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## **Chimerism in health, transplantation and autoimmunity**

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### **Citation**

Koopmans, M., & Kremer Hovinga, I. C. L. (2009, March 24). *Chimerism in health, transplantation and autoimmunity*. Retrieved from <https://hdl.handle.net/1887/13697>

Version: Corrected Publisher's Version

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## **CHIMERISM IN SYSTEMIC LUPUS ERYTHEMATOSUS: THREE HYPOTHESES**

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*Rheumatology (Oxford) 2006; 46: 200-208*

## ABSTRACT

Systemic lupus erythematosus (SLE) is an immune-mediated disease characterized by the presence of autoantibodies and a wide array of clinical symptoms. Despite intensive research, the aetiology of SLE is still unknown and is probably multifactorial. Both genetic and environmental factors have been associated with SLE, but these factors alone are insufficient to explain the onset of SLE.

Recently, it has been suggested that chimerism plays a role in the pathogenesis of autoimmune diseases, including SLE. Chimerism indicates the presence of cells from one individual in another individual. In an experimental mouse model, the injection of chimeric cells induces a lupus-like disease. In addition, chimerism is found more often in kidneys from women with SLE than in healthy controls.

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There are several mechanisms by which chimeric cells could be involved in the pathogenesis of SLE. In this review, three hypotheses on the role of chimerism in SLE are discussed. The first two hypotheses describe the possibilities that chimeric cells induce either a graft-versus-host reaction in the host (comparable with reactions seen after bone marrow transplantation) or a host-versus-graft reaction (comparable with reactions seen after solid organ transplantation). The third hypothesis discusses the possible beneficial role chimeric cells may play in repair mechanisms due to their stem cell-like properties. This review provides insights into the mechanisms by which chimerism may be involved in SLE and proposes several lines of inquiry to further investigate chimerism in SLE.

## INTRODUCTION

The term chimerism is used to indicate the presence of cells from one individual in another. Individuals can become chimeric in several ways. Pregnancy-related causes of chimerism can lead to chimerism of either the pregnant woman or the fetus. The former comprise completed pregnancy, miscarriage and induced abortion.<sup>1-4</sup> The latter comprise maternal-fetal cell transfer, cell transfusion from a twin, either a surviving twin or a vanished twin (i.e. a twin lost early in gestation) and transfer of cells, via the maternal circulation, from an older sibling.<sup>3,5,6</sup> Causes of chimerism not related to pregnancy comprise blood transfusions and bone marrow or solid organ transplantations.<sup>7-9</sup>

Fetal cell chimerism is considered a natural consequence of normal pregnancy, resulting from local permeability of the placenta. It occurs in most, if not all, women during pregnancy,<sup>10,11</sup> and therefore, fetal cell chimerism has become of primary interest in view of prenatal screening and testing.<sup>12</sup> Chimeric fetal cells may present as hematopoietic progenitor cells (CD34+ and CD34+CD38+ cells), trophoblast cells, nucleated erythrocytes, T lymphocytes and other leukocytes.<sup>4,13-16</sup>

Although most fetal cells are removed from the maternal circulation by the immune system, several studies have reported the presence of chimeric cells in the peripheral blood and tissues of healthy women long after pregnancy.<sup>14,15,17-19</sup> Apparently, some fetal cells escape elimination by the immune system and survive in the maternal circulation of healthy women for many years after delivery, which may be considered a physiological phenomenon. Recently, however, reports have appeared implicating chimerism as the cause of immune-mediated diseases.<sup>20-23</sup>

Systemic lupus erythematosus (SLE) is an immune-mediated disease that occurs predominantly in women during their fertile years. The occurrence of autoantibodies reactive to several cell components is specific for SLE, but its aetiology is unknown. Recently, we demonstrated that chimeric cells are present twice as often in kidneys of women with lupus nephritis as in normal kidneys.<sup>24</sup> Other studies have shown that in women with SLE, chimeric cells are present in the peripheral circulation.<sup>25-27</sup> In one

case study, chimeric cells were found in several tissues of a woman with SLE, including intestines and lungs.<sup>28</sup>

As already mentioned, maternal chimerism also exists, defined by the presence of maternal cells in offspring.<sup>5,29,30</sup> Maternal chimerism may also persist for many years,<sup>29,30</sup> and may be of pathogenic importance in, for example, neonatal lupus syndrome,<sup>31,32</sup> juvenile idiopathic inflammatory myopathies,<sup>33</sup> and juvenile dermatomyositis,<sup>34</sup> all sharing important similarities with adult SLE.

In order to determine what types of experiments will most efficiently elucidate the role of chimeric cells in SLE and other autoimmune diseases, it is necessary to determine the various pathogenic mechanisms that theoretically could be involved. In this review, we discuss three hypotheses on the role of chimeric cells in immune-mediated diseases, with emphasis on the role of chimerism in SLE (Figures 1-3).

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### **HYPOTHESIS 1: CHIMERISM INDUCES A GRAFT-VERSUS-HOST REACTION**

The first hypothesis is that the chimeric cell is a T cell that induces a graft-versus-host (GVH) reaction. Because of the numerous similarities between autoimmune diseases and graft-versus-host disease (GVHD),<sup>35-38</sup> it seems likely that a GVH-like reaction is involved in the pathogenesis of these diseases.

