Pregnancy

The word 'chimera' comes from a mythological animal that is a combination of lion, goat and snake. In modern biology, 'microchimerism' is the stable presence of low numbers of foreign cells in an individual. For instance, approximately 8% of identical twins are chimeric for each other's leukocytes because of a shared blood supply *in utero*. In single pregnancies, the placenta allows passage of maternal and fetal cells in both directions, which explains how fetal and maternal microchimerism can occur after pregnancy. Cord blood samples collected for transplantation contain up to 20% maternal cells by *in situ* hybridization and up to 40% maternal cells by PCR (Lo *et al.*, 1996). These foreign cells can persist in both mother and child, giving rise to microchimerism. Bianchi *et al.* reported that $CD34^+$ and $CD34^+CD38^+$ fetal cells were present in maternal circulation up to 27 years after pregnancy (Bianchi *et al.*, 1996). This microchimerism is more likely when the fetus is HLA compatible with the mother. Fetal microchimerism is not as well characterized but is an intriguing new area of investigation.

What types of cells are seen in microchimerism due to maternal–fetal exchange via the placenta? Highly differentiated cells such as fetal nucleated erythrocytes or placental trophoblasts in maternal blood are a useful marker of placental health. When an increased number of nucleated erythrocytes and trophoblasts are present in maternal circulation, abnormal placental barrier function such as in preeclampsia or fetal aneuploidy can also be present (Bianchi, 2000). These differentiated cells do not survive long in maternal circulation. However, fetal stem and progenitor cells can proliferate, differentiate and travel to various maternal tissues. Cord blood is an important source of fetal stem cells, which are known to have a mobile and plastic phenotype, and it is the likely source of cells in maternal microchimerism. Fetal hematopoietic stem cells, and presumably their progeny T and B lymphocytes, monocytes and NK cells, have been demonstrated in maternal circulation and tissue. Similarly, maternal stem cells can survive and proliferate in the tissues of offspring because of the two-way traffic of cells via the placenta.

Stem Cells

Multiple types of stem cells have been identified, and the list of stem cells in adult individuals continues to expand. Adult bone marrow contains hematopoietic stem cells, mesenchymal stem cells and multipotent adult progenitor cells that can form cells of all lineages: ectodermal, mesenchymal and endodermal (Grove *et al.*, 2004).

Many studies support the concept of transdifferentiation — the reprogramming of stem cells to differentiate into multiple different cell types appropriate to their local environments (Alonso and Fuchs, 2003). Thus the maternal–fetal exchange via the placenta, coupled with the enormous potential of stem cells to produce a variety of cell types, might produce a microchimerism of not only hematopoietic cells but also cells of all possible lineages, including skin cells.

Microchimerism and Transplantation

The study of microchimerism in transplantation biology allows manipulation of the variables and has led to some remarkable findings. Recipients of transplanted hematopoietic cells remain chimeric for donor and recipient immune cells for a long time after transplantation. Because bone marrow stem cells are diverse and plastic, other tissues also become chimeric for donor and recipient after bone marrow transplantation. Bone marrow-derived cells can contribute to tissue repair (skeletal muscle, cardiac muscle, liver, lung, kidney, central nervous system). Bone marrow-derived Y chromosome-positive keratin-positive cells can be found in skin of female recipients of bone marrow transplanted from male donors (Grove *et al.*, 2004).

Microchimerism also occurs in recipients of solid organ transplants (lung, liver and kidney). Starzl and colleagues proposed that organ engraftment is a form of partial tolerance that is dependent on leukocyte chimerism generated by 'passenger leukocytes' and stem cells in solid organ grafts (Starzl, 2004). In these situations, the microchimerism studied is of leukocytes, transmitted to the recipient via transplantation of passenger leukocytes in a solid organ such as intestine, lung, liver or kidney. Anderson and Matzinger studied microchimerism produced by passenger leukocytes in skin grafts in mice and found that the outcomes varied depend-

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ing mainly on the recipients' immunological maturity and on the antigenic differences. They concluded that donor cells could be either tolerogenic or immunogenic, depending on the conditions (Anderson and Matzinger, 2001). Therefore, the rules for the sequelae of microchimerism due to transplantation in humans are complex and are still being defined.

