Review Article

Chimerism
A New Look

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Introduction: Microchimerism has become a familiar term in the past few years. Many groups all over the globe, specializing in a diverse array of basic and medical sciences, have turned their attention to microchimerism, its possible role in disease or repair, and its mechanism of action in the host body. We reviewed the current knowledge about this novel term.

Materials and Methods: We search the PubMed, using all the derivatives of *chimera*. All papers and their bibliographic information published by December 2005 were reviewed and 61 were selected.

Results: Microchimerism is the presence of foreign or nonhost cells in a body. These are cells that live, differentiate, and persist in the host body by definition. These cells can enter the host body in a variety of manners. The most familiar aspect is microchimerism resulting from organ transplant. For many years now scientists have been debating over the interpretation of this phenomenon. We know that donor cell engraftment in the recipient body is a sign of transplantation success. What this means is that the body has developed tolerance toward the foreign organ and created a chimer.

Conclusion: How long this chimeric state will last, whether these cells will induce or be induced to create a chronic complication in the long run, or will these genetically distinct cell types live peacefully in one body to the end of the host's life are the essence of the ongoing discussion and what probes researchers to continue their search.

Keywords: chimerism, stem cell, immune system, transplantation

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INTRODUCTION

As a general rule, nothing is perfect. The human immune system is no exception. A mechanism causing immunity under *normal* conditions may induce tolerance at some points due to an environmental trigger or it might go over the line and break out into a systemic autoimmunity. Therefore, we are almost always dealing with a two-sided blade and the best we can do is to balance the knife and keep everything safe. Many times, nature takes on the role of protection and we might never know it.

For some decades now, we know there is fetomaternal trafficking across the placenta. This fact has been immensely helpful for prenatal diagnosis.[1] But, if these cells enter the maternal body, are they destroyed or do they stay intact? Do they engraft into the mother's body? Will they differentiate? We know the answers to these questions now. The cells that enter the maternal body are not necessarily destroyed. A proportion of them is very likely to stay alive. Some researchers believe fetal cell survival is directly proportionate to fetomaternal compatibility.[2] They argue that if

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fetus HLA is vastly different from the maternal one, these cells will be recognized as foreign elements and destroyed by the maternal immune cells. If the HLA is identical, these cells survive and will give no cause for concern. However, if the HLA is not identical but compatible enough for the maternal body to accept, they will enter the circulation and populate the host body. In such cases, it might be a matter of time before they attack the body and show their dark side.

We must keep in mind that tolerance toward fetal cells or any foreign cell is more likely during the months of pregnancy, because the body is under an immunosuppressed condition to tolerate the fetal graft living within its womb. Thus, it would be ideal if a cell is going to engraft and if the body is going to become tolerant to a non-self-genetic make-up under natural circumstances. Functional studies in this respect are very limited, but these foreign cells have been detected in many tissues including the thyroid gland,[3] the cardiomyocytes,[4] and the peripheral blood.[5] Therefore, we know they disperse. Recent animal studies show such dispersion, as well.[6] No mechanism has been defined for this scattering, but a fair amount is reported to populate the lymph nodes. These cells are called *chimeric cells*. In cases of organ transplantation, the amount of the donor's chimeric cells is great and what results in is chimerism. In the case of pregnancy, blood transfusion or other possible means, as this amount is very little, it is referred to as *microchimerism*.

ROOT OF THE WORD *CHIMERA*

In Greek mythology, there is a fabled creature possessing the strength and body parts of many animals (Figure). What is special about *chimera* is its being almost indestructible. Such a creature is able to compensate for some of its shortcomings, because it not only possesses its own strength, but also has the added strength of another. That was the idea when it entered medical terminology; an experimental animal or a human that accepts another genetic make-up, tolerates it and becomes its permanent host. Where the two-sidedness of the blade comes into play is that chimera—in other words, chimeric cells—might not always be favorable. Of course, it is not very plausible to think of microchimerism as an unfavorable event overall, as it is the work of nature. Another reason we could use as encouraging

The Chimera of Arezzo is a bronze statue found in Arezzo, Italy, in 1553 (Archeological museum in Firenze). Chimera is a mythic three-headed monster.

evidence is its role in transplantation success.[7] This is applicable both to solid organ and bone marrow and stem cell transplantation. For many decades, scientists have been debating over the interpretation of this phenomenon. We know that donor cell engraftment in the recipient's body is a sign of transplantation success.[8] The main concerns are duration this chimeric state will last, whether these cells will induce or be induced to create a chronic complication in the long run, and whether these 2 genetically distinct cell types live peacefully in one body to the end of the host's life.

