Cancer Letters 287 (2010) 136–141

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Fetal cell microchimerism in human cancers

Laura Fugazzola *, Valentina Cirello, Paolo Beck-Peccoz

Department of Medical Sciences, University of Milan and Endocrine Unit, Fondazione Policlinico IRCCS, Milan, Italy

ARTICLE INFO

Article history:
Received 15 April 2009
Received in revised form 14 May 2009
Accepted 15 May 2009

Keywords:
Microchimerism
Cancer
Thyroid
Mouse
Fetal cells
Pregnancy

ABSTRACT

The transfer of fetal cells into the maternal circulation occurs normally during pregnancy and the post-partum persistence of these cells in the maternal blood and tissues, known as fetal cell microchimerism, has been clearly demonstrated. However, the long-term consequences of this phenomenon are only beginning to be appreciated. In particular, whether microchimerism could be involved in the carcinogenetic process or whether fetal microchimeric cells could be able to differentiate in host tissues, participating in the maternal response to injury, is still matter of study. In this review, the possible role and the consequences of fetal cell microchimerism, as emerged from studies in animal models and in women with different types of cancer, will be presented.

1. Introduction

Fetal cell microchimerism (FCM) is defined as the persistence of fetal cells in maternal organs and circulation for decades without any apparent graft-versus-host reaction (GvDH) or graft rejection. It can take place in case of blood transfusions, organ transplants and, more frequently, during pregnancy. Indeed, in the latter case a bidirectional exchange of cells has been observed between the fetus and the mother, starting from the 4th to 6th week of gestation [1]. This traffic of cells is primarily composed by immune cells (T and B-lymphocytes, monocytes, natural killer), including hematopoietic stem cells $CD34^+$ and $CD34^+/38^+$ committed to early B and T-cells with the capacity for multilineage differentiation [2]. The number of fetal progenitor cells, called pregnancy-associated progenitor cells (PAPCs), circulating in the blood of a pregnant women, has been estimated to be 0–2 mL^{-1}, but it can vary according to the gestational age. In normal second-trimester pregnancies, the number of fetal cells in the maternal circulation has been estimated to be 1–6 cells/mL of maternal venous blood [3]. At 36th weeks of gestation, 100% of pregnant women have fetal cells in their circulation. After delivery, this fraction rapidly decreases, and 30–50% of healthy women have detectable fetal cells in their blood from four weeks to decades after delivery [3]. Likely, PAPCs can survive by homing in maternal stem cell niches, such as the bone marrow and representing a long-term reservoir of stem cells [4,5]. In case of tissue injury, PAPCs could migrate to the damaged organ and differentiate as part of the maternal repair response. However, it is unknown whether PAPCs can respond to all types of maternal injury or only to those that recruit stem cells, as demonstrated in animal models [3]. These fetal cells could have a higher proliferative capacity or more plasticity than their equivalent adult cells, but it is currently unknown if fetal stem cells may have any advantage over maternal stem cells [1,4].

Low-grade persistence of fetal cells in maternal blood and tissues has been linked either to the induction of immunological tolerance between the mother and the fetus or to the development of autoimmune diseases, especially those having features of chronic-GvDH (i.e., systemic sclerosis, primary biliary cirrhosis, Sjögren

* Corresponding author. Address: Endocrine Unit, Fondazione Policlinico IRCCS, Via F. Sforza, 35, 20122 Milan, Italy.
E-mail address: l.fugazzola@policlinico.mi.it (L. Fugazzola).

0304-3835/$ - see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.canlet.2009.05.017

syndrome, erythematous systemic lupus, type 1 diabetes mellitus, thyroiditis and rheumatoid arthritis) [6–19]. Indeed, several Authors have hypothesized that FCM might be involved in chronic inflammatory responses leading to tissue damage ("*bad microchimerism*" hypothesis), also based on the fact that microchimeric fetal cells are semiallogeneic to those maternal and that autoimmune diseases are more frequently observed in female gender [6,9]. On the contrary, the role of microchimeric cells in the pathogenesis of non-autoimmune diseases (i.e., hepatitis C, thyroid adenoma and multinodular goitre, cervical, breast, thyroid, lung, colon, uterus, ovarian cancers, hematological malignancies and melanomas) is still controversial, but most studies favor the hypothesis that fetal microchimeric cells might provide a rejuvenating source of progenitor cells, participating in maternal tissue repair processes or in the immune surveillance of malignant cells [20–29]. It has been postulated that the encounter of fetal effector cells with maternal tumoral antigens, or the presentation of these antigens from fetal-derived APC to maternal effectors could determine an immune surveillance against malignancy ("*good microchimerism*" hypothesis). In particular, PAPCS could engraft and differentiate into mature immunocompetent cells in various tissues, leading to the repopulation of areas of tissue damage [23]. Nevertheless, it must be underlined that these microchimeric cells could also have no biological effects on human's health ("*innocent bystanders*" hypothesis) [30].

