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Unknown Effects of the Fetal and Maternal Microchimerism
(Osman Demirhan)

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1. Introduction

The term chimera is used to describe a being composed of parts from different sources or living beings that emerged or were created as a mixture of different living things. The genetic chimera describes a mixed organism consisting of two or more different zygotes. Often during pregnancy, a reciprocal exchange of cells occurs between the mother and the fetus, including some cells of the immune system. These pluripotent cells cross the placental barrier and enter the host's body, can settle in different organs and survive for decades. Thus, an individual may have a small population of foreign cells and hence nucleic acids of another genetically different individual. This phenomenon is known as microchimerism (Mc). The physiological consequences of Mc are not clear. However, it can be said thatit may have beneficial or harmful effects or have no effect at all. Cases of chimerism are generally classified into three categories; 1. occurring after a blood or bone marrow transplant (artificial); 2. formed by the fertilization of two oocytes by two spermatozoa and the development of the organism (tetragametic); 3. routine stem cell transfer between mother and fetus during pregnancy. The most common known form of microchimerism (Mc) is cell transfer that occurs during pregnancy; transfer of the baby's stem cells to the mother (fetal microchimerism=FMc) and the transfer of the mother's stem cells to the baby (maternal microchimerism=MMc). Fetal and maternal cell exchanges are quite common during pregnancy. Now, we know that the placenta is not an immunologically inert barrier, but rather, it allows the reciprocal transport of maternal and fetal cells in a state of mutual tolerance during gestation. To develop microchimerism, it is not also necessary to continue a pregnancy and deliver an infant. Surgical and spontaneous abortions can deliver up to 500,000 nucleated fetal cells into a woman's circulation (1).

2. The mystery of microchimerism

Today, the Mc is the subject of the most interest and little is known about. The research into Mc, and more specifically feto-maternal Mc, is still in its infancy. It is wondered whether fetal stem cells passed to the mother will affect the mother's health or the next generation (descendants) during or after pregnancy. Stem cells are versatile cells that have the ability to differentiate into different body and tissue cells under appropriate conditions and stimuli. These cells play very important roles such as direct differentiation into required cell types and tissue repair. The existence of fetal cells in the circulating blood of the mother has been known for nearly a century. Pregnancy is the most common and natural cause of Mc. During pregnancy, two-way stem cell exchange takes place between the mother and the fetus via the placenta. As a result of this; potentially Mc formation occurs in both mother and baby. Thus, no one is born pure (without foreign cells), so we are all born microchimeric. Three hypotheses regarding the role of Mc have been proposed. The first of these; Persistence of fetal microchimeric cells (FMcCs)in maternal tissues caused a chronic inflammatory response causing tissue damage (leading to an immunological response similar to graft-host disease), secondly; FMc may play a protective role in the repair of damaged tissues, in the development of cancer and in the control of viral infections, and thirdly; Mc may be an accidental physiological event of no biological significance occurring during pregnancy. Despite these possible views, fetal-maternal microchimerism (F-MMc) contains many unknowns.

3. Breastfeeding and microchimerism

F-MMc occurs most frequently during pregnancy and is known to occur during breastfeeding (2). Progenitor stem cells found in the mother's bloodstream have also been demonstrated in colostrum and breast milk (3). Human milk contains stem cells that can differentiate into cells of the three embryonic germ layers. It is not known how these cells affect the baby. It is believed that stem cells in breast milk are unlikely to form tumors. Stem cells are being investigated in many neonatal diseases and promising positive results are obtained. The widespread occurrence of chimerism will guide understanding the health problems that may occur and guide new approaches for the treatment of diseases. However, it has been reported that stem cells in breast milk are fully active in many target tissues (4). It has been shown that MMc cells detected in the blood and brain of the offspring differentiate into glia and neuron cell types in the brain (5). During breastfeeding, MMc stem cells are not recognized as allergens by the baby's immune system. They cross the gastrointestinal tract and contribute to the immune development andtissue growth/repair of the newborn or infant (6). The presence of stem cells in breast milk and their demonstration in the baby's body have revealed the

necessity of investigating the possible role of these cells in the treatment of diseases.

4. The physiopathological effects of microchimerism

The observations suggest whether the McCs a woman receives from her mother influence the course or outcome of her own pregnancies. It encompasses three generations of multiple mother-child relationships, as a pregnant woman receives a different cell population from the fetus during pregnancy. Currently, chimerism studies are largely focused on autoimmune diseases (AD) and female cancers in human diseases. For genetic diagnosis during pregnancy, the FMcCs in the mother's blood should be searched for information about the complications of pregnancy, as well as information about the pathogenesis of AD such as rheumatoid arthritis that healed during pregnancy. The investigation of the long-term consequences of fetal-maternal microchimerism (F