WHERE DOES STORY OF CHIMERISM BEGIN?

The story of chimerism begins with a hypothesis put forth some years earlier.[9] The underlying general idea was that autoimmune disease occurs more frequently in women. Many women develop symptoms in their 30s or later. This is an age in which hormone changes have passed, old age complications have not taken effect, and most women have children. Bearing children leads to development of microchimerism. Some autoimmune diseases resemble, in form and presentation, chronic graft versus host disease (GVHD). The chronic GVHD is a disease developing in recipients of bone marrow transplantation.[10] It has come to be looked upon as an autoimmune (or allo-autoimmune) disease. Thus, microchimerism could be a cause of autoimmune development.

HOW PREVALENT IS CHIMERIC STATE AFTER PREGNANCY?

Microchimerism is so prevalent, in fact, that we now know it to be a natural phenomenon. Thus, we may conclude that the detection of microchimerism per se is not a signal for health or disease or a risk of any kind, at least none that we know of at this time. Nelson, who originally presented the hypothesis of chimerism being a possible risk for autoimmune disease, published an article in which male microchimerism was detected in mothers with no history of male pregnancy and went on to conclude that it might be induced by other means, some that we are not even aware of.[11] It might even transfer across generations or transfer to a fetus from a previous pregnancy, or a twin. This comes as no surprise knowing that placental transfer is two sided and the fetus is just as likely to become microchimeric by receiving cells from the mother. Therefore, we might in fact carry cells from our ancestors and never become aware of them. Women could donate them to their children, and never realize the diversity of genetic combinations they possess and turn over to their babies.

Microchimerism is a state induced by acceptance of a foreign cell into a body. This is done artificially by transplantation and naturally through pregnancy, blood transfusion, etc. These cells populate many organs and are not confined to the path they must take. Hypothetically, these cells should be undifferentiated cells if they are able to roam about and home to various organs. These cells have been reported to express an antigen appropriate to the organ they reside in. Following this line of reasoning, articles have been published recently stating these cells to be stem cells.[12] These cells are named *pregnancy-associated progenitor cells*.[13] They could therefore be considered a more youthful source of stem cells, perhaps a gift, a token of gratitude given to the maternal host by the fetal donor.

WHAT ROLE COULD STEM CELLS PLAY IN A BODY?

The stem cells could function as a fountain of youth. They have the potential to differentiate into many different cell types. They are called upon to repair damaged tissue and differentiate into the cell type that the microenvironment they enter dictates to them. One of the reasons people become more susceptible in their old ages is because their repair potential decreases. One explanation is that the stem cell pool deteriorates with age. It might be interesting to note that women have longer lives in general. An intriguing study would be delving into the relationship between pregnancy and aging of women. Could this novel source enrich their stem cell pool and give them better chances of damage repair? Could these new refugee soldiers be fortifying the body that accepts them? Could this be the work of nature? Will we reach new conclusions if we look at these microchimeric cells in a positive light and not the potential damage they might be imposing? We must not forget that nature always has two sides to tell about the same story, so we are not denying the possibility that these cells could turn pathologic under certain conditions. What we mean to emphasize here though is the idea that a phenomenon recognized to be natural, and a cell population mostly composed of stem cells could more reasonably be a helpful source and their populating an organ is an outcome of a pathologic condition driving them to the site rather than them being the primary trigger to start a diseased condition.

In 1957 and 1959, microchimerism was reported in twins.[14,15] Liegeois and colleagues showed these cells to have "a stable state of low-ratio proliferation" in the body of successful allogenic bone marrow transplant recipients.[16] Later, Gaillard and colleagues made this statement: "Fetal cells are able to survive and multiply in the hematopoietic organs of the pregnant mouse.[17]" Thus, pregnancy seems to bring about a physiological microchimerism. Meanwhile, in the field of transplantation, a new idea was proposed; induction of chimerism before transplantation could lead to better tolerance.[18]

Starzl and associates[19] reported systemic microchimerism after successful liver transplant and suggested immunosuppression in transplant recipients to promote the microchimeric state. However, negative reports were given where rejection was noted after long-term grafting in recipients who had developed microchimerism,[20,21] while positive speculations surfaced time and again.[22] Some groups were more skeptic about its role,[23] saying that the low frequency observed and the insignificance of HLA match with induction of microchimerism

raises "doubts about a major role of chimerism in development of long-lasting specific tolerance following kidney allografting." Some considered the evidence pointing toward the "apparent dichotomous role of donor cell chimerism in the processes of organ rejection and acceptance.[24]" Reports in the same range were given regarding other transplantations, like that of the heart and the lung.[20] But, studies denying the presence of microchimerism persisted as well.[25] This inconsistency can be attributed to the different methods used and variations in test set up conditions.

