PIONEER
ACADEMIC PUBLISHING LIMITED

Current Research in Medical Sciences
ISSN 2958-0390
www.pioneerpublisher.com/crms
Volume 1 Number 1 December 2022

Physiological and Pathological Effects of Fetal and Maternal Microchimerism

Osman DEMİRHAN[1]

[1] Department of Medical Biology, Faculty of Medicine, Çukurova University, Adana-Turkey
Correspondence: Osman DEMİRHAN, Department of Medical Biology, Faculty of Medicine, Çukurova University, Adana-Turkey.

doi:10.56397/CRMS.2022.12.03

Abstract

Microchimerism (Mc) is a bidirectional exchange of fetal and maternal cells during pregnancy. Pregnancy is the most common and natural cause of chimerism. Therefore, we are all born as microchimera. Although there are many unanswered questions it is thought that chimerism has an important role in human health. For many years, the clinical effects of microchimeric cells (McCs) in organ repair and cancer therapy have just begun to be understood. While the mission of chimerism is straight forward, the subject is profound. Chimerism carries the potential for disease as well as for health benefits. This article describes the role of Mc in the etiology of psychotic disorders. In this review, we consider Mc to be a physiological phenomenon, but it can also transform into pathology under inappropriate conditions. We describe in detail below the possible physio-pathological roles of F-MMcCs.

Keywords: microchimerism, Fetal-Maternal Microchimeric Cells, autoimmune diseases, viral disease, cancer, psychiatric disorders

1. Introduction

The term chimera describes a single organism with cell or DNA lines originating from two or more different zygotes. This is different from mosaicism, which results from postzygotic genetic mutations or nondisjunction events in a single zygote. Microchimerism (Mc) is the presence of small amounts of foreign cells or DNA in an individual's circulation or tissues. Human chimerism may occur naturally or artificially. Three forms of naturally occurring chimerism in man are known. These are: blood group chimerism, microchimerism and fusion chimerism. A small amount of fetal DNA can be found in the mother's blood during pregnancy. Fetal microchimerism (FMc) is the most common type of naturally occurring human chimerism (Parivesh A, Barseghyan H, Délot E & Vilain E., 2019). During pregnancy, two-way cell exchange takes place between the mother and the fetus via the placenta (Boddy AM, Fortunato A, Sayres MW & Aktipis A., 2015). Fetal cells cross the placenta to the mother and integrate into the mother's organs. As a result of this; potentially Mc formation occurs

in both mother and baby. Thus, no one is born pure, so we are all born microchimeric. Why are we born microchimeric? The existence of fetal cells in the mother's circulating blood has been known for nearly a century. However, the biological implications of the discovery of these microchimeric cells are still largely unexplored. Fetal microchimeric cells (FMcCs) survive in maternal blood and other tissues for many years after birth. There are many unanswered questions about chimerism. However, it is thought to have an important role in human health. How these cells survive, how they adapt to the new environment, and how they acquire their ability to differentiate has not yet been explained. It is thought that chimerism may have an important role in human health. Related to this, the clinical effects of maternal microchimeric cells (MMcCs) in organ repair, cancer development and treatment are only just beginning to be understood. However, the physiological function or purpose of chimerism is not fully known and still remains a mystery. Chimerism is assumed to have both health and physiopathological effects. New experimental work in this area offers opportunities to provide new perspectives in elucidating the biological roles of these cells in the genesis and development of diseases. FMc may have conflicting roles for maternal health. These functions may be beneficial, detrimental, or neutral to maternal pathophysiology (O'Donoghue K, SultanH. A, Al-Allaf FA, Anderson JR, Wyatt-Ashmead J & Fisk NM., 2008).

Although little is known about the biological role of FMc, it is still an unknown issue. Nevertheless, the presence of fetal cells has been associated with both positive and negative effects on maternal health. In this regard, three hypotheses have been put forward in the last decade. The first of these; it is thought that FMcCs in maternal tissues may cause an immunological response similar to graft-host disease, with chronic inflammatory responses leading to tissue damage. Second hypothesis; it has been reported that FMc cells may have a protective role in the repair of damaged tissues, in the development of cancer and in the control of viral infections, and that it is only an accidental physiological event with no biological significance during pregnancy. Despite these possible insights, F-MMc contains many unknowns. In this article, it has been revealed that Mc is actually a physiological event and Mc cells can undergo physiopathological transformation under unsuitable conditions. The possible roles of the F-MMcCs, as well as the possible roles mentioned above, are described below (Figure 1).

