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Review Article

Unknown Mystery of Microchimerism

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Abstract

Chimera is defined as a monsterous made up of parts of multiple animals in mythology. Today, the term chimera is used in the fields of genetics and molecular biology to describe living entities that emerge or are created as mixtures of separate entities. Therefore, microchimerism (Mc) is defined by the presence in an individual of a small number of cells or DNA belonging to a genetically different individual. Pregnancy is the most common and natural cause of chimerism and occurs by the bi-directional passage of hematopoietic cells through the placenta between mother and fetus. Bidirectional cell exchange between pregnant woman and fetus during pregnancy potentially leads to microchimerism (Mc) in both the mother and the fetus. Therefore, we are all born as microchimeric.

Keywords: Microchimerism; Fetal-Maternal Microchimeric Cells; Autoimmune Diseases; Viral Disease; Canser; Jung-Archetypal

Introduction

The presence of fetal cells in the maternal circulation has been known for a century. However, the biological effects of this cell migration have not been extensively studied. Fetal microchimeric cells (FMcCs) remain in the mother's bone marrow, blood and tissues for many years after birth. Although, we haven't found FMcCs in the human brain [1], in a recent study, it was confirmed that maternal mikrochimeric cells (MMcCs) were detected in the blood and brain of the offspring of transgenic female mice, and differentiated into both neuron and glial cell types in the brain [2]. In this study, the cells identified as maternal cells can be the mother's own cells, as well as the fetal cells that are passed on from mother to offspring by breastfeeding. There is no clear explanation on this matter. But, the study definitively demonstrated that breast milk cells in mice can induce Mc in the brain via breastfeeding. Nevertheless, it is not yet known exactly how microchimeric cells (McCs) migrate to the new environment and how they survive, integrate and differentiate in this environment. Although there are many unanswered questions, it is thought that chimerism has an important place in terms of human health. For many years, it has been suspected that maternal microchimeric cells (MMcCs) could have clinical implications for organ repair and cancer treatment. The meaning of chimerism is deep and mysterious. Chimerism has both disease potential and health benefits and provides a great experimental tool to deepen our understanding of microchimeric cell biology. It can be stated that chimerism advances scientific knowledge in a way that provides opportunities for new insights into how we view disease, genetics, and even the natüre [3]. Although the exact role of fetal microchimerism (FMc) is little known, it remains an unresolved topic. However, three hypotheses have been put forward in the last decade. The first one speculates that FMcCs can induce a response similar to graft-versus-host disease with chronic

inflammatory responses leading to tissue damage in maternal tissues. The second hypothesis is that FMc may have a protective role in the repair of damaged tissues, cancer surveillance, and control of viral infections. Finally, some claim that FMcCs are formed by chance during pregnancy, which is of no biological significance. However, the phenomenon of fetal-maternal microchimerism (F-MMc) involves a number of questions. In this review, we consider Mc to be a physiological event.

Microchimerism is part of the immune system and to strengthen the immune system, throughout the history of mankind, information about the mother's immune system is transmitted to the next generation

FMcCs are more frequent in the blood of healthy women compared with patients with neoplasms, which indicates that FMcCs have the potential to participate in immune surveillance These FMcCs do not return to the MMcCs, but are involved in the construction of various tissues and organs. At the same time, it is assumed that fetal cells in the mother after birth are apparently not rejected and permanent. It is known that the number of FMcCs increases in autoimmune diseases. On the other hand, although the biological purpose of MMcCs is unknown, some findings can be obtained by characterizing their phenotypes in tissues. MMcCs that occur during pregnancy are not eliminated by the fetus's immune system and can persist into adult life. MMcCs that migrate to the fetus can integrate with the immune and organ systems of the fetus. MMcCs can survive in the child's body for life and play a role in triggering or maintaining chronic inflammatory autoimmune diseases in the context of certain major histocompatibility genes. Infectious diseases can disrupt the routine cell migration between mother and fetus. When the fetal immune system is exposed to infectious agents, the mother's cellular defense system goes out of routine to protect the fetus.

It is not known when allogeneic antigens on maternal cells can be detected and attacked by fetal cells. It is not known why the fetal immune system does not eliminate allogeneic maternal cells. There is evidence that MMc is common in newborn mice. MMcH have been detected in the bone marrow, spleen, liver, lymph nodes, thymus and heart, brain and lungs i immunocompromised mice [4-6]. There is a link between measles and influenza infections in the mother during pregnancy and the development of schizophrenia spectrum disorder in children. Similarly, it has been reported that there is a parallel relationship between antibodies against the herpes simplex virus developed in the mother during pregnancy and the frequency of psychosis that increases in the child's adulthood [7]. According to this; immune cells of the fetus may be reactive to maternal antigens and therefore are known to trigger a reaction. These reactions show that they are an effective mechanism in the initiation or exacerbation of autoimmune diseases [8].