Finally, besides the role of FCM in maternal diseases, the specific effects or the consequences of this phenomenon in healthy women remain to be clarified. In particular, microchimeric fetal cells have been commonly found among peripheral blood mononuclear cells (T lymphocytes, B cells, NK cells and monocytes) [31], but rarely in normal tissues of healthy parous women.

2. Approaches used to investigate microchimerism

It must be underlined that either male and female cells enter the maternal circulation. Nonetheless, it is easy to argue that the detection of a XY male cell in the XX mother is extremely less difficult than the distinction between fetal and adult female cells. Thus, the commonest approach to detect foreign cells is the assay of male-specific gene markers in females with a previous male pregnancy. Women with a previous history of abortions or blood transfusions or transplantation, must be excluded from studies on FCM. In the majority of studies, the assessment of male microchimeric cells is done by the detection of the Y chromosome by PCR amplification or Fluorescence in situ hybridization (FISH). However, the methods employed have not yet been standardized and the interpretation of the results obtained requires consideration of the techniques used.

PCR amplification of Y-chromosome specific genes such as SRY and DYS14 is the more sensitive method and allows the detection of one male cell per 100,000 female cells [1]. It can be performed on blood or tissues, but a disadvantage of this technique is the possible contamination which leads to false positive results.

FISH analyses allow to visualize XY male nuclei among XX female nuclei, allowing the morphological definition and spatial localization of microchimeric cells, which are usually identified as isolated or in cluster (Fig. 1). A disadvantage of this technique is that overlapping cells can produce artifacts, implying the need for time and labor intensive experiments.

Finally, it should be considered that male cells in a female could derive also from spermatozoa of the partner, from an older brother or from a vanished male twin, indicating that the definitive demonstration that the male cells identified in a woman derives from her fetus can be achieved only by the analyses of paternally inherited DNA polymorphisms [1,32].

3. Lessons from animal models

To better understand feto-maternal trafficking and the role of microchimeric cells in the maternal tissues, animal models have been used. In particular, FCM has been studied in mice [33–37] and, more recently, in rats [38]. Although mice and rats have a different placentation with respect to humans, a major advantage of these studies is represented by the low gestational period and the opportunity to control breeding between a transgenic male mice carrying the GFP (green fluorescence protein) and a wild type female, easily identifying fetal cells acquired during pregnancy. Moreover, microchimeric cells can be well defined by immunohistochemistry or can be microdissected

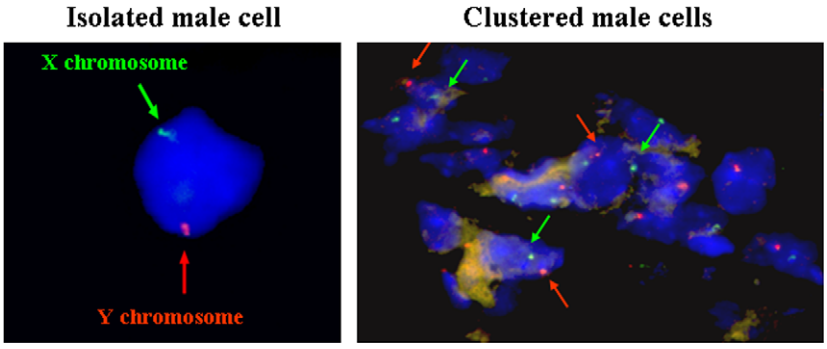

Fig. 1. FISH analysis leads to the morphological definition and spatial localization of microchimeric cells, which are usually identified as isolated or in cluster. X (green signal) and Y (red signal) chromosomes are identified by specific probes (indicated by arrows) in the nuclei of male cells.