Is there evidence that a GVH-like reaction is triggered by chimeric cells in the development of SLE? In experimental mouse models, described in the 1980s by Via and Shearer<sup>39</sup> and others, a GVH reaction was induced by injecting parental T cells into the offspring of (C57BL/xDBA/2) mice. The injection of T cells from the C57BL/ parent into the F1 host induced an acute GVH reaction accompanied by profound immunodeficiency, anaemia, and hypogammaglobulinemia, which under certain circumstances was lethal. This reaction was the result of donor (parental) T helper cells, which were activated by antigen presenting cells (APCs) or B cells from the recipient (F1), which in turn activated the donor cytotoxic T cells, which eventually eliminated recipient cells. This reaction

is referred to as either an immunosuppressive, lethal, or acute GVH reaction.<sup>39,40</sup> However, if T cells from the DBA/2 parent were injected, a response occurred that was accompanied by lymphoid hyperplasia, by production of antibodies against the nucleus (ANA), dsDNA, erythrocytes, and thymocytes, and, most importantly, by an immune complex glomerulonephritis resembling human lupus nephritis.<sup>39,41-43</sup> In this situation, donor parental T helper cells were able to continuously stimulate F1 host B cells because of a low frequency of cytotoxic T cell precursors. This reaction is referred to as immunostimulatory or chronic GVH reaction.<sup>39,40</sup>

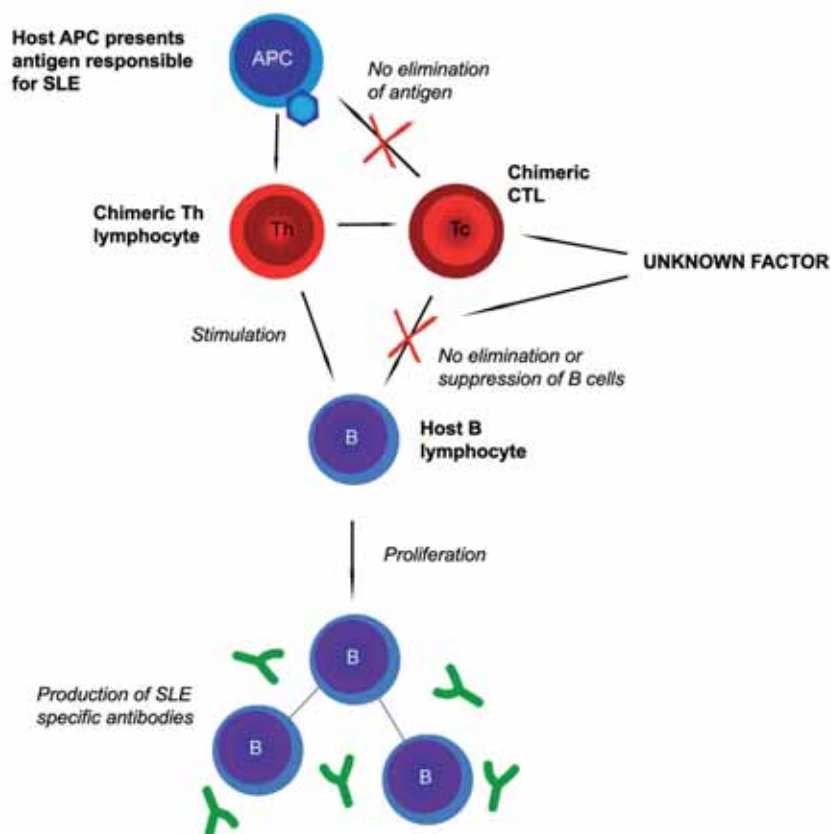
In the mouse model, SLE is more an 'alloimmune' reaction in which chimeric cells react against host cells than a true autoimmune reaction. Unaware of the relatively common existence of chimeric cells in humans, Via and Shearer<sup>39</sup> concluded that chimeric cells leading to polyclonal B cell activation would be unlikely in human SLE. Given the current knowledge that chimerism occurs in humans, the question arises whether, under certain conditions, chimeric cells are indeed capable of inducing an immunostimulatory GVH reaction (Figure 1).

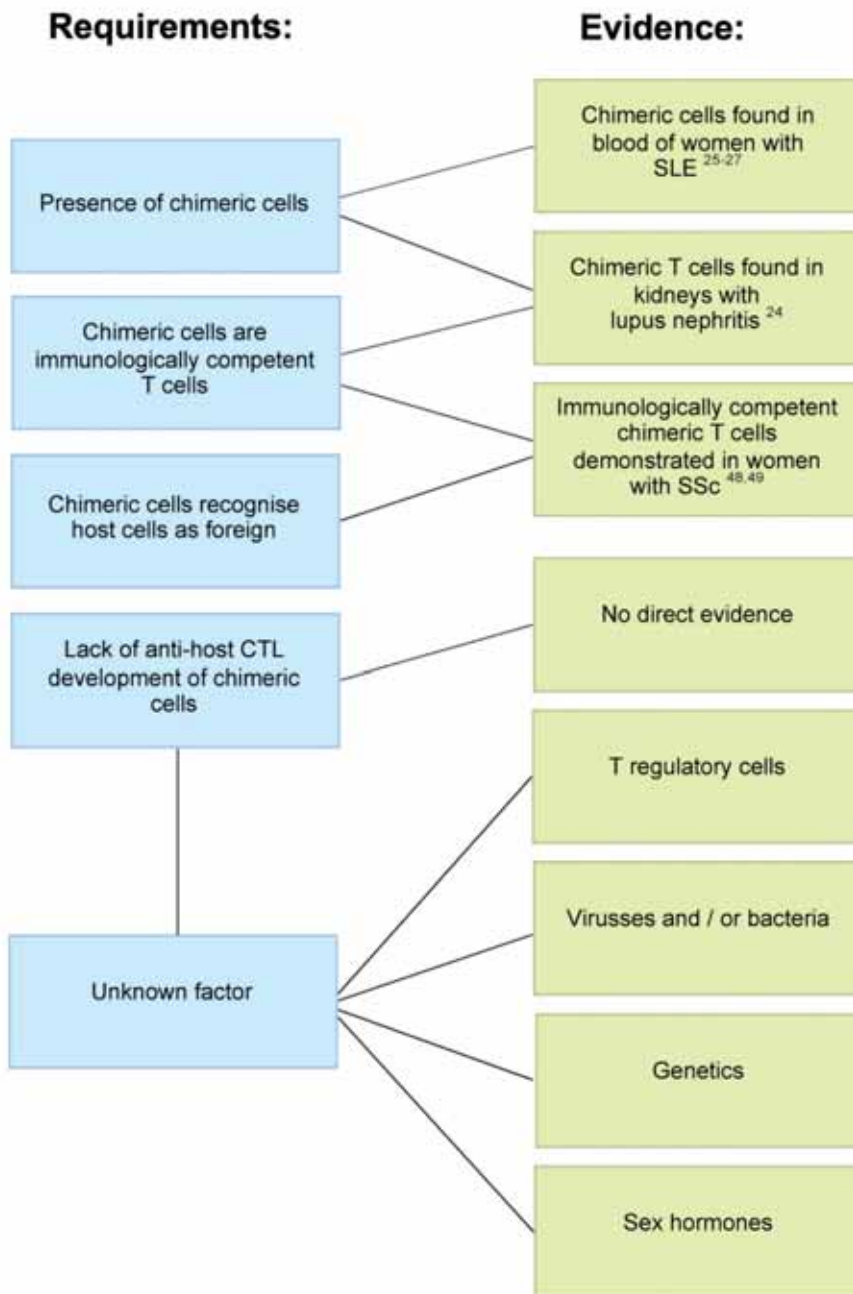
At least three conditions are required for a chimeric cell to induce a GVH reaction.<sup>44</sup> First, the host must accept the presence of chimeric cells. Secondly, the chimeric cells must be immunologically competent T cells. Thirdly, the chimeric cells must recognize the cells of the host as foreign. In experimental models, it is the immunostimulatory GVH reaction that resembles human SLE, and this reaction only occurs if there is no development of anti-host CTL, due to a lack of CTL precursors. Therefore, lack of anti-host CTL development can be added as a fourth condition under which a chimeric cell might induce SLE in humans.