Microchimerism and Autoimmunity

What are the consequences of microchimerism? It has been proposed that microchimerism may lead to autoimmune disease in some individuals with a permissive genetic makeup. Autoimmune diseases in recipients of transplanted hematopoietic cells are well known. These include graft-versus-host disease, which can be lupus-like or scleroderma-like, Sjögren's syndrome, primary biliary cirrhosis, myositis, myasthenia gravis, hyper- and hypothyroidism and autoimmune cytopenias (thrombocytopenia, leukopenia, neutropenia). Disease in transplant recipients resembles that in individuals with the corresponding primary autoimmune diseases. The dysregulation of tolerance in the transplant recipient is thought to allow development of autoreactive T-cell clones, leading to autoimmune disease. Whether this results from microchimerism or simply from immunocompromise is not known.

The best-studied example of immune-cell microchimerism as a possible factor in primary autoimmune disease is scleroderma, which has a peak incidence in women after the childbearing years. Women with scleroderma are more likely than matched control subjects to have had an HLA-compatible fetus, and Y chromosome-positive cells can be found in fibrotic maternal tissue of women with scleroderma many years after delivery of a male baby (Artlett, 2005). Fetal microchimerism has been proposed as an explanation for scleroderma in males and children. This hypothesis for microchimerism as a cause of scleroderma is still in debate (Adams and Nelson, 2004).

Studies on other autoimmune disorders and in normal individuals have led to conflicting data. For instance, other autoimmune diseases with female predominance and a later onset do not have demonstrable microchimerism (Sjögren syndrome, primary biliary cirrhosis). Also, microchimerism can be shown in normal individuals and in non-autoimmune diseases such as infectious hepatitis and cervical cancer (Johnson and Bianchi, 2004). A case control study of individuals with a variety of connective tissue diseases led to the conclusion that microchimerism was common in all individuals, including normal ones (Gannage *et al.*, 2002). Bianchi, who first reported microchimerism in humans, concludes that multiple factors may determine whether microchimerism is a cause of disease: presence of foreign cells not only in blood but also in diseased tissue; tissue type; disease type; history of pregnancy; and immune status are all important (Johnson and Bianchi, 2004). To date, the connection between microchimerism and disease has not yet been definitively made. In fact, it has also been suggested that fetal cells may provide a renewable source of stem cells that can help with repair of maternal tissues, a positive rather than a negative outcome of microchimerism. One hypothesis is that stem cells may migrate to sites of inflammation and differentiate into cells that participate in repair. Thus, finding microchimeric cells in diseased tissue does not necessarily mean they were responsible for the initial injury.

Microchimerism and Skin Disease

In addition to scleroderma, other examples of microchimerism and skin disease due to the two-way traffic between mother and fetus have been proposed. For instance, it has been suggested that fetal cells in the maternal circulation produce the eruptions associated with pregnancy, such as pruritic urticarial papules and plaques. Pemphigoid gestationis is thought to be an immune reaction to the father's histocompatibility antigens on fetal cells in maternal tissue. Erythema toxicum neonatorum, which occurs in the first few days postpartum, may be a mild graft-versus-host disease-like reaction to maternal cells in the newborn.

A new paradigm — the presence of cells other than leukocytes in microchimerism as a possible factor in skin disease — is explored in the article by Khosrotehrani *et al.* in this issue (2006). The authors identified maternally derived cytokeratin-positive cells in archival paraffin-embedded sections of the skin of 11 of 12 male children with pityriasis lichenoides by fluorescent *in situ* hybridization with X and Y chromosome-specific probes. These maternally derived cells were also present in biopsies of skin from male control subjects without skin disease, but with a lower frequency (4 of 7) and density (approximately 20-fold lower in pityriasis lichenoides patients than in normal subjects).

The search for foreign cells in skin disorders has produced conflicting data. Inherent in these experiments are the technical difficulties of fluorescent *in situ* hybridization or PCR analysis in archived specimens. Background can be high and interpretation difficult. Often the sequences of interest are also found in normal control subjects. For instance, women with lichen sclerosis with and without squamous-cell carcinoma, vulvar Paget's disease, and normal vulvar skin who had male children were no different when Y chromosome sequences were evaluated by PCR in paraffin-embedded sections.

