New Insights in Microchimerism: New Topic for Our Journal?

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Concern, reflections and hypotheses about feto-maternal relationships have probably been emerging for as long as philosophers and scientists have existed. The peculiar links between a mother and her fetus have fascinated intellectuals in very diverse fields. Besides, as all readers of this journal know very well, more academic studies have widely focused on this subject. The fetal consequences of maternal diseases, such as infections, thyroid or cardiac abnormalities have been well described during last decades. In the same way, the maternal consequences of pregnancy, such as worsening of lupus erythematosus and multiple sclerosis, or triggering of diabetes, have also been the field of large studies. Finally, preeclampsia has been at the center of multiple specialties and appears to result from abnormalities in the early relationship between fetal-maternal tissues. Beside these known phenomena, new insights into fetal-maternal relationships have come from studies devoted to microchimerism. Recent papers as well as recent meetings held in Paris (Oct 1999) and Detroit (July 2000) devoted to this subject have drawn interest to this phenomenon. Microchimerism is defined by the presence in an individual of a very low level of cells originating from another individual [1]. Besides pregnancy, which appears to be the most frequent source for microchimerism, other conditions may result in microchimerism. These are mainly solid-organ transplanta-

tions [2, 3] and red blood cell transfusions [4, 5]. Microchimerism resulting from feto-maternal trafficking during pregnancy has also been very well known since the late 1960s, the more sophisticated studies being done after the polymerase chain reaction (PCR) tool was discovered and used to amplify Y-positive cells in the blood of females bearing male fetuses [6, 7]. Interestingly, Bianchi et al. [8] recently showed that fetal cells could persist in the circulating blood of women up to 27 years after delivery, opening new perspectives for the fate and the role of microchimerism. These were hemopoietic CD34+ stem cells. In a reverse way, maternal cells may also migrate into fetuses. The first evidence for this materno-fetal trafficking came from cord blood analysis. Since marrow transplantation using cord blood gave a low incidence of graft-versus-host diseases (GvHD), several groups have analyzed this tissue and surprisingly found that maternal cells were present in it [9, 10]. In addition, maternal cells were detected in children with immunodeficiencies, and were able to determine GvHD in some [11]. Finally, findings from a recent publication demonstrated that in up to nearly 50% of normal adults, circulating maternal cells – picked up by PCR targeting of non-shared maternal HLA alleles – were found [12]. Therefore all these studies go far from the classical view of fetal cell transfer in the mother's blood during pregnancy, since we now know that fetal and maternal

cells may persist for decades in the blood – and maybe in tissues – of mothers and children.

Besides these findings, investigators working in rheumatology hypothesized that some autoimmune diseases, predominating in females and for whom similar features may develop in GvHD, could result from allogeneic cells [13]. Taking advantage of the fact that fetal cells are able to persist for years, Nelson et al. [14] showed that the level of fetal cells was higher in women with scleroderma than in control women. In addition, HLA class-II analysis demonstrated that compatibility of the child's tissues from the mother's perspective was more frequently found in families with scleroderma [14, 15], this type of situation being known to favor post-transfusional GvHD. Artlett et al. [16, 17] obtained similar results, also showing that the fetal circulating cells in women with scleroderma were T and/or monocytes. All these original data led to the development of a new concept in the fetomaternal relationship, namely that fetal cells may be responsible for deleterious immune events in the mother years after delivery. However, soon after, other studies emphasized that microchimerism could frequently be found in normal individuals, in different lymphocytic subpopulations [18]. As microchimerism is statistically associated with the development of some autoimmune diseases, this phenomenon is probably not able to act alone, but is rather part of a multistep phenomenon. Other autoimmune diseases predominating in women will certainly be the field of studies evaluating the role of microchimerism.

Other new data concerning microchimerism were devoted to pregnancy. The group in Basel has interestingly found that the level of fetal cells was increased during preeclampsia [19]. The increased fetal cells were nucleated erythroblasts [19]. This disturbed trafficking of fetal cells into the maternal periphery with preeclampsia

may be secondary to placental abnormalities, but may itself play a role once it has appeared. These findings of disturbed trafficking are in accordance with very old data showing that trophoblast cells could be found in the lungs of women with preeclampsia. We have shown that fetal DNA could be found in the skin lesions of polymorphic eruptions of pregnancy, raising the hypothesis that during pregnancy fetal cells may induce inflammatory reactions [20]. Finally, Lo et al. [21] were the first to demonstrate a very original finding, namely the presence of free fetal DNA in the mother's serum and plasma. The level of this free DNA is very high, increases throughout pregnancy and disappears within 2 h after delivery [22]. Similar to fetal cells, the fetal free DNA level in pregnant women is higher in preeclampsia and aneuploid pregnancies [23, 24]. The significance of the presence of this material remains unknown. However, picking this material may allow noninvasive prenatal diagnosis close to what many groups evaluate on fetal circulating cells [25, 26]. Indeed, multiplex PCR on fetal DNA in plasma allowed almost 100% Rhesus D and sex evaluation. Of note, free donor DNA has also been demonstrated in solid organ transplantation [27].

This large amount of information opens many questions concerning the future of microchimerism. What are the factors which influence the prolonged establishment of such trafficking? What cells traffic and into which tissues? What drives microchimerism to pathological consequences? Is free fetal DNA transcribed and translated? All these interesting questions will probably stimulate future research programs. Knowledge of fetal-maternal interactions will hopefully increase. The maternal consequences of these interactions, which appear to be larger and later than previously thought, will most probably constitute a new topic for this journal.

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