Is there evidence that these four conditions occur in human SLE? First, the acceptance of chimeric cells by the host was demonstrated by several studies reporting the presence of chimeric cells in the blood of women with SLE.<sup>25-27,45</sup> Secondly, there is evidence that at least a subpopulation of the chimeric cells in SLE are T cells.<sup>24</sup> The third condition, addressing whether chimeric T cells are immunologically competent was never investigated in SLE, but this issue was addressed in patients with systemic

sclerosis (SSc). Artlett et al.<sup>46</sup> reported that some of the chimeric cells in women with SSc were T cells, which was confirmed by others,<sup>3,4,47</sup> and both CD4+ and CD8+ chimeric T cells were identified.<sup>48</sup> These findings are suggestive of the presence of immunological active chimeric cells. Evidence for the immunological competence of chimeric T cells was demonstrated by Scaletti et al.<sup>49</sup> in systemic sclerosis: in this study, chimeric T cell clones were generated that showed a proliferative response and cytokine production to major histocompatibility complex (MHC) antigens on host cells. Taken together, these data provide evidence that the first three conditions required for a chimeric cell to induce a GVH reaction in humans are met.

**Hypothesis 1:  
Chimerism induces a graft-vs-host reaction**





**Figure 1.** Chimerism induces a GVH reaction. There is no CTL reaction of chimeric Tc cells against SLE-specific antibodies producing B cells nor against SLE-specific antigens. Therefore, chimeric Th cells can continuously stimulate host B cells to proliferate and secrete SLE specific antibodies. APC, antigen presenting cell; GVH, graft-versus-host; Th, T helper; Tc/ CTL, cytotoxic T cell. Colors: red, chimeric cell; blue, host cell.

Lack of anti-host CTL development is the fourth condition in which a chimeric cell induces an immunostimulatory GVH reaction in the SLE mouse model. There are different viewpoints on why a lack of anti-host CTL development would occur in humans: it could either be due to a functional deficit, or to a regulating mechanism suppressing CTL development. These regulating mechanisms may comprise the presence of T regulatory cells that suppress CTL function. In any case, the lack of an anti-host CTL response of human chimeric cells is difficult to demonstrate, and this issue has not been investigated yet. Functional studies are needed to investigate the importance of the lack of anti-host CTL development of chimeric cells in human SLE. For instance, it would be interesting to investigate the functional responsiveness of CD8+ T cells from children of women with SLE.

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### **HYPOTHESIS 2: CHIMERISM INDUCES A HOST-VERSUS-GRAFT REACTION**

The second hypothesis is that the chimeric cell is the target of a host-versus-graft (HVG)-like reaction. Antigens from the chimeric cells induce an immune response leading to an autoimmune-like reaction, either by a direct response to chimeric cells (Figure 2a) or by cross-reactivity due to molecular mimicry (Figure 2b).

#### ***Host-versus-graft reaction: the direct response***

In the population of pregnancy-derived chimeric cells, progenitor cells are present with the capacity to differentiate into a variety of cells, e.g. endothelial or epithelial cells. Indeed, chimeric cells have been found as parenchymal cells in maternal tissues,<sup>50</sup> a phenomenon which will be discussed in more detail in hypothesis 3. Chimeric parenchymal cells in maternal tissue could elicit a maternal HVG response similar to an acute rejection episode after solid organ transplantation.

Is there evidence in humans for a direct HVG-like reaction leading to an autoimmune-like response? In this scenario, the host has to recognize the chimeric cell as foreign. Fetus-derived chimeric cells may be considered foreign cells because they contain inherited paternal antigens. During and after pregnancy, anti-paternal human leucocyte

antigen (HLA) antibodies have been found in up to 30% of mothers.<sup>51</sup> A number of studies investigated whether HLA class alleles of fetus and mother were related to the occurrence of autoimmune disease.<sup>4,18,34,52-55</sup> Stevens et al.<sup>54</sup> investigated maternal HLA class II compatibility in men with SLE, and they observed that men with SLE significantly more often showed bidirectional HLA class II compatibility with their mothers compared with healthy controls. Also in women with SSc, HLA class II compatibility with their children was found more often than in healthy controls.<sup>18</sup>

