Cancer Letters 276 (2009) 8–13

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Fetal microchimerism and cancer

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ARTICLE INFO

Article history:
Received 27 March 2008
Received in revised form 13 May 2008
Accepted 23 July 2008

Keywords:
Microchimerism
Breast cancer
Tumor immunology

ABSTRACT

The acquisition and persistence of fetal microchimerism, small numbers of genetically disparate cells from the fetus in the mother, is now a well-recognized consequence of normal pregnancy. Fetal microchimerism has been associated with several classical autoimmune diseases, but its role in normal health remains undefined. One potential function of fetal microchimerism might be in the surveillance for malignant cells. Convergent evidence is reviewed here in cancer epidemiology and transplantation biology that suggests a new paradigm in which fetal microchimerism serves as an additional line of defense against the development of breast cancer in parous women.

1. Introduction

In the United States, approximately one woman in eight will be diagnosed with breast cancer in her lifetime [1]. Risk modifiers for development of breast cancer are both genetic and environmental. Germline genetic risk modifiers identified thus far are few (e.g., BRCA1 and BRCA2) and overall account for only 2–10% of all cases [2–4]. Environmental risk modifiers such as endogenous and exogenous hormones, reproductive factors, anthropometric characteristics, and certain lifestyle factors are known to impact a woman's risk for breast cancer although the mechanisms underlying these effects are still largely unclear and under active investigation. A history of prior childbirth has been repeatedly observed as a protective factor against breast cancer risk, as also potentially for some other cancers. Here I review recent evidence for possible roles for fetal cells originally acquired by a woman during pregnancy in breast and other cancers.

2. What is known about reproduction and breast cancer?

Studies examining reproductive history of women and cancer risk have demonstrated the common theme that parity is often protective. The protective associations of parity have been described for breast cancer, Hodgkin's lymphoma [5], Non-Hodgkin's lymphoma [6], myeloid leukemias [7], chronic lymphocytic leukemia [8], bladder [9], rectal [10], ovarian [11], pancreatic [12] and brain cancer [13]. The protective effect of parity against breast cancer in particular has been reported in multiple studies and from a diversity of international populations [14–17]. The current review is focused on breast cancer both because of the magnitude of the problem for public health and because of the robustness of its association with parity.

Historically, the protective effect of parity has been attributed to hormonal influences on the breast epithelium. Breast epithelium remains in a partly undifferentiated state prior to pregnancy. The hormonal milieu of pregnancy leads to terminal differentiation of the breast epithelium [18]. It has been suggested that risk of malignancy increases proportionate to the duration that breast epithelium remains in an undifferentiated state (i.e., older age at first pregnancy) [19]. While pregnancy-induced hormonal maturation may contribute to protection from can-

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doi:10.1016/j.canlet.2008.07.025

cers of the breast and other endocrine responsive organs, it is mechanistically difficult to envision that pregnancy-associated hormonal changes mediate the protection against all the other cancers noted above. As an alternative explanation, other investigators have examined the role of priming the maternal immune system during pregnancy by exposure to fetus-derived neoantigens that resemble breast cancer antigens [20–24]. For instance, antibodies can be detected in the maternal sera that are specific for oncofetal peptide [21] and leukocytes specific against oncofetal antigen can be cloned from the peripheral blood of parous women [25]. Although it is likely that hormonal changes and maternal immune responses to fetal neoantigens contribute to some of the observed protection arising from pregnancy, the questions remain as to why all parous women are not protected similarly and whether other recently appreciated factors associated with pregnancy are involved.

3. A (brief) history of microchimerism

Seminal reports began to appear 29 years ago that fetal genetic material routinely appeared in the peripheral blood of the pregnant woman [26–28]. Several years later, Bianchi, et al. demonstrated the persistence of male fetal cells in parous women as late as 27 years post-partum [29]. Since the appearance of these original reports many studies have found fetal microchimerism in peripheral blood mononuclear cells (PBMCs) [30–33]. Moreover, the proportion of parous women with fetal microchimerism has been reported in immunologically active subsets within peripheral blood including T (prevalence of 30–58%), B (45–75%), NK (44–62%), and antigen presenting (26–58%) cells [30,34].