From the onset of the 21st century, medical literature is peppered with experiments, opinions, and successful or hopeful signs of positive effect of microchimerism on graft acceptance, whether from solid organ or bone marrow transplants.[26,27] Trauma-induced microchimerism (through blood transfusion) has also been studied.[28,29] Here again, we see microchimerism associated with a diseased condition. Mircochimerism has been looked at the other way, too. It has been reported in diseases of the neonate such as severe combined immunodeficiency and erythema toxicum neonatorum.[30] Chimeric cells have been sited decades later in the offspring blood and organs.[31] Other studies have looked at juvenile idiopathic inflammatory myopathies,[32(juvenile systemic scleroderma,[33] rheumatoid disorders,[34] biliary atresia,[35] neonatal lupus syndrome-congenital heart block,[36] and dermatosis,[37] where microchimerism and its effect are directed toward the child. There is much discrepancy in the results obtained. None show a definite correlation between microchimerism and the onset of disease.

Some groups believe the level of HLA compatibility has a relationship with the persistence of microchimerism, and thus, is a contributing factor to this possible cause or risk factor in autoimmune disease induction.[2,38] Conversely, others challenge the idea of HLA subtypes being a risk factor of this kind.[39]

Animal models of fetomaternal microchimerism have been studied sporadically.[40-42] Animal studies put this phenomenon in a positive and hopeful light. Almost all of them show acceptance of fetal cells and successful engraftment not only in hematopoietic tissues, but also in different organs. These studies have entertained the idea and strengthened the notion of these microchimeric stem cells harbored in the body having repair potentials yet unappreciated and undiscovered.

Since 2000, a different view has been presented. Conclusions start to point to the fact that many other means for microchimeric induction are possible that do not relate to pregnancy at all, and the idea that this is a natural phenomenon and much more common than expected took momentum. Here, the new information shadowed the strength of an argument in favor of microchimerism having a determining role in bringing about an auto- or allo-autoimmune state. Studies started to look at the pattern of microchimerism, questioning whether they get around to different organs in humans as well and found fetal cells homing to multiple organs. They postulated their preferential sequestration to the spleen, site of immune cells. Here, we see evidence of thought lines turning toward fetal *progenitor* cells being a source of help to the mother in as much as saying "The presence of these male cells may also be a result of disease, possibly through the migration of terminally differentiated and/or progenitor cells to areas of tissue damage.[43]" Some start to mention "that immunoablation followed by stem cell rescue could be of potential therapeutic benefit.[33]" Looking at it clearly, we see that it is exactly what is naturally happening in the body. The pregnant mother is being conditioned to an *immunoablation* state, or an immunosuppressed state, so it can tolerate and accept the *graft* or fetus. Then the stem cells, new, unused, and full of potential enter this conditioned host or recipient, home to different organs, and stay there until called upon. When we are copying the act of nature for the benefit of human kind, offering this as a possible therapeutic solution to hopeless disease states, why not possible that nature's purpose for this act is beneficial as well?

In a case review, Johnson and colleagues reported a study on a woman who had suffered from systemic lupus erythematous.[44] In their search for fetal cells they found male cells "in every histologically abnormal tissue type that was examined," while the normal tissue lacked these cells or at least detectable concentration of them. They did not give a definite verdict on the role of these microchimeric cells in the respective tissues. But, with the facts that are now accumulated, could we say, these fetal cells that had

entered the body as stem cells years ago were called upon and summoned to the sites of inflammation and disease when the body needed their aid and played their part in helping heal and repair the organ? Could that be the reason they are found there? Could that explain why normal tissue lacked them, meaning normal tissue was not in any hazard, and this novel source of stem cells was not needed nor summoned to those sites?