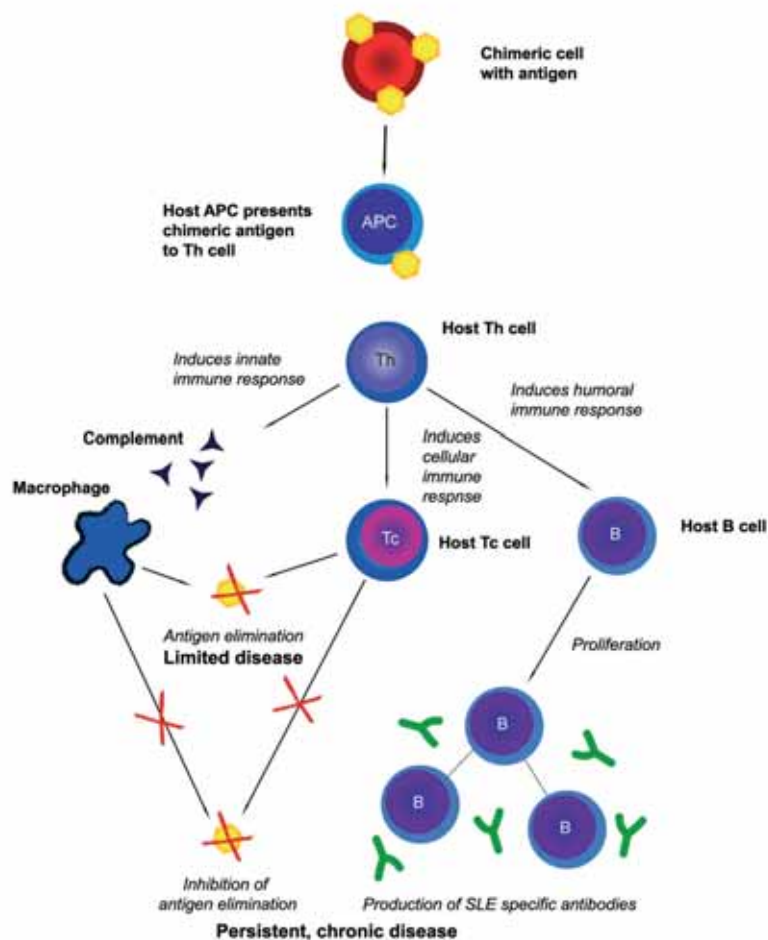
During pregnancy, several mechanisms prevent the immune system of the mother from reacting against the paternal antigens on fetal cells.<sup>56</sup> However, after delivery when these immune tolerance mechanisms of the mother are no longer in effect, the mother may well react against the paternal antigens of the chimeric cells, that may meanwhile have become integrated into her tissues. For the HVG response to occur, chimeric cells would have to be present in involved tissues. This was demonstrated in a study by our group in which chimeric cells were found in renal biopsies of women with lupus nephritis.<sup>24</sup> Because the HVG reaction often results in the removal of chimeric cells, local disease manifestations may be limited, and this may parallel the clinical situation of a patient who experiences a relatively short and limited occurrence of SLE.

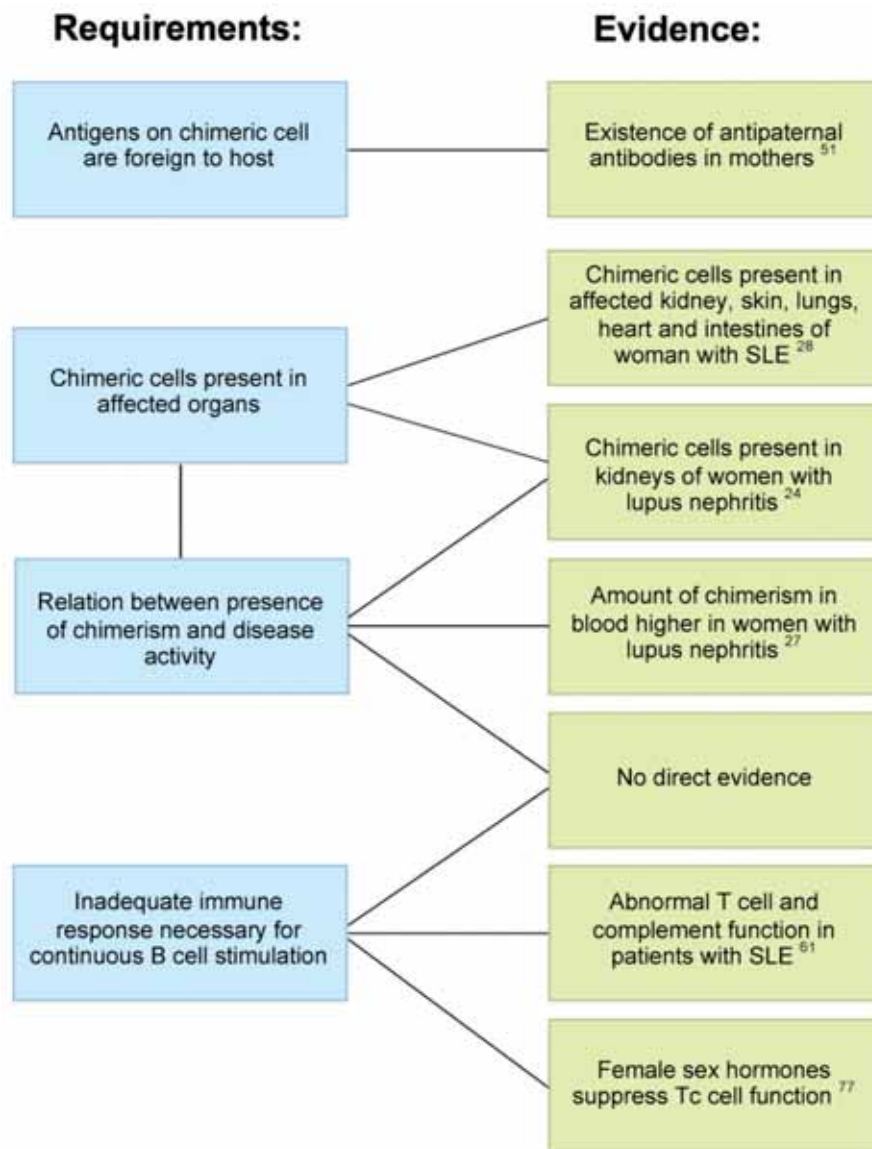
If removal of chimeric antigens fails, for example due to an inadequate immune response of CD8 or natural killer cells, the chimeric cells would continuously stimulate the immune system, leading to a persistent chronic autoimmune-like response; a scenario that is applicable to SLE patients that develop a chronic disease.