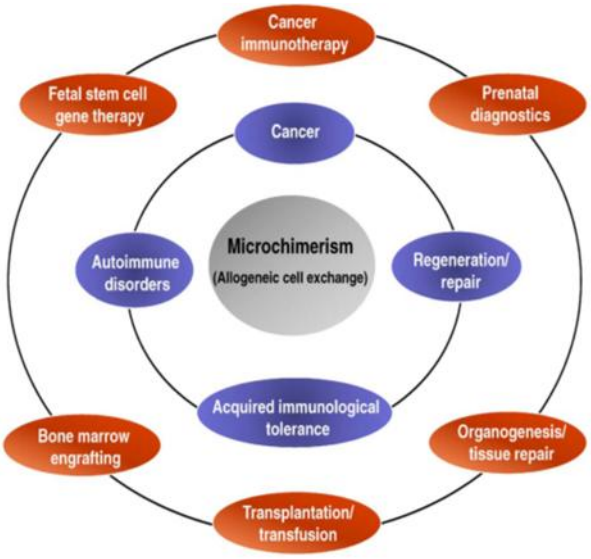

Figure 1.

Description: Fetal and maternal cell change, persistence of allogeneic stem cells in tissues and organs, defined biological states and relations with diseases (inner circle). Therapeutic strategies (outer circle); Induction of immune tolerance and multipotential transfer of cells in a haplo-identical mother and child (4).

2. Microchimerism Can Be a Part of the Immune System, Transmitting the Mother's Immune Information to New Generations to Strengthen the Immune System Throughout Human History

FMcCs are found more frequently in the blood of healthy people compared to women with cancer (Gadi VK, Malone KE Guthrie KA & Porter PL, Nelson JL., 2008). This suggests that these cells have the potential to be involved in the surveillance of the immune system. The first studies on microchimerism were done on a group of autoimmune diseases. Autoimmune diseases are a heterogeneous group of diseases and are characterized by pathological responses directed to the individual's own tissue (Klonisch T & Drouin R., 2009). Since most autoimmune diseases are common in women, the frequency of some

autoimmune diseases increases after pregnancy and resembles chronic graft versus host disease, it has been thought that microchimerism may play a role in the pathogenesis of these diseases. It has been hypothesized that fetal cell microchimerism plays a role in autoimmune diseases. (Kamper-Jorgensen, M., Hjalgrim, H., Andersen, A.N.N., Gadi, W.K., Tjonneland, A., et al., 2014). At the same time, fetal cells may remain in the mother after birth without any overt immune rejection. Similar to autoimmune diseases, papillary thyroid cancer and breast cancer are more prevalent in females; therefore, fetal microchimerism may contribute to the etiology of these diseases. It is known that the number of FMcCs increases in autoimmune diseases (Brandon NJ, Ehli1 EA, Davies GE & Boomsma DI., 2020), but the biological role of MMcCs is not fully known. Maternal cells passed to the baby during pregnancy cannot be eliminated by the baby's immune system, which may persist into adulthood and adapt and integrate with the fetal immune system and organ systems. In addition, it has been associated with the triggering of chronic inflammatory autoimmune diseases due to maternal tissue compatibility of these cells. Infectious diseases also increase physiological cell migration between mother and fetüs (Davies D & Demirhan O., 2019). Thus, the mother's cellular immune system goes out of routine and becomes more active to protect the fetus. It is not known whether maternal cells attack antigens alone or together with fetal cells due to allogeneic similarity. It is known that normally the fetal immune system does not give an immune reaction, probably because of allogeneic genetic similarity to the mother's cells. Indeed, it has been reported that the presence of MMc is common in newborn mice, and the presence of MMcCs in the hematopoietic organs, heart, brain and lung of immunocompromised mice (Piotrowski P & Croy BA., 1996; Arvola M, Gustafsson E, Svensson L, et al., 2000; Marleau AM, Greenwood JD, Wei Q, et al., 2003). There is a high correlation between the occurrence of schizophrenia in the offspring of mothers exposed to measles and influenza infections during pregnancy. However, it has been reported that there is a relationship between the increased amount of maternal antibodies against the herpes simplex virus during pregnancy and the increased risk of psychosis in the child in adulthood (Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R & Jones PB., 2015). According to the research; fetal immune cells may be reactive to maternal antigens and trigger a counter-reaction. This may be an effective mechanism in the onset or exacerbation of autoimmune diseases (Ando T & Davies TF., 2003).