Fetal microchimerism has also been found in visceral organs and hematopoietic tissues. Notably, fetal microchimerism did not always express hematopoietic lineage markers but instead expressed tissue specific markers. Khosrotehrani, et al. found non-hematopoietic fetal microchimerism in a variety of tissues [35,36]. Stevens, et al. described male hepatic lineage cells of presumed fetal origin in maternal livers [37]. Fetal microchimerism has been identified in harvested mobilized hematopoietic stem cell product, both enriched and unselected for CD34-expressing progenitors, from healthy women donors [38]. Furthermore, fetal microchimerism was identified in the mesenchymal stem cell population within bone marrow [39].

Because the long-term persistence of fetal microchimerism has been appreciated recently, the role and functionality of fetal microchimerism in human disease is just beginning to be explored. The majority of studies have examined fetal microchimerism in autoimmune diseases because the incidence of most autoimmune diseases is increased in women and is often particularly increased in post-reproductive years. Three overall mechanisms have been proposed by which fetal microchimerism might contribute to disease in the mother. First, fetal microchimerism could function as an effector of allo-immune reactions. For example, in a study of women with scleroderma male T cells that were alloreactive to maternal antigens were cloned from peripheral blood and skin specimens [40]. Second, fetal antigen presenting cells (APCs) displaying maternal antigens or tissue-differentiated allogeneic fetal microchimerism could serve as targets for effectors from the maternal immune system. Tissue-differentiated fetal microchimerism has been identified in diseased tissue in thyroiditis and goiter, hepatitis, lupus, and other diseases [35–37,41,42]. Third, fetal cells could serve as an endogenous allogeneic source of progenitor cells to repair tissues that have been damaged by inflammation [36,37,39]. Supporting the latter possibility, a murine model described trafficking of fetal microchimerism stem cells to damaged maternal tissues where they appeared to participate in the regenerative process [43].

4. How does one detect fetal microchimerism?

In general two techniques have been most widely utilized to identify fetal microchimerism, PCR and fluorescent in situ hybridization (FISH). For PCR-based approaches, genomic DNA is typically extracted from blood (whole blood, plasma, PBMC) or from tissues. A sequence unique to the fetus is selected for PCR amplification. For instance, in pregnancies where the gender of the fetus is male or when a woman is known to have previously given birth to a male, sequences specific to Y-chromosome genes (*DYS14*, *SRY*) are targeted by the primers. When the child (fetus) has been previously genotyped for paternally derived polymorphisms, allele specific PCR has been used. For example, polymorphisms of human leukocyte antigen (HLA), GST, RhD, GSTM1, and ACE genes have been previously targeted for PCR-based detection of microchimerism [44–46]. Another approach to studying fetal microchimerism is to conduct FISH with probes that are specific to the Y and X chromosomes so as to identify male cells in tissues (or in blood) of women who have had sons. One advantage of the second method is that concurrent immunohistochemistry can also be applied to tissue sections to both determine phenotype and source (male cells by FISH) of microchimeric cells [35–37].

5. Breast cancer and fetal microchimerism

To date, my colleagues and I have reported two independent studies showing an inverse association of breast cancer risk with the presence of fetal microchimerism [47,48]. Stated differently, parous women who harbor fetal microchimerism are more likely to be free of cancer than women who do not. In the first study [47], healthy women or unselected women with carcinoma *in situ* (stage 0) or invasive breast cancer (stages I–IV) were evaluated for fetal microchimerism in Ficoll purified PBMCs using Y-chromosome specific real-time quantitative PCR. Male genomic DNA, presumably from sons, was detected in 14% of the breast cancer cohort compared to 43% in the control cohort. When absence of FMc was treated as a protective factor against breast cancer, the odds ratio was 0.23 ($p = .006$). The protective effect increased when analysis was corrected for women with known prior male births or no che-