Imaizumi and colleagues performed a study on experimental autoimmune thyroiditis in mice.[45] When they isolated the thyroids and examined the green florescent (microchimeric) cells, they found them to be immune cells such as T cell and dendritic cells. We must ask ourselves, if these were the "enemy"? Would they stay in the body so long? We are speaking about fully competent hosts. It seems unlikely they have come to combat the host, but could they be here to aid it? It seems that the host's body is the only "house" they have had since they were "new born" stem cells with no previous memory to hold onto. In a study done on thyroid specimens, microchimeric cells were found in the diseased tissue of many patients, but no detectable population was observed in healthy individuals. They do point to the microchimeric cells as having been stem cells.[46]

Microchimerism has been implicated repeatedly in hyporesponsiveness of the fetal/maternal immune system towards the fetal allograft and in the longevity of organ transplants.[47] Some have taken a more favorable look at this phenomenon in the wake of its seeming helpfulness in haploidentical graft acceptance.[48] What we would like to add to this view is this: there is a possibility that microchimerism is a favorable event. This phenomenon may indeed cover and stop many diseased and potentially unfavorable conditions taking form in the maternal body before they present themselves. We can test the hypothesis the other way around, saying that any diseases that present were stronger than the combined effort of the body's defense system and microchimeric fetal stem cells could combat.

A study on Sjogren's syndrome detected microchimeric cells in the salivary gland and the inflammatory sites, but not in the peripheral blood.[5] The more common view taken in light of this evidence is that because microchimeric cells are more frequent at the site of lesion, they are a destructive force vitalizing the inflammation and promoting disease, possibly even leading to autoimmunity. But, from the same exact evidence, another conclusion could be drawn: when these accepted cells, circulating the body like any other host cell, come to be found more at the site of disease—keeping in mind their greater vigor, younger life, and stem cell origin—they could be the extra help come to the site because of the SOS signals sent by that area to recruit repair forces. They are not as concentrated in other areas because their help is not required there. Here, we can refer to another phenomenon in scientific history which might prove to be relevant in the near future. When lesions were first studied, the infiltrating cells were hypothesized to be the destructive force. The reason was their abundance in the inflamed sites. Later, the theory reversed. The cells in the infiltrates turned out to be immune cells, the essential components in the immune reaction.

By 2000, the idea that these placenta-crossing fetal cells have stem cell potentials had become a familiar speculation, although not studied very deeply. Then, investigators demonstrated a new intriguing result. They found a rare population of mesenchymal stem cells in the maternal body, mesenchymal stem cells that are with fetal markers.[49] They did go on to say they are a rare population and they are not detected postnatally. However, they speculated this could be due to their engraftment in the maternal tissues early on. This is an idea worth looking into. We know much about mesenchymal stem cells these days.[50] Worth noting is their immunosuppressive or immunomodulatory potential, their lack of MHC class II antigens, etc. Besides, a study on posttransplantation engraftment points to the presence of mesenchymal stem cells in the peripheral blood after allogenic transplantation and shows their ability to engraft in the bone marrow.[51] Another study focused on engraftment potential of amnion and chorionic cells from the fetus.[52] The intriguing conclusion is that these cells had mesenchymal stem cell-like profiles that "did not induce allogeneic nor xenogeneic lymphocyte proliferation responses and were able to actively suppress lymphocyte responsiveness." Such cells are suggested for "an advantageous source of progenitor cells with potential applications in a variety of cell therapy and transplantation procedures." If we can use such cells,

or at least investigate the possibility of using cells with such potential for the improvement of human health, what is to say nature has not been doing this all along? When fetal mesenchymal stem cells are engrafting in the maternal body without rejection, a natural allogenic transplantation is in fact taking place.

Autoimmune or autoimmune-like diseases after bone marrow transplantation have been noted several times.[53] As we mentioned before, GVHD is not looked upon as an autoimmune disease per se. This issue, though not proving the matter of microchimerism being capable or responsible for any disease induction, holds the issue in a certain interesting light inviting investigation in this field to actively pursue its course.

Taking the view of fetal cells entering maternal circulation as stem cells, a study was performed on organ specimens that showed favorable results to this end.[54] Namely, XY+ cells were detected in the epithelial, hematopoietic, and hepatic cells, bearing respective markers (cytokeratin, CD45, heppar-1, respectively). Like mentioned earlier, these stem cells entering the body are suggested to be mesenchymal stem cells.[55] These cells enter the maternal circulation in the first trimester of pregnancy and rapidly engraft to the marrow where they reside and possibly differentiate at a later time. This is interesting because the rare population of mesenchymal stem cells is noted for differentiating into all tissue lineages.