It is thought that human beings not only inherited genes from their parents, but also acquired some of the gains they gained in the evolution process from their first ancestors with microchimeric cells. It is thought that some unconscious information from the beginning of nature is passed on to the next generations through heredity. This collective unconscious consists of what Jung called "archetypal" (Jung CG & Hull RFC., 1981) images. These images are passed on from person to person for generations. These images are the product of not only human history, but also pre-human evolution. Archetypes are the source of people having tendencies similar to those developed by their ancestors in the past. This transition is thought to occur via both MMcCs and FMcCs. It is assumed that MMcCs can collectively transmit unconscious information and specialized cells to the fetus, while FMCs can pass through the mother's body and receive information from collective unconscious sources and that these cells are passed back to the baby through breastfeeding. In this way, it is thought that the transfer of conscious external information to the offspring is provided by maternal-fetal cell transfer.

3. Microchimerism Physiopathology; Fetal-Maternal Microchimerism May Be the Cause of Diseases

All physiological events in the human body may not always go normally (such as physiopathological conditions). Since the fetal immune system is not yet fully developed, the mother's leukocytes migrate to the fetus and are known to protect the baby from viral diseases. This may increase routine microchimeric cell migration between mother and fetus. In order to protect against infectious agents, MMcCs passed to the fetus do not return and may settle in various tissues and organs of the fetus. Various opinions have been put forward about the functions of these mother cells, which settle in the tissues and do not return. In this regard, it is known that the

intelligence and behavior of the fetus are most affected. The best-known evidence of an increased risk of mental disorders in the children of mothers who contracted infections during pregnancy is the strong relationship between schizophrenic children and maternal respiratory tract infections (Betts KS, Williams GM, Najman JM et al., 2015; Demirbek B & Yurt E., 2011; Brown AS., 2006) (Figure 2)

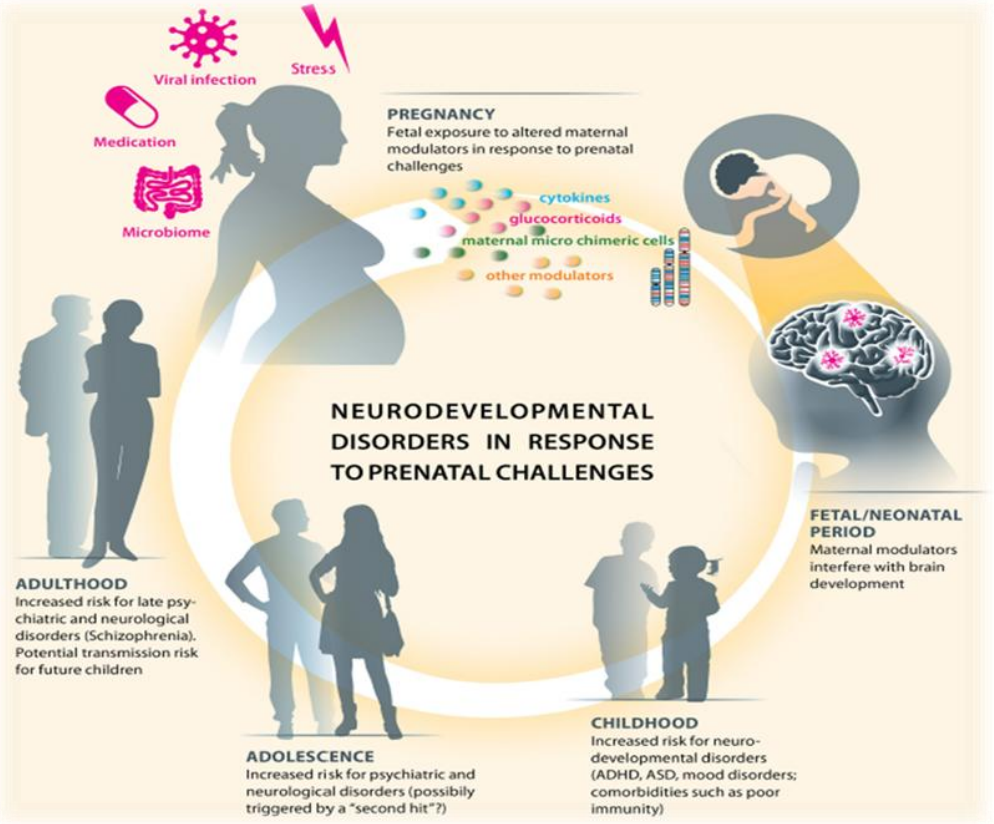

Figure 2. Prenatal difficulties and related changes in immune and endocrine markers may cause postnatal neurodevelopmental disorders

Maternal health, during pregnancy, for example; may be affected by stress or infections. These conditions lead to increased levels of cytokines and glucocorticoids, and potentially to an increased frequency of maternal microchimeric (MMcC) cells in infants. After migrating to the fetal brain, MMcCs can significantly disrupt the physiological development of the brain by acting as maternal modulators. Genetic susceptibility and disruption in brain development may increase the risk of neurodevelopment of the child after birth. In addition, postnatal environmental risks, drug addiction, traumas and infections may have contributed to the triggering of prenatal diseases (such as neurodevelopment, psychiatric and neurological diseases) (Ando T & Davies TF., 2003).