When the human is born, the general image of the world is present in itself. The information that the genes carries is not just from the parents, they contain all the information from their first ancestor, even the evolution of all living things. It is thought that some information coming from the beginning of nature is transferred to the next generations through inheritance. If the collective is unconscious, it consists of images that the Jung has called "archetypal" [9]. These images are passed on from person to person over generations. These images are not only the product of human history, but also the pre-human evolution. Archetypes are the source of the fact that people have similar tendencies to the one that their ancestors developed in the past. We think that this transition is with both MMcCs and FMcCs. While MMcCs jointly transmit information with unconsciousness and the specialized cells to the fetus, through FMCs, they passed through the mother's body and received information from collective unconscious sources and the FMcCs cells that acquire this information return the fetus by breastfeeding. In these ways, transfer of information to the offspring of the conscious outside information is guaranteed by maternal-fetal cell transfer.

We advocate the following opinions in this regard

MMc may be transferring the bio-psycho-social informations, immunity informations, traumas, myths and archetypes to the new generation. During zygote formation, informations may be lost due to mismatching genetic codes between mother and father. To minimize the loss of information, a fetal-maternal microchemical pathway may be preferred. Jung's archetypes thought to be genetically transitive and the information that provides our perception is also actually provided by microchimeric transitions. In the direction of all this information, as a geneticist, I think that all human biopsychosocial information can not pass through chromosomes and that the ancestral informations are copied from the mother with FMcCs to new generations.

Microchimerism physiopathology; Fetal-maternal microchimerism may be an explanation of the diseases?

There may be times when not every physiological event is always going right. For example, your mother's passing viral disease

[10]. Maternal leukocytes protect the fetus from viral disease since the fetus's immune system is not yet fully developed. Maternal infective diseases may increase the routine cell migration between mother and fetus. It plays a role in the construction of various tissues and organs without returning the mother's cells that pass to the fetus to protect against fetal infections.

Various comments are made about the functions of these MMcCs that settle in fetal tissues and do not return. The damages in intelligence and behavior in this regard are the best known. The best known evidence among these is the link between schizophrenia disease seen in children and maternal respiratory tract infection [11,12]. There is an increase in the number of schizophrenia in children of mothers who conceive in the winter and spring months. Therefore, the risk of schizophrenia in offspring in the second trimester increases 3-fold with the presence of infection [11]. In many animal studies, it has been shown that infections in prenatal or early postnatal offspring can lead to autistic features or neurological and behavioral abnormalities resembling schizophrenia [13,14].

Little is known about the etiology of autistic disorders (ASD). It has been reported that maternal rubella infection has a significant effect in autism and is an increased risk for other maternal viral infections [15-17]. In the epidemiology of autism, it has been reported that maternal rubella infections increase 200 times in autism [18]. Considering that prenatal infections such as rubella, cytomegalovirus or *Toxoplasma gondii* have a teratogenic effect on the central nervous system, prenatal infection is a suitable risk factor for ASD [19]. It has been reported that influenza infection during pregnancy in pregnant rodents showed this risk factor in animals and the offspring showed various behavioral and histological abnormalities similar to human mental illness [20]. However, in one of our study, MMc levels were found to be higher in women with postpartum depression than in healthy women [21].

It is thought that MMcCs first transform into maternal microchimeric stem cells, then differentiate to participate in the construction of fetal tissues and organs, and some of them do not differentiate and survive to repair future tissue damage [22]. FMcCs in the mother's breast do not actually contribute to the health of the mother, and after these cells mature and shaped in the breast, they pass back to the baby by breastfeeding. If the mother has a miscarriage or abortion, the FMcCs will not be transferred to the child and will remain in the mother's breast tissue and will have to wait. These FMcCs, which do not return to the fetus, cause alloimmunity (GVHD) even at low concentrations and can even cause cancer. McCs have multiple potentials that play important roles in immunological competence and autoimmune disorders, cancer, tissue repair, and transplant rejection or graft-host reactions. Researchers have suggested that some fetal cells escape from maternal immune surveillance mechanisms and may play a role in the pathogenesis of some autoimmune diseases resembling chronic graft-host responses [23,24].

It has been suggested that fetal immune cells react to maternal antigens and thus may trigger a graft-shock reaction. Some autoimmune diseases seen in women may be alloimmune and may develop as a result of chronic graft-host response that develops due to fetal cells. Recent research suggests that Mc may play a role in the development of autoimmune diseases and that autoimmune diseases may not be an autoimmune disease but an alloimmune disease. It has been found that the amount of FMcC in the blood and tissues of women with autoimmune disease is higher than that of healthy women. The disease stages of autoimmune diseases and their healing process are also observed in psychiatric diseases. FMcCs are also thought to cause maternal cancers. Thus, McCs could potentially serve as effector cells or as the result of an immune response. Some studies have shown that McCs are found more in subjects with autoimmune thyroid disease than in other thyroid diseases [25,26].

Can the maternal microchimeric stem cells transform into physiopathological form?