A similar mechanism was demonstrated in an experimental HVG mouse model in which an SLE-like disease was induced by injecting BALB/c mice at birth with spleen cells from either (C57BL/6 x BALB/c) F1 or (A/J x BALB/c) F1 hybrids.<sup>57</sup> In this model, antinuclear, anti-ssDNA, thymocytotoxic, and rheumatoid factor-like antibodies developed, together with glomerulonephritis that resembled human lupus nephritis. This reaction was interpreted to be the result of partial tolerance towards donor-alloantigens, as indicated by a clonal deletion of donor-specific cytotoxic T cells and of donor-specific T helper 1 (Th1) cells, and by the persistence of T helper 2 (Th2) cells providing help to donor B cells.<sup>58</sup> This

model suggests that the selective escape from tolerization of donor-specific Th2 cells is the basis of the chronic autoimmune-like development of an HVG response. Studies investigating the immune response of human SLE have demonstrated that abnormal T cell signalling may be involved in the occurrence of persistent inflammation and B cell proliferation in patients with SLE.<sup>59,60</sup> In contrast to the mouse model, however, both Th1 and Th2 are thought to have a pathogenic role in human SLE.<sup>61</sup> To what extent the mechanisms described in the experimental mouse models parallel the pathogenic mechanisms of SLE in humans, is still not completely clear.

**Hypothesis 2a:  
Chimerism induces a host-vs-graft reaction-the direct response**

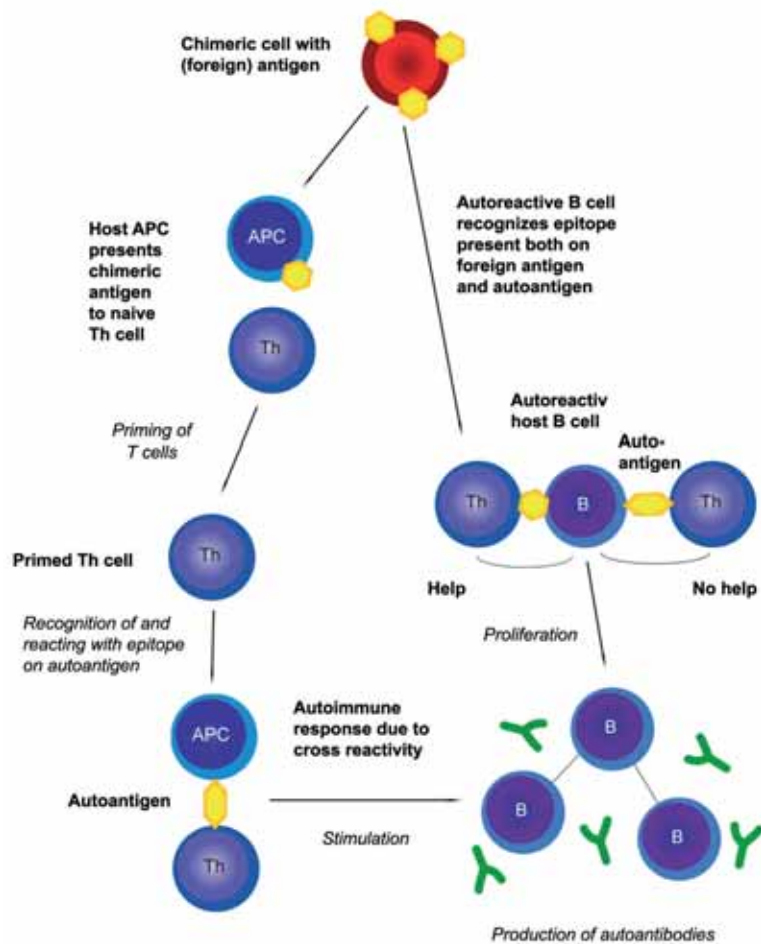


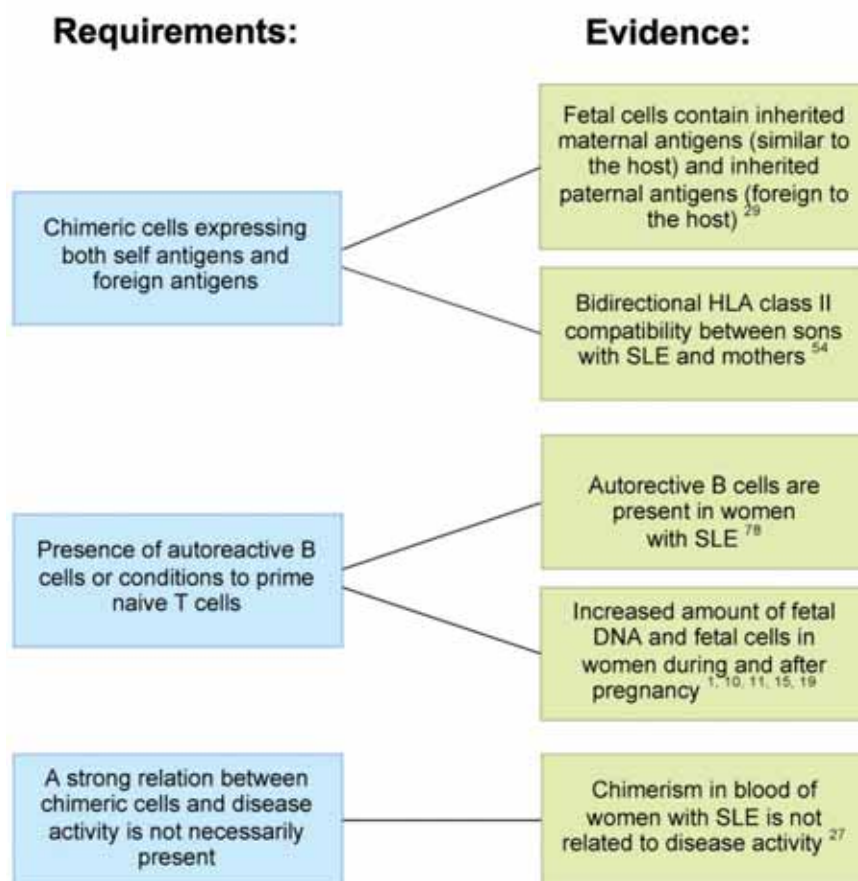


**Figure 2A.** Chimerism induces a HVG reaction – the direct response. Host APCs present a chimeric antigen to a host Th cell, which induces a cascade of reactions through the activation of complement, host Tc cells, and host B cells. If the immune system of the host cannot eliminate the chimeric antigen, the whole process starts again from the top, leading to a continuous stimulation of B cells and a persistent, chronic disease (shown on the bottom). A succesful, local immune response against antigens of chimeric cells causes limited disease, e.g. vasculitis or glomerulonephritis (shown in the middle on the left). APC, antigen presenting cell; HVG, host-versus-graft; Th, T helper; Tc/CTL, cytotoxic T cell. Colors: red, chimeric cell; blue, host cell.