An increased risk of schizophrenia has been found in children born to mothers who became pregnant in the winter and spring and who contracted viral infections. In scientific studies; it has been reported that the risk of developing schizophrenia increases 3 times in the children of mothers who are infected in the second trimester of pregnancy (Penner JD & Brown AS., 2007). The rubella epidemic in 1964 increased the frequency of patients with schizophrenia from 1% to 20% (O'Donoghue K, SultanH. A, Al-Allaf FA, Anderson JR, Wyatt-Ashmead J & Fisk NM., 2008). In animal studies, it has been reported that the mother's prenatal or early postnatal infection causes acute and permanent neurological

behavioral abnormalities similar to autistic features or schizophrenia in the offspring (Meyer U, Feldon J & Dammann O., 2011; Patterson PH., 2011a). Little is known about the etiology of autism spectrum disorders .

However, it has been reported that the mother's measles infection during pregnancy has a very significant effect on the formation of autism, and other viral infections pose a high risk for the mother (Hyman SL, Arndt TL & Rodier PM., 2006; Moy SS, Nadler JJ., 2008; Patterson PH., 2002). In epidemiological studies, it was reported that autism increased 200 times in children of mothers who had measles infection (Brown AS., 2006). Infections such as prenatal infections, measles, cytomegalovirus or toxoplasma gondii have teratogenic effects on the central nervous system. This may also be a possible risk factor for autism spectrum disorders (Chess S., 1997). It has been reported that these risk factors show human-like behavioral disorders of influenza infection in pregnant rodents and histological abnormalities in offspring (Johnson RT., 1994). The common response to these pathogens is the maternal immune response. It has also been reported that exposure to conditions that cause high immune response, such as maternal autoimmune diseases, allergies, asthma and acute stress, increase the risk of schizophrenia (Marleau AM, Greenwood JD, Wei Q, et al., 2003; Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R & Jones PB., 2015). All these findings show that neuroinflammation and the immune system play an important role in the pathophysiology of schizophrenia (Betts KS, Williams GM, Najman JM et al., 2015). However, there are reports that immune activation poses a risk for the onset of schizophrenia in adolescents (Betts KS, Williams GM, Najman JM et al., 2015; Demirbek B & Yurt E., 2011). Indeed, the increase in schizophrenic cases after bone marrow transplantation confirms the importance of immunity in schizophrenia. Mc may be the causative factor in the development of schizophrenia and postpartum psychosis (Demirhan O, Ozturk N, Aydin N, Yildizdas HY, Demirbek B, et al., 2019). From all these findings, we can say that Mc can explain the history of especially psychotic disorders and postpartum clinical conditions.

Many MMcCs that migrate to the fetus to fight infectious diseases cannot return to the mother's body. Appropriate agents in the fetus can differentiate these cells into stem cells. This causes alloimmunity. We must now accept that maternal microchimeric cells cause autoimmune diseases, play a role in the etiology of alloimmune diseases and are necessary in the treatment of psychiatric diseases. If the MMcCs passed to the fetus participate in the development of the brain, they cause the formation of two different DNAs in the brain. In this case, two different sets of neuromeditor receptors would have been found in the same brain tissue. The production of each DNA is individual. In this situation, chaos begins to wreak havoc and the architecture of the brain changes. Indeed, mild neurological symptoms have been reported in infants born with altered brain architecture (Demirbek B & Yurt E., 2011). However, it has been reported that Mc plays a role in the history of autoimmune disease and may be a factor in the development of schizophrenia and postpartum psychosis (Demirbek B & Demirhan O., 2019). When fetal-maternal cells cannot produce stem cells that can sustain their own existence, schizophrenia may recover after the first attack, since these nomadic cells in the brain of a schizophrenic patient decrease. If these cells produce new stem cells, then schizophrenia will become chronic. FMMc cell migration may explain the concept of hallucinations. In other words, if there are two different DNAs in the brain tissue, the production of the euromediator-receptor will be individualized. Even if dopamine produced by schizophrenic brain cells reaches Mc cells, it will not be able to bind to the receptor due to the difference in resonance frequency. In this case, due to dopamine starvation, nomadic cells will continue to demand dopamine and dopamine will be constantly produced and released. Thus, there will be a relative abundance of dopamine in the environment and eventually dopamine will activate auditory receptors and the schizophrenic patient will perceive it as a sound. Indeed, vibrational frequency is known to induce behavioral changes in Drosophila melanogaster flies (Kacsoh BZ, Bozler J & Bosco G., 2018).

