Microchimerism: Fears and Hopes

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Key Words

Chimerism · Fetomaternal transfer

For those who are not used yet to this rather recent concept, microchimerism refers to the presence of very low numbers of allogeneic cells in an individual. Most interest in this phenomenon has been raised after the demonstration by the group of Diana Bianchi, a researcher working previously on prenatal diagnosis, that fetal cells – present in the peripheral blood of women during pregnancy – may persist decades after delivery [1]. Fetal semi-allogeneic cells were indeed largely known to be tolerated during pregnancy, through various pathways. However, the cause of such an escape of foreign cells from the maternal immune surveillance for a very long time remains an unanswered intriguing question. Some have hypothesized that such an escape could be due to a leakage of paternal antigens from fetal cells, while others evoked a homology in the major histocompatibility complex leading to a ‘compatibility from the mother’s view’ [2]. Nevertheless, whatever the mechanism of this tolerance, the evidence that such foreign cells could persist has been the rationale for many authors to evaluate a possible implication of chimeric cells in deleterious consequences for the host. Why these investigators focused on such a harmful role is easy to understand: several diseases classified as auto-immune predominate in females, the gender in whom persisting fetal circulation from a previous pregnancy may occur, and in addition several of these ‘auto-immune diseases’ looked like ‘allo-immune diseases’,

namely graft-versus-host reaction (GvHD). Based on this, several groups have shown an association between fetal cell persistence and systemic sclerosis (SSc) [3–6]. In addition, such fetal cells were also found in involved tissues such as the skin [4]. At that point, a fascinating perspective appeared possible: spontaneous SSc could be an anti-maternal reaction of the fetus, similar to posttransfusional GvHD. However, many points were quickly raised against this pathway. First, nearly all studies found a significant level of normal females with chimerism. Second, sclerodermoid GvHD displays several clinical, pathological and immunological differences to SSc [7]. Third, no increase in SSc appeared to be reported after red blood cell transfusion [8]. Finally, other studies failed to find more chimerism in females with SSc as compared with controls [9, 10]. Therefore, a real controversy about the implication of chimerism in SSc is still to be debated. Some consider that the presence of chimeric cells would act as one step in a multistep phenomenon in the pathogenesis of SSc, either by direct T cell antihost reactivity or by inhibition of host T regulatory cells with consecutive auto-immunity. Other authors believe by contrast that these fetal cells are recruited into damaged tissue in order to participate in tissue repair as we well see below.

Quickly, after investigating SSc, several auto-immune diseases were evaluated. Interestingly, using different techniques, 2 groups showed in 2000 that juvenile dermatomyositis was associated with the presence of maternal cells in the blood and the muscle of affected sons, while controls with non-inflammatory myopathies had no such cells [11, 12]. We were therefore in the same scenario as in SSc: allogeneic cells, coming from the reverse traf-

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fic (mother to child), were possibly inducing an attack against the host. The case published in this issue [13] with a very peculiar picture resembling dermatomyositis in a child was investigated by Kowalick et al. Female XX cells were found in muscle and in peripheral blood cells appearing as CD4 cells. Such a finding is interesting: are maternal lymphocytes transferred and directly responsible for a GVHD in muscle and skin? This remains impossible to decide since the maternal cell type in the muscle was not identified in the present case. Interestingly, Scaletti et al. [14] have demonstrated the presence of fetal antimaternal cells in females with SSc. However, normal individuals may also have different types of maternal cells without any consequence [15]. Finally, Stevens et al. [16] have recently investigated a small series of infants with neonatal lupus. Using combinatory techniques, they finally found that maternal cells in the child's diseased heart were not effector cells, but indeed muscular cells.

This interesting finding is in accordance with others that now point to the capacities of chimeric cells to act as a source of stem cells. A summary of this hypothesis is given in the results of Khosrotehrani et al. [17]. These have

shown that, in previously pregnant females, differentiated cells of fetal origin were frequently detected in several types of injured organs [17]. At the same time, another group demonstrated the presence of mesenchymal stem cells in the marrow of previously pregnant females [18]. Therefore, at that time, it appears that microchimerism, particularly of fetal origin, may include stem cells. These appear to be able to migrate preferentially into injured tissue – whatever the mechanism of injury – and differentiate into organ cells to help for repair. In thyroid goitre and hepatitis C, this was the case [17, 19, 20]. In neonatal lupus, this could also be the case, maternal stem cells migrating to repair damaged heart tissue [16]. Fetal stem cells may theoretically have a longer life span. One may even hypothesize that these may be in the future sorted and used for a natural therapy, avoiding ethical conflicts such as those of embryonic stem cells. All these original data attribute a new role to chimerism, a positive role, since such a transfer appears here as a way to cure a lesioned tissue rather than only a way to damage tissue. Chimerism was a source of fear for the host but may finally also become a cause of hope.

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