MMc has been associated with pathological conditions such as autoimmune diseases, systemic sclerosis, systemic lupus erythematosus and neonatal lupus syndrome [27]. Operating within physiological limits, McCs can also become physiopathological. It has been suggested that FMcCs may be effective in rejuvenating progenitor cells, repairing maternal tissues, controlling malignant cells or in association with cancer [28-30]. Changes in the microniches of these cells can also lead them in unwanted different directions. The age of the MMcCs passing through the fetus is as old as your mother and is older than the FCs. In addition, MMcCs are under the influence of the GVHD? MMcCs can act as a source of stem cells for new cell generation. MMcCs can undergo apoptosis and regenerate several times under the influence of the inflamma-

tory response. This destruction-regeneration event can shorten the telomeres of MMcCs. After a while, under the stress of this destruction and restructuring, MMcCs may be able to become cancer cells. What we're focusing on here is if Mc can play a role in carcinogenesis? Whether F-McCs has a beneficial or harmful effect must depend on what type of cell they turn into. Large populations of fetal origin immune cells that survive in healthy adult tissues can cause malignant lesions. In recent years, McCs' view that they can play a role in the initiation and pathogenesis of cancer has become the focus of intense research. However, the role that F-MMcCs can play in cancer is only just beginning to be understood. The pathogenic MC concept was first proposed by Nelson [23]. Some researchers have recently stated that these McCs help tissue repair, pathogenicity, and progression of cancer [31].

The presence of MC has been documented in autoimmune diseases and non-autoimmune diseases such as hepatitis C, breast, thyroid, cervix, lung cancers, hematological malignancies, and some tumors such as melanomas. The presence of these cells has been postulated to play a protective role for these diseases. It has also been suggested that FMc has a positive effect on tumor burden in malignant tumors, however, some evidence suggests that FMCs may play a role in neoplastic progression. It has been suggested that FMcCs are present in damaged tissue regions and that they may have originated from bone marrow-derived or locally proliferating stem cells [32]. It has also been suggested that FMcCs have tumorigenic potential and can act as cancer stem cells [33]. In a mouse model, it has been shown that fetal cells are involved in the formation of most lung tumors. According to these studies, it is unclear whether FMcCs are involved in tissue repair or contribute to tumor growth. It has been hypothesized that FMcCs are involved in chronic inflammatory responses that lead to tissue damage or are involved in the repair of damaged tissue and the fight against infections. Unfortunately, the biological roles of these cells have not yet been fully determined. Why are McCs common in cancer patients' tissues but not in controls?

Some evidence suggests that FMcCs may play a role in neoplastic progression in malignant tumors. FMcCs have been found in tumor sections of malignancies such as thyroid, breast, cervix, lung cancers and melanomas, and it has been shown that they differ from epithelial, hematopoietic, endothelial and mesenchymal cells. The frequency of lung tumors was found to be several times higher than the surrounding healthy lung tissue. It has also been shown that FMcCs accumulate in lung tumors in women decades after birth [34]. As a result of mutation or microenvironmental effects, these cells may lose their normal function of controlling cell proliferation and differentiation, and therefore cancer may develop. It seems plausible that as a result of genetic or epigenetic changes in their microenvironmental niches, these cells could act as cancer stem cells and cause tumors.

Endothelial male cells can contribute to tumor progression. This situation shows that FMc has a pathogenic mechanism. Indeed, the high prevalence of breast cancer in women who have given birth and a clear predisposition to thyroid cancer in women do not show the protective effect of FMc. The average frequency of fetal cells in the blood of healthy women is significantly higher than those with breast cancer. Breast carcinomas or melanomas are known to be more severe during pregnancy. This may be related to their active role in the complex tumor formation process, including the emergence of MMcCs in tumor tissues, tumor initiation and integration into the tumor stroma [35], neoangiogenesis, facilitation of metastasis [36] and the spread of the tumor, including induction of immune responses [37,38]. However, FMcCs can differentiate into mature thyroid follicles of the mother with favorable environmental and developmental factors [39]. At the same time, although the existence of FMcCs has been definitively demonstrated in many studies, so far their role has only been hypothesized on the basis of relational studies and has not yet been fully elucidated. We believe that Mc can be an important alternative explanation in explaining the etiology of diseases. All this information suggests that pluripotent McCs can turn into cancer stem cells. Therefore, we can say that Mc may have a role in cancer development.

Conclusion

We believe that Mc may be an important alternative explanation to the etiology of psychiatric diseases, postpartum debression and cancer development. The strongest evidence for maternal infection increasing risk for a mental disorder in the offspring is the connection between schizophrenia and maternal respiratory infection. Mc is known to play an etiological role in autoimmune diseases, and may also be the causative factor in the development of schizophrenia and cancers. McCs may interfere with the neural development of the fetus and may increase the risk of offspring neurological dysfunction and psychiatric disorders. Fetal microchimerism can also

be one of the possible causes of postnatal depression. However, we suggest that the phenomenon of fetal-maternal microchimerism (F-MMc) inspires numerous questions. In this review, we think that Mc is a physiological phenomenon. But, this phenomenon can also turn into physiopathology under inappropriate conditions. The biological significance of harboring Mc in the mental and cancer diseases requires further investigation.

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