We can compare the vibration frequency to the radio frequency switch that starts our car. All keys are similar in appearance. However, one key cannot start another car because the radio

frequencies are different. The resonance frequency of the neuromodulatory receptor produced by each different DNA is also different. For this reason, it should be considered normal to see psychotic behaviors in the mother after birth. In our study, it was reported that there was a significant difference in FMcCs frequency between women with postpartum depression and healthy women, and that these cells were significantly higher in sick women than in healthy controls (Demirbek B & Yurt E., 2011). Mc may be an important alternative in explaining the etiology of psychiatric disorders. Thus, numerous studies are known to show that prenatal infections show both acute and persistent autistic or schizophrenic-like behavioral abnormalities in offspring (Meyer U, et al., 2011; Patterson PH., 2011a). It is assumed that it will be an important step towards the effects of the immune system on the brain and behavior and in patients with schizophrenia (Demirbek B & Demirhan O., 2019).

It has been reported that MMcCs differentiate to participate in the structure of fetal tissues and organs, and some cells survive as stem cells to repair tissue damage in the future (Shi L, Fatemi SH, Sidwell RW & Patterson PH., 2003). FMcCs in the breast tissue of the mother are mature newly equipped cells that are passed back to the fetus through breastfeeding. If FMcCs in the mother's breast are not transferred to the fetus by breastfeeding, they have to wait in the breast tissue and multiply. Previously, when these alloimmune cells are few in number, they do not react because the mother's immune system cannot detect them as foreign cells. However, when these cells multiply and form a colony, they are perceived as foreign cells by the mother's immune system and a war/reaction develops against them. Inflammation resulting from this reaction can transform these stem cells into cancer cells. Although these FMcCs are at low maternal concentration, they may show immunological competence that may play a role in alloimmunity, autoimmune diseases, graft versus host reactions, and cancer. It has been reported that some fetal cells, similar to chronic graft-versus-host responses in allogeneic graft recipients, escape from maternal immune surveillance mechanisms and play a role in the pathogenesis of some autoimmune diseases (Ay G., 2004; Nelson JL., 1996; M Klintschar, P Schwaiger, S Mannweiler, S Regauer & M Kleiber., 2001). It is known that fetal immune cells can be reactive to maternal antigens and trigger the vaccine-shock reaction It is thought that Mc plays a role in the development of autoimmune diseases and autoimmune diseases may actually be an alloimmune disease, not an autoimmune disease (Ando T & Davies TF., 2003). It is known that the amount of FMcCs in the blood and tissues of women with autoimmune disease is higher than that of healthy women (Demirbek B & Yurt E., 2011). It has been observed that psychiatric diseases enter the healing process with the stages of autoimmune diseases. At the same time, it is seriously considered that FMcCs may be involved in the formation of cancer in the mother. Therefore, McCs can serve as potential cells in cancerization or as targets of immune response. Studies have revealed that individuals with autoimmune thyroid disease have higher numbers of McCs than other thyroid diseases (Ando T, Imaizumi M, Pritsker A & Davies TF., 2001; Ando T, Imaizumi M, Graves PN, Unger P & Davies TF., 2002).

4. Maternal Microchimeric Stem Cells form Physiopathological Can It Transform?

McCs that function within physiological limits can also go outside this limit in some adverse conditions. Many studies have revealed that FMcCs may play a role in rejuvenating progenitor stem cells, repairing maternal tissues, controlling cancer cells or developing cancer. Negative changes in the micro-niches of these cells can lead them to different unwanted cells. The MMcCs passed to the fetus can function as a source of stem cells for the production of new cells as well as participating in the structure of tissues. Under normal physiological conditions, the number of limited number of MMcCs that migrate to the fetus can reach several times with chronic inflammatory effect. However, MMcCs can undergo frequent apoptosis and reproduce under the influence of the inflammatory state. This destruction and regeneration can also shorten the telomeres of MMcCs. In this case, it shortens cell life. After a while, MMcCs under this destruction and remodeling stress can transform into cancer cells due to their pluripotent properties. It seems possible that these microchimeric cells with high plasticity may play a role in the development of

cancer. It turns out that whether F-McCs will have a beneficial or detrimental effect will depend on the direction of changes in the microenvironment.