Within the scope of the persisting direct HVG response, a relation between the presence of chimeric cells and disease activity would be expected in humans with SLE. To our knowledge, only one study tried to approach this subject, by showing that women with SLE complicated by lupus nephritis had more male DNA in their blood than women with SLE without renal involvement.<sup>27</sup> However, a clear-cut relationship between the level of chimerism and disease activity was lacking. To further test the HVG hypothesis, future studies should investigate the relationship between the presence of chimeric cells in a particular organ and the extent to which this organ is affected by SLE.

**Hypothesis 2b:  
Chimerism induces a host-vs-graft reaction-molecular mimicry**





**Figure 2B.** Chimerism induces a HVG reaction – because of molecular mimicry, cross-reactivity of chimeric antigens and self-antigens occurs leading to autoimmunity. In the first route (shown on the left), the host APCs present chimeric antigen to naïve Th cells. If these foreign antigens share epitopes with autoantigens of the recipient, the Th cells become primed for these autoantigens. The primed Th cells can then interact with autoantigens and stimulate autoantibodies-producing B cells. In the second route (shown on the right), autoreactive B cells recognize an epitope present both on an autoantigen and a foreign antigen. Normally the B cells present these autoantigens but receive no help from autoreactive Th cells, which are functionally deleted. If a cross-reacting foreign antigen is present, the B cells can present peptides of this molecule to non-autoreactive Th cells, leading to proliferation and secretion of autoantibodies. APC, antigen presenting cell; HVG, host-versus-graft; Th, T helper; Tc/CTL, cytotoxic T cell; Colors: red, chimeric cell; blue, host cell.

**Host-versus-graft reaction: molecular mimicry**

The HVG reaction against chimeric cells can deteriorate into a chronic autoimmune-like disease not only by a direct response, but also by molecular mimicry. In this scenario, the chimeric cells induce an HVG reaction, which in itself is self-limited, but due to cross-

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reactivity based on molecular mimicry between the chimeric antigens and self-antigens of the host, autoimmunity occurs. There are two routes by which molecular mimicry can result in autoimmunity.

First, cross-reactive antigens on chimeric cells may stimulate host naïve autoreactive T cells. This reaction starts when a chimeric cell presents antigens on its surface that are recognized as foreign by the host. Host APCs present these foreign antigens to the naïve T cells. If these foreign antigens share epitopes with self-epitopes of the recipient, the host T cells become primed for self-epitopes. Once T cells are primed for self-epitopes, they can interact with autoantigens.

Second, cross-reactive antigens on the chimeric cell may stimulate host autoreactive B cells. Normally, an autoreactive B cell recognizes a self-epitope on an auto-antigen and presents the antigen to a Th cell, but because autoreactive Th cells are functionally deleted, the process stops here. However, if an antigen derived from a chimeric cell contains epitopes resembling both self-epitopes and foreign epitopes, host Th cells will recognize the foreign epitopes on the antigen and will activate host B cells to proliferate, differentiate, and secrete autoantibodies directed to both foreign and self-antigens.

What are the conditions under which a chimeric cell induces cross-reactivity? Most importantly, the chimeric cell has to express antigens that have similarities with the host, but differ sufficiently from them to induce an immune response. Fetus-derived chimeric cells fulfil these criteria because they contain both self-antigens derived from the mother and foreign paternal antigens.

Evidence supporting the HVG hypothesis is difficult to collect because the antigens that initially induced the cross-reactivity may be absent at the time of disease. In the future, functional studies investigating the immune reaction of the mother to the DNA and cells of her children, as well as intervention studies in experimental models may provide insights into the likeliness of the HVG hypothesis.

### **HYPOTHESIS 3: CHIMERIC CELLS REPAIR INJURED TISSUE**

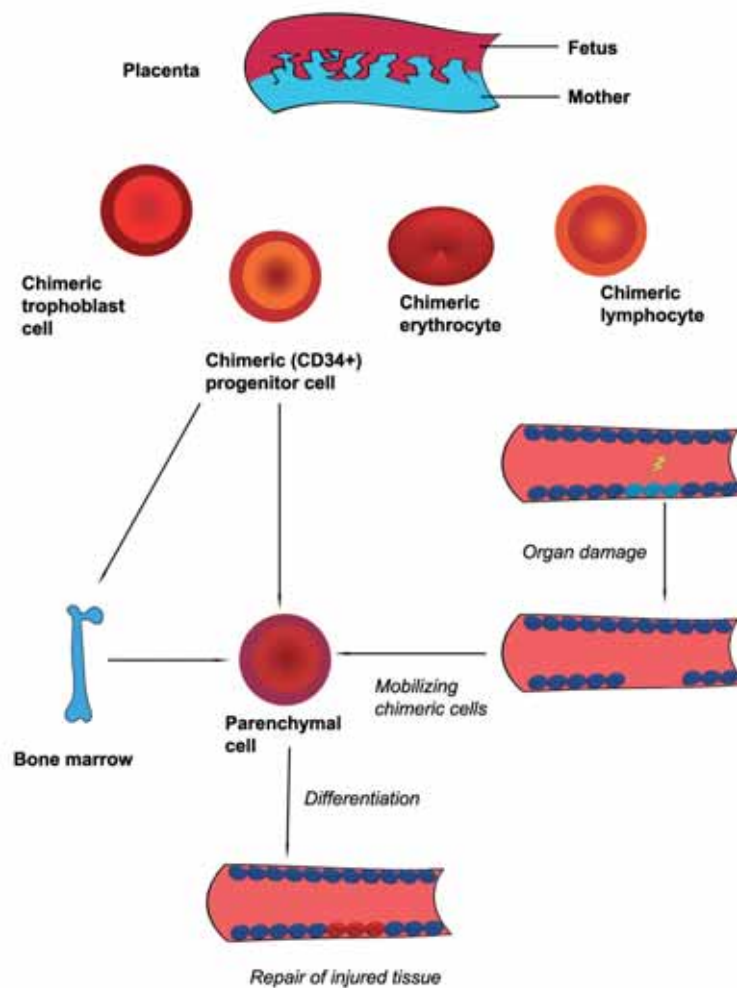
The third hypothesis is that the chimeric cell is not directly involved in the pathogenesis of autoimmune disease, but that its presence in host tissues represents the result of a repair mechanism. This hypothesis suggests that chimeric cells develop from progenitor cells into parenchymal cells and replace damaged host cells after tissue injury. In 1996, Bianchi et al.<sup>14</sup> reported that during pregnancy, fetus-derived CD34+ progenitor cells are present in the maternal circulation. Recently, this group reported that women who had been pregnant with a son in the past had Y chromosome positive cells with a CD45, cytokeratin, or heparin-1 phenotype in tissues affected by various diseases.<sup>50</sup> They concluded that pregnancy may result in the acquisition of a fetal cell population with the capacity for multilineage differentiation and for tissue injury repair. The finding that chimeric progenitor cells are also found in bone marrow would emphasize their longstanding existence.<sup>17</sup> In this study, the authors even suggest that the chimeric cells provide the recipient with a rejuvenating source of progenitor cells.

