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Review

Maternal microchimerism—Allogenic target of autoimmune disease or Normal Biology?☆

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Abstract

Chimerism is the state of cells from two distinct individuals living within one body. Fetal cells pass into a mother during pregnancy, where they may persist at low levels for years, creating a state of fetal microchimerism. At the same time, maternal cells pass into the fetus, leading to maternal microchimerism that can persist into adulthood. Hematopoietic stem cell transplantation also creates a state of chimerism, and can lead to a complication of chronic multi-organ inflammation called graft-versus-host disease, (GVHD). The similarities between GVHD and some autoimmune diseases like scleroderma, lupus and myositis suggest that chimerism may be involved in the pathogenesis of both. Maternal and fetal microchimerism in the blood and in tissues have been associated with autoimmune diseases. However, many healthy individuals harbor maternal and fetal cells. Human and animal studies have begun to elucidate the mechanisms for normal tolerance to maternal and fetal microchimeric cells, and how this tolerance may be broken in states of chronic inflammatory disease.

Keywords: Microchimerism; Autoimmune disease; Pregnancy

1. Introduction

During pregnancy maternal and fetal cells traffic back and forth between the mother and the fetus [1]. In the last decade evidence has accrued that fetal cells can persist in the mother for decades after the pregnancy [2,3]. Maternal cells also persist in the child well into

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adulthood [4]. The state of genetically distinct cells living long term in another individual is referred to as *microchimerism* (Mc): fetal cell persistence in the mother is termed *fetal microchimerism* (FMc) and maternal cell persistence in the child *maternal microchimerism* (MMc). As foreign cells, both FMc and MMc have been implicated in some autoimmune diseases, especially those that resemble graft-versus-host disease (GVHD) after stem cell transplantation [5–8]. FMc, hypothesized to contribute to the predisposition of autoimmune diseases in females, has been a significant area of recent research [3,9]. In patients who have never been pregnant, (children, males, and nulligravid females), MMc may present a source of foreign cells that initiate or perpetuate chronic inflammatory disease. Mc is a common phenomenon in normal biology, but in certain circumstances it may be involved in either initiation or perpetuation of autoimmune disease.

After organ or bone marrow transplantation a patient becomes chimeric. Early in the history of hematopoietic stem cell transplantation, it was recognized that transplantation chimerism can lead to chronic GVHD [6,8,10]. Chronic GVHD has clinical similarities with some autoimmune diseases, including systemic sclerosis (SSc), primary biliary cirrhosis, Sjögren's syndrome, and some features of systemic lupus and myositis, although there are also pathological differences [5]. The chances that a patient will develop chronic GVHD are highly dependent upon the HLA genes of the donor and host. Thus, insights from transplantation chimerism contributed to the hypothesis that Mc and HLA relationships between host and nonhost cells are involved in the pathogenesis of spontaneously occurring autoimmune diseases.

1.1. Mc in normal mammalian biology—mouse models

Maternal cells are transported to the fetus during pregnancy and there is evidence that MMc is a common phenomenon in newborn mice and in humans (Fig. 1A). In immunodeficient mice, MMc has been found in bone marrow, spleen, liver, lymph nodes and thymus and also nonlymphoid organs including heart and lung [11]. MMc was found as early as 12 days of gestation [11,12], and persisted at least 6 months after birth [13]. In immunocompetent animals maternal cells have not been identified before day 16 of gestation. After 16 days MMC was found only in the bone marrow and spleen [11,12,14–16]. Maternal cells may also be transferred through breast milk to the newborn [13,17,18]. Persistence of MMc after birth may depend on oral tolerance to maternal antigens transmitted through breast milk [18]. Chimeric maternal cells have been shown to be functional, producing immunoglobulin [13]. However, maternal cells do not regenerate the immune system for immunodeficient animals. Similarly, early studies in murine models identified fetal cell persistence [19,20].

However, the mouse is not a good model for events during human pregnancy [21]. The anatomical difference between mice and humans may affect maternal–fetal cell transfer (Table 1). Many of the mouse studies were performed by blastocyst transfer rather than natural pregnancy. Mouse placenta is labyrinthine and hemotrichorial (3 cell layers lie between maternal and fetal circulation: 2 layers of trophoblasts and 1 layer of syncytiotrophoblasts), whereas the human placenta has villi and is hemochorial (containing only 1 layer of trophoblasts). In addition, most mouse models use inbred strains with limited major histocompatibility complex (MHC) haplotypes, whereas in humans maternal–paternal MHC disparity is normal, and may be required for a successful pregnancy [12,14–16,22]. Until the mechanism