Today, the function of F-MMcCs in cancer history is only just beginning to be understood. For this reason, many studies have been conducted on the role of these cells in the formation of cancer. McCs may play a role in the onset of cancer. The first opinion on this subject was reported in 1996 (Ando T, Imaizumi M, Pritsker A & Davies TF., 2001). In later years, it was suggested that these stem cells could be a driving force in cancer development and progression, tissue repair and disease. Mc cells have been found frequently in hepatitis-C, breast, thyroid, cervix, lung cancer, hematological cancers, some tumors such as melanoma, autoimmune diseases and non-autoimmune diseases. It was previously assumed that these foreign stem cells have a protective role against these diseases. In malignant tumors, it has been thought that FMMcCs may play a role in the progression of cancer, but they may also be positively effective in the fight against the development of cancer. It has been suggested that FMcCs in damaged tissue areas may originate from the bone marrow (Demirbek B & Yurt E., 2011), but it has been reported that these cells have the potential to form cancer and act like cancer stem cells (Nelson JL., 2009). As a matter of fact, it has been reported that FMcCs play a role in the formation and proliferation of lung cancer in mouse models. It remains unclear whether FMcCs participate in tissue repair or contribute to cancer growth. However, these cells are hypothesized to be involved in chronic inflammatory responses that cause or repair tissue damage and gain resistance to infections. Why are McCs frequently observed in cancer patient tissues but not in healthy control individuals? It has been shown that the frequency of FMcCs in lung cancer tissue is several times higher than in the surrounding healthy tissue and that they accumulate in the lung cancer tissue of post-pregnancy women even years later (Nelson JL, Gillespie KM, Lambert NC, Stevens AM, Loubiere LS, Rutledge JC, et al., 2007). Disease may develop as a result of the loss of control of these cells, genetic regulatory genes that control normal cell proliferation and differentiation, as a result of mutations or microenvironmental changes. In other words, it can be said that these cells can cause cancer by turning into cancer stem cells as a result of genetic and epigenetic changes or changes in micro-environmental niches. Indeed, it has been reported that FMc plays a role in the pathogenesis or progression of cervical cancer (Li L & Neaves WB., 2006). It has been reported that FMcCs are significantly lower in women with breast cancer compared to healthy women (Cha DH, Khosrotehrani K, Kim Y, Stroh H, Bianchi DW & Johnson CL., 2003). These results indicate that circulating fetal cells can differentiate and contribute to the development of tumors.

In a study, we conducted in patients with lung cancer (LC) and bladder cancer (BC) (Taştemir Korkmaz D, Demirhan O, Abat D, Demirberk B, Tunç E & Kuleci S., 2015). A significant difference in the frequency of McCs has been reported between patients with LC and BC. FMcCs are approximately four times higher in patients with BC than in LC patients, suggesting that BC may be associated with McC. A similar situation was reported to be 4 times higher in patients with colon cancer compared to patients with breast cancer (Kamper-Jørgensen M, Biggar RJ, Tjønneland A, Hjalgrim H, Kroman N, Rostgaard K, Stamper CL, Olsen A, Andersen AM & Gadi VK., 2012). However, FMcCs are found in 50% of papillary thyroid tumors (Srivatsa B, Srivatsa S, Johnson KL & Bianchi DW., 2003) and are common in women with breast cancer (Cha DH, Khosrotehrani K, Kim Y, Stroh H, Bianchi DW & Johnson CL., 2003). It is predicted that FMcCs, which have the potential to differentiate into blood cells, can participate in the repair processes of mesenchyme and epithelial cells and play a role in the fight against cancer. However, considering the significant increase in breast and thyroid cancers in women who have given birth, it is suspected that FMcCs may have a protective effect. Indeed, it is known that the frequency of FMcCs in the blood of healthy women is higher than that of women with breast cancer. This suggests that the aggregation of FMcCs in cancer tissue is involved in the development of cancer. In particular, it is not known whether FMcCs will differentiate in maternal tissues, but it is thought that they may help in repairing the wound against injuries in the mother's tissues. It has been suggested that they may play a role in the repair of inflammatory

tissues as well as previously suggested for some autoimmune diseases and cancers. It is also known that FMcCs can differentiate in mature thyroid follicles of the mother with appropriate environmental and developmental factors. However, it has been reported that the presence of MMcCs in the cancer stroma may be actively associated with the formation of new vessels, which initiates the formation of cancer, and the spread of cancer (Gadi VK., 2008; Juan C. Galofré, Leonidas H. Duntas, L. D. Premawardhana & Terry F. Davies., 2012; Demirbek B & Demirhan O., 2019). All these information and findings reveal that McCs are an important alternative way to explain the etiology of diseases, and that pluripotent McCs may play a role in cancer development by transforming into cancer stem cells.