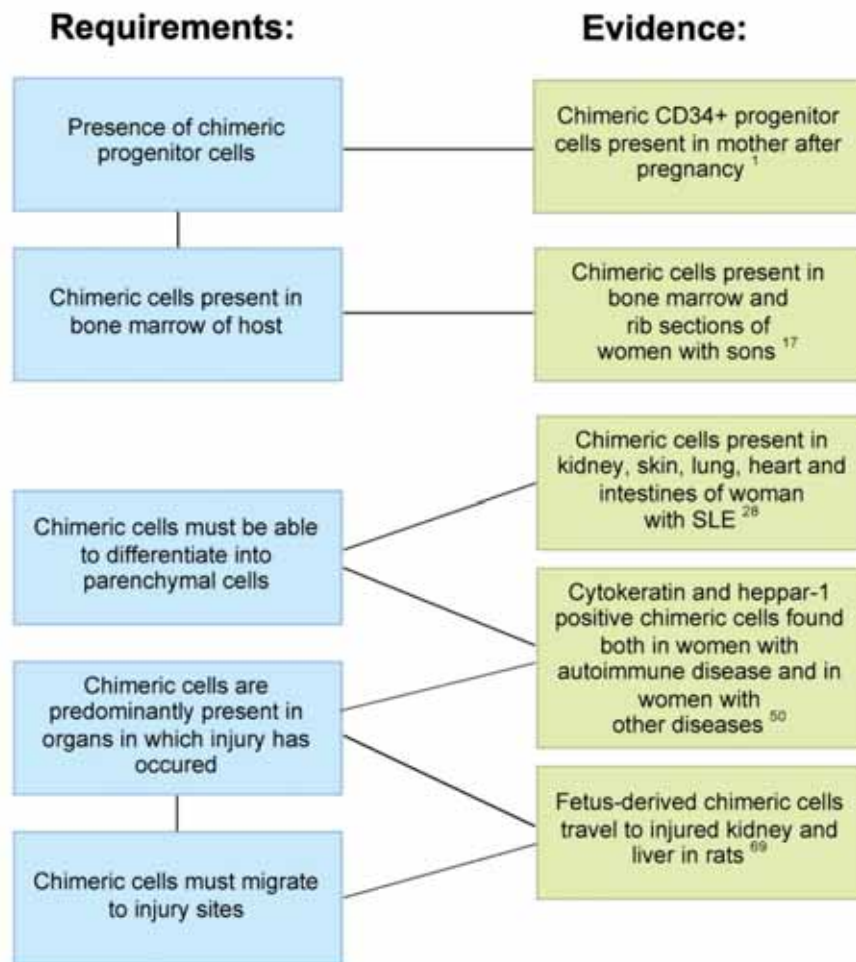
Is there evidence for chimeric cells being important in repair mechanisms in autoimmune disease? Because the organ injury in autoimmune diseases such as SLE can be extensive, the amount of tissue chimerism reflecting repair would be expected to be high. Indeed, tissue chimerism has been described repeatedly in various autoimmune diseases,<sup>18,33,46,62-65</sup> but some studies found that chimerism occurs just as frequently in diseases that are not immune-mediated, though more often than in healthy controls.<sup>64,66,67</sup> Consequently, experiments investigating the repair capacity of chimeric cells have not been limited to the study of autoimmune-damaged tissue, but have been directed toward non-autoimmune injured tissue as well.

In experimental mouse models, cells of fetal origin were detected in the blood, bone marrow, spleen, liver, heart, lung, kidney and brain of the mother by detecting green fluorescent protein-positive (GFP+) cells in a GFP- mother who mated with an enhanced GFP (EGFP) male.<sup>68</sup> Because in this report no mention is made of injury, the chimeric cells may reflect the physiological turnover of cells in organs, a process called 'maintenance'. Using the same model, Wang et al.<sup>69</sup> specifically studied whether fetus-derived chimeric

cells migrate to sites of injury and replace damaged cells. After delivery, kidney injury was induced in the mother mice by administering gentamicine, and liver injury was induced by giving them ethanol. GFP+ cells were found in the injured kidney in tubules, in the liver as hepatocytes, and in the bone marrow.<sup>69</sup> Another study showed the presence of fetus-derived cells in murine maternal brains after induction of excitotoxic lesions.<sup>70</sup> It may be concluded from these studies that various types of injury may give rise to chimeric cell repair, and that injury caused by autoimmune disease is no exception.

### Hypothesis 3: Chimeric cells repair injured tissue





**Figure 3.** Chimeric cells repair injured tissues. Chimeric, pregnancy-derived progenitor cells differentiate into parenchymal cells and replace injured host cells. Colors: red, chimeric cell; blue, host cell.