In summary, microchimerism not only of leukocytes but also of other cell types may be a common event in both normal and diseased tissues, a "true-true unrelated" situation. Host reaction to microchimerism as a cause of skin disease has not yet been definitively demonstrated.

CONFLICT OF INTEREST

The author states no conflict of interest.

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See related article on page 374

(P)PARsing Epidermal Development

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Overexpression of PPAR-α, a developmental transcription factor important in epidermal embryogenesis, in basal keratinocytes causes epidermal thinning when activated constitutively during development, but not if activated in adults; and lack of PPAR-α transiently delays stratum corneum formation within a window late in epidermal development (day 18.5 to birth). In contrast, pharmacologic activation of PPAR-α inhibits proliferation and induces differentiation in mouse epidermis regardless of developmental stage. Thus, PPAR-α is an important regulator of epidermal homeostasis.

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Nuclear hormone receptors are transcription factors that regulate the expression of target genes by binding to regulatory DNA sequences and interacting with co-regulatory protein complexes. A large molecular family of these receptors has been identified by homology searches. Soon after the sequences became available, individual receptors were characterized for their tissue distribution, ligand identity, patterns of target gene activation, and interaction with co-regulatory proteins. To better understand their physiological roles, individual receptors were tested in genetic animal models of loss and gain of function.

In this fashion, peroxisome proliferator-activated receptor-α (PPARα) was found to be a nuclear hormone receptor that is activated by fatty acid-derived ligands. Since Issemann and Green cloned mouse PPARα in 1990 and Sher *et al.* cloned its human homologue in 1993 (Issemann and Green, 1990; Sher *et al.*, 1993), several groups have generated mouse models of PPARα deficiency. Such animals displayed abnormal lipid and xenobiotic metabolism in the liver, heart, muscle, and kidney, indicating a role of PPARα in fatty acid oxidation and detoxification of xenobiotic compounds. Although PPARα was originally evaluated for its systemic activities, its expression was soon also noted in skin.

PPARα is present in both epidermis and dermis beginning at day 13.5 of development. Yet shortly after birth it becomes undetectable in the interfollicular epidermis, although expression persists in the hair follicles (Michalik *et al.*, 2001). Injury to adult murine skin, such as hair plucking, induces re-expression of PPARα in the adult interfollicular epidermis, and re-expression can also be observed in the edges of full-thickness wounds. Conversely, in PPARα-deficient mice, the early phase of wound healing is delayed, and this delay is retained when the deficiency is targeted to the epidermis only and not to the dermis (Michalik *et al.*, 2005). In pups lacking PPARα, a delay in stratum corneum formation is observed between day 18.5 of epidermal development and birth (Schmuth *et al.*, 2002), whereas in PPARα-deficient adults, only a modest decrease in the expression of involucrin, loricrin, and filaggrin persists. This indicates that other mediators can compensate for the absence of PPARα; that is, there is redundancy (Komuves *et al.*, 2000).

In this issue, Gonzalez *et al.* (2006) report on the skin phenotype of transgenic mice constitutively overexpressing PPARα in the epidermis. These mice die within 2 days after birth, presumably because of abnormal development of the tongue and mammary gland epithelia; overexpression of PPARα also results in epidermal thinning and sparse fur in these animals, which could contribute to the lethality. Importantly, corresponding to the transient effects of PPARα deficiency on developing epidermis, PPARα overexpression exerts its effects only during a developmental window; that is, after birth it does not cause the abnormalities.

Consequences of a gain of PPARα function have previously been studied using pharmacologic activators. In explants of developing rat epidermis, the expression of proteins required for epidermal differentiation (filaggrin, loricrin, involucrin) was stimulated by the PPARα agonist farnesol (Hanley *et al.*, 1997). In contrast to the VP16PPAR-α bitransgenic mice reported here (Gonzales *et al.*, 2006), there was a concomitant induction of the granular layer. These differences could be explained by differences between *in vitro* and *in vivo* experimental systems and by differences in the timing of the PPARα signal. Nevertheless, in adult mice, pharmacologic activation of PPARα induces epidermal differentiation, inhibits proliferation, and increases

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