5. Conclusions

Despite the complexity of chimerism, which we are trying to explain, it carries many important ambiguous questions. The maternal immune response to fetal cells in maternal health or disease is not yet clear. However, the presence of FMcCs has been associated with both positive and negative effects on maternal health. However, there is strong evidence that chimerism may have a pathogenic role in autoimmune diseases, psychiatric diseases and cancer. It is also seen that chimeric cells migrate to tumor tissues and play a protective role. Microchimerism is a physiological phenomenon, but microchimeric cells have a transformation into the physiopathological pathway due to their pluripotent property. Knowing the prevalence of chimerism and clarifying its relationship with health can facilitate the quality of life of important diseases of unknown etiology. More work is needed to generate testable predictions for this.

References

Parivesh A, Barseghyan H, Délot E, Vilain E. (2019). Translation of genomic disorders/sex development differences into clinical diagnosis. *Curr Top Giant Biol., 134*, 317–375.

Boddy AM, Fortunato A, Sayres MW, Aktipis A. (2015). Fetal microchimerism and maternal health: areview and evolutionary analysis of cooperation and conflict beyond the womb. *BioEssays News Rev. Mol. Cell Dev. Biol., 37*, 1106–1118.

O'Donoghue K, SultanH. A, Al-Allaf FA, Anderson JR, Wyatt-Ashmead J, Fisk NM. (2008). Microchimericfetal cells cluster at sites of tissue injury in lung decades after pregnancy. *Reprod. Biomed, 16*, 382–390.

Klonisch T, Drouin R. (2009). Fetal–maternal exchange of multipotent stem/progenitor cells: microchimerism in diagnosis and disease. *Trends in Molecular Medicine, 15*(11), doi:10.1016/j.molmed.2009.09.002.

Gadi VK, Malone KE Guthrie KA, Porter PL, Nelson JL. (2008). Case-control study of fetal microchimerism and breast cancer. *PLoS One, 3*(3), e1706.

Kamper-Jorgensen, M., Hjalgrim, H., Andersen, A.N.N., Gadi, W.K., Tjonneland, A., et al. (2014). Male microchimerism and survival among women. *International Journal of Epidemiology, 43*, 168–173.

Brandon NJ, Ehli1 EA, Davies GE, Boomsma DI. (2020). Chimerism in health and potential implications on behavior: A systematic review. *Am J Med Genet*, 1–17.

Davies D, Demirhan O. (2019). Pregnancy-related microchimerism unknown pathophysiological effects. *Front Womens Healt, 4*, 2–4.

Piotrowski P, Croy BA. (1996). Maternal cells are widely distributed in murine fetuses in utero. *Biol Reprod., 54*(5), 1103–1110.

Arvola M, Gustafsson E, Svensson L, et al. (2000). Immunoglobulin-secreting cells of maternal origin can be detected in B celldeficient mice. *Biol Reprod., 63*(6), 1817e24.

Marleau AM, Greenwood JD, Wei Q, et al. (2003). Chimerism of murine fetal bone marrow by maternal cells occurs in late gestation and persists into adulthood. *Lab Invest., 83*(5), 673e81.

Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. (2015). Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet psychiatry, 2*(3), 258–70.

Ando T, Davies TF. (2003). Postpartum Autoimmune Thyroid Disease: The Potential

Role of Fetal Microchimerism. *The Journal of Clinical Endocrinology & Metabolism, 88*(7), 2965–71.

Jung CG, Hull RFC. (1981, August 1). The Archetypes and The Collective Unconscious (Collected Works of C.G. Jung Vol.9 Part 1) Paperback.

Betts KS, Williams GM, Najman JM et al. (2015). The relationship between maternal depressive, anxious, and stress symptoms during pregnancy and adult offspring behavioral and emotional problems. *Depress Anxiety, 32*, 82–90.

Demirbek B, Yurt E. (2011). Can Microchimerism Find Itself a Place in Psychiatric Research? *Current Approaches in Psychiatry, 3*(2), 296–308.

Brown AS. (2006). Prenatal infection as a risk factor for schizophrenia. *Schiz. Bull., 32*, 200–202.

Penner JD, Brown AS. (2007). Prenatal infectious and nutritional factors and risk of adult schizophrenia. *Exp. Rev. Neurotherap, 7*, 797–805.

Meyer U, Feldon J, Dammann O. (2011). Schizophrenia and autism: both shared and disorder-specific pathogenesis via perinatal inflammation? *Pediatr. Res., 69*, 26R–33R.

Patterson PH. (2011a). Maternal infection and immune involvement in autism. *Trends Mol. Med., 17*, 389–394.

Hyman SL, Arndt TL, Rodier PM. (2006). Environmental agents and autism: once and future associations. *Int. Rev. Res. Ment. Retard., 30*, 171–194.