From a critical point of view, the notion that chimeric cells in tissue truly reflect a repair process cannot be proven by studying human tissue samples at one point in time, and without investigating the phenotype. Other processes, such as tissue maintenance may also be responsible for the occurrence of chimeric cells in tissues, which seems to be the case in normal tissues.<sup>19</sup> Further, it has not been demonstrated yet that the chimeric cells have the same function as host cells. The ultimate criterion for a chimeric cell being

beneficial to the host in tissue repair would lie in the demonstration of its function in its new environment.

In the repair hypothesis, the chimeric cells do not elicit an autoimmune response as in the previous two hypotheses. The function of the chimeric parenchymal cell is regarded as purely beneficial, but there may be a pitfall: suppose that after having successfully repaired injury, chimeric parenchymal cells become a trigger for a detrimental host-versus-graft immune response as described in hypothesis 2. In this scenario, organ sites that have been injured would be at risk for a host-versus-graft immune response at a later time. Future research should investigate whether organs that are particularly affected by an autoimmune disease such as SLE had previously sustained injury.

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### DISCUSSION

We have discussed three different hypotheses that attribute a causative role to the chimeric cells found in patients with autoimmune diseases, especially in patients with SLE. The three hypotheses address different characteristics of the chimeric cells such as phenotype, location, and pathogenic role. It is still too early to speak out a preference for one of these hypotheses on the basis of functional evidence. Moreover, it may be that only a combination of these hypotheses will explain how chimeric cells are involved in the disease process. In recent articles, increasing attention is paid to the repair hypothesis (hypothesis 3),<sup>17,50,71</sup> implicating that chimeric cells are not directly involved in the pathogenesis of autoimmune diseases. However, it should not be forgotten that after successful repair by chimeric cells, a host-versus-graft reaction to these chimeric cells could be induced at a later time, for instance if an altered immunologic response occurs (hypothesis 2).

Other than having either a disease-inducing or a beneficial role, the chimeric cells could be 'innocent bystanders' that do not influence the immune system of the host. It could even be argued that searching for a significant difference between the amount of chimeric cells in women with and without disease is irrelevant. After all, if chimeric

cells are distributed equally throughout the body, and the density of cells increases in diseased tissue (e.g. due to inflammatory infiltrates), more chimeric cells will be found in diseased tissues than in healthy tissues, but this finding would have no relation to the disease process. The relationship between inflammation and the presence of chimerism, reported by Johnson et al.,<sup>28</sup> could be indicative of this theory. This theory is even more supported by the finding that chimeric cells of various immunological cell phenotypes, like T cells, B cells, macrophages and NK cells, have been demonstrated in tissues and blood of autoimmune-affected individuals.<sup>15,24,46,50,55</sup> Until future investigations have provided functional data of the immune competence and differentiating capacities of chimeric cells, the possibility of chimeric cells being innocent bystanders should not be forgotten.

In our descriptions of the hypotheses we have mainly focussed on fetal chimerism in relation to autoimmune disease in women. Maternal chimerism may play a role in autoimmune disease in men and in children.<sup>31,33,34,72</sup> Both stem cells and T cells of maternal origin have been found in cord blood. Evidence for the immunological competence of maternal chimeric T cells was demonstrated by Reed et al.<sup>55</sup> in juvenile dermatomyositis: in this study, chimeric T cells showed increased cytokine production to antigens on host cells. Considering the concept of fetal-maternal cell transfer, it is important to realize that the proportion of, for instance, stem cells and immunocompetent T cells in chimeric fetal and maternal cells is different. However, because the number of transferred chimeric cells is not necessary related to their pathogenic effect, all three hypotheses can also be applied to maternal chimerism. An interesting disease in which maternal chimerism may play a role is neonatal lupus syndrome (NLS), with associated congenital heart block, rash, hepatitis, thrombocytopenia and neutropenia, occurring in the fetus in association with specific anti-Ro and anti-La autoantibodies in the mother.<sup>73</sup> It is unknown why only 1% of fetuses with these antibodies develop NLS with congenital heart block,<sup>73</sup> but Stevens et al.<sup>31</sup> recently demonstrated a relation to the presence of maternal chimeric cells in the heart. This finding fits into hypothesis 2, by which a HVG reaction to parenchymal cells leads to autoimmune disease. These authors suggested that also a GVH reaction (hypothesis 1) could explain for the presence of maternal cells in NLS.<sup>32</sup> A third option is that maternal cells could contribute to tissue

repair (hypothesis 3) because maternal CD34+ cells have been detected in cord blood,<sup>74</sup> and differentiated tissue-specific maternal chimeric cells have been identified in NLS.<sup>31</sup> Concluding, the difference in subpopulations of maternal and fetal chimeric cells may explain why autoimmune disease in newborns and young children is less common than in adults, but further research needs to investigate this issue more thoroughly.

Because pregnancy is very common and autoimmune diseases are rare, it is likely that only certain subsets of chimeric cells have pathogenic potential. In women who have been pregnant several times, a heterogeneous population of fetal chimeric cells is bound to be present. Moreover, it should be mentioned that unrecognized pregnancies can also lead to persistent chimerism in the mother. Studies investigating the occurrence of unrecognized miscarriages have reported that the rate of pregnancy loss prior to the first missed period is approximately 22-30%.<sup>75,76</sup> These findings explain why a clear-cut relationship between pregnancy status and autoimmune disease is practically impossible to investigate, and why until now a direct relation between pregnancy and the occurrence of SLE has not been demonstrated.

In conclusion, the recent finding that many people have chimeric cells which are tolerated long-term and have a stem cell capacity is a fascinating phenomenon that may have both beneficial and harmful consequences in terms of disease. This review structures the results that have been collected in studies investigating the role of chimeric cells and relates them to three pathogenic mechanisms, thereby providing clues for future investigations. In the case of autoimmune diseases, it is critical to determine whether chimeric cells are primarily involved in tissue repair and are therefore beneficial, or whether they initiate a destructive immune response, and cause disease.

## **ACKNOWLEDGMENTS**


We thank Prof. Dr. Els Goulmy and Dr. Astrid van Halteren for critically reading the manuscript. We kindly acknowledge the Gratama Foundation for their support.

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