It is exciting to think we may be able to develop targeted therapies if we understand the mechanism underlying this phenomenon. The conditions under which the semi-allogenic fetus is tolerated and the modifications the maternal body undergoes for this purpose to be accomplished, plus the function of microchimeric cells, and where, when, and for what purpose they enter the circulation or act as active cells (whether that means immune cells or organ specific cells) are areas that must be actively pursued to arrive at these answers. To examine how natural and widespread microchimerism really is a study was performed on healthy populations very recently, examining the presence of Y chromosome in the liver, the kidney, and the heart of healthy individuals.[56] Results showed that these organs have a fair chance of presenting chimeric cells obtained from different sources at various stages of their lives.

Khosrotehrani and coworkers launched a study on the natural history of microchimerism and pregnancy on an inbred group of mice.[57] They detected a widespread engraftment of fetomaternal cells in the tissues, with an emphasis on lymphoid tissues. Their study gives a favorable outlook to the matter of microchimerism in a body and invite investigations into the possibilities that this issue may offer. Tan and colleagues found these fetal cells in maternal brain, opening up an avenue of new ideas and untested possibilities for brain repair without extensive manipulation.[58]

Some studies have focused on multiple sclerosis (MS) and the possible role microchimerism could play in its onset or persistence. It has been stated in various studies that relapse and disease severity decreases during pregnancy in MS patients.[59,60] Confavreux and colleagues[61] demonstrated that "the decrease in the relapse rate during pregnancy [in MS patients] was more marked than any therapeutic effect reported to date." One more place to consider the usefulness of understanding the natural phenomenon of microchimerism is concerning its relationship with mesenchymal stem cells. As mentioned above, the earliest fetal cells noted to enter the maternal body are found in the first trimester and they engraft to various organs with alacrity. Much of this population has been characterized as fetal mesenchymal stem cells. These cells are noted for their immunosuppressive potential. These cells could be a factor in the improvement seen in the disease condition of pregnant women. True, this matter has been attributed to hormonal changes and T-cell shift from a type 1 helper T cell profile to a type 2 helper T cell; however, with the new emerging evidence, mesenchymal stem cells could well be a plausible addition to the array of factors cooperating in this systemic network to establish the suppressed state a pregnant woman experiences. After all, we know that no isolated factor creates a condition. When we performed the tests in our MS patients, our results gave no significant indication of a relationship between microchimerism and MS induction.[62] The frequencies of microchimerism in the patients and controls were not significantly different. We did, however, observe that among the subjects who were positive for microchimerism, the patients displayed a significantly higher titer. We can conclude that first, the presence of cells in the peripheral blood can be

a sign of migration, and thus, higher quantity means greater need in a different place. These fetal cells are migrating in higher numbers in patients exhibiting microchimerism. Therefore, they may be recruiting to a site of inflammation, injury, etc. Second, MS is a chronic autoimmune disease. Consequently, the factors triggering this disease must have been in the degenerated microenvironment long before symptoms occur. These microchimeric cells are moving in that direction after the onset and outbreak.

CONCLUSION

Considering the plethora of information in scientific literature and their links upon probing, fetal microchimerism can be said to be a *nondestructive* component of the maternal body. Their natural engraftment (successful allogenic transplantation) into maternal tissue, their stem cell features (fountain of youth for the maternal body), and their presence in healthy individuals (almost as frequently as patients) seems to be ample support for their harmless nature. On the other hand, their higher quantity in the detected population was almost exclusively disease related; thus, a more focused study is to be designed to evaluate the reason behind this higher titer. A plausible suggestion is that they are a sign of disease severity or a signal for inflammation. Immune cells do not circulate the peripheral blood in high titers under normal circumstances. The immune network must somehow be involved in a combat and need recruitments to a specific site for these cells to enter the peripheral blood in large numbers. This could mean that microchimeric levels in the peripheral blood are different if measured at various time periods. This issue was pointed out in a study by Tajik and associates[63] where they demonstrated variations in microchimerism detection over a 30-month period follow-up on kidney transplant patients, saying: "Among the microchimeric recipients, none were positive on all posttransplant analyses. Interestingly, nonmicrochimeric cases were negative throughout the study." They offered no explanation for this observation. Today, we may have the information to offer a possible interpretation. Under immune active circumstances, immune cells and stem cells will migrate to the concerned site. The microchimeric cells, whether as immune cells or stem cells, could be part of the recruitments. Thus, in such cases microchimerism should be higher. However, to draw a definite conclusion, functional studies are warranted. These are only speculations worth investigation.

CONFLICT OF INTEREST

None declared.

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