Moy SS, Nadler JJ. (2008). Advances in behavioral genetics: mouse models of autism. *Mol. Psy., 13*(1), 4–26.

Patterson PH. (2002). Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. *Curr. Opin. Neurobiol, 12*, 115–118.

Chess S. (1997). Follow-up report on autism in congenital rubella. *J. Autism Child Schiz., 7*, 69–81.

Johnson RT. (1994). Infections during pregnancy. *Adv. Neurol., 64*, 153–162.

Demirhan O, Ozturk N, Aydin N, Yildizdas HY, Demirbek B, et al. (2019). Effect of fetal microchimeric cells on the development of postnatal depression. *Med Clin Arch.,3*, 1–6.

Demirbek B, Yurt E. (2011). Can Microchimerism Find Itself a Place in Psychiatric Research? *Current Approaches in Psychiatry, 3*, 296–308.

Demirbek B, Demirhan O. (2019). Microchimerism may be the cause of psychiatric disorders. *Arch Psychiatr Ment Health, 3*, 042–046.

Kacsoh BZ, Bozler J, Bosco G. (2018). Drosophila species learn dialects through communal living. *Plos Genetics, 14*, e1007430.

Meyer U, et al. (2011). Schizophrenia and autism: both shared and disorder-specific pathogenesis via perinatal inflammation? *Pediatric Research, 69*, 26R–33R.

Patterson PH. (2011a). Maternal infection and immune involvement in autism. Trends in *Molecular Medicine, 17*, 389–394.

Shi L, Fatemi SH, Sidwell RW, Patterson PH. (2003). Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci., 23*, 297–302.

Ay G. (2004). Autoimmune thyroid diseases and fetal microchimerism. *Harran Tıp Fak Der., 1*(3), 41–47.

Nelson JL. (1996). Maternal-fetal immunology and autoimmune disease: is some autoimmune disease auto-alloimmune or allo-autoimmune? *Arthritis Rheum., 39*, 191–946.

M Klintschar, P Schwaiger, S Mannweiler, S Regauer, M Kleiber. (2001). Evidence of fetal microchimerism in Hashimoto's thyroiditis. *J Clin Endocrinol Metab., 86*, 2494–2498.

Ando T, Imaizumi M, Pritsker A, Davies TF. (2001, June 20–23). Identification of fetal microchimerism in the human thyroid. Abstract OR23–1. 83rd Annual Meeting of the Endocrine Society; Denver, CO, USA.

Ando T, Imaizumi M, Graves PN, Unger P, Davies TF. (2002). Intrathyroidal fetal microchimerism in Graves' disease, *Journal of Clinical Endocrinology and Metabolism, 87*(7), 3315–3320.

Nelson JL. (2009). Naturally acquired microchimerism: for better or for worse.

Arthritis Rheum., 60(1), 5–7.

Nelson JL, Gillespie KM, Lambert NC, Stevens AM, Loubiere LS, Rutledge JC, et al. (2007). Maternal microchimerism in peripheral blood in type 1 diabetes and pancreatic islet beta cell microchimerism. *Proc Natl Acad Sci USA. 104*(5), 1637–42.

Li L, Neaves WB. (2006). Normal stem cells and cancer stem cells: the niche matters. *Cancer Res., 66*, 4553–4557.

Cha DH, Khosrotehrani K, Kim Y, Stroh H, Bianchi DW, Johnson CL. (2003). Cervical cancer and microchimerism. *Obstet Gynecol., 102*, 774–781.

Taştemir Korkmaz D, Demirhan O, Abat D, Demirberk B, Tunç e, Kuleci S. (2015). Microchimeric Cells, Sex Chromosome Aneuploidies and Cancer. *Pathol. Oncol. Res., 21*, 1157–1165.

Kamper-Jørgensen M, Biggar RJ, Tjønneland A, Hjalgrim H, Kroman N, Rostgaard K, Stamper CL, Olsen A, Andersen AM, Gadi VK. (2012). Opposite effects of microchimerism on breast and colon cancer. *Eur J Cancer., 48*, 2227–2235.

Srivatsa B, Srivatsa S, Johnson KL, Bianchi DW. (2003). Maternal cell microchimerism in newborn tissues. *J Pediatr., 142*, 31–35.

Gadi VK. (2008). Fetal microchimerism and cancer. *Cancer Res., 68*, 9567–9569.

Juan C. Galofré, Leonidas H. Duntas, L. D. Premawardhana, Terry F. Davies. (2012). Advances in Graves' Disease. *J Thyroid Res., 2012*, 809231.

Demirbek B, Demirhan O. (2019). Pregnancy-related microchimerism unknown pathophysiological effects. *Front Womens Healt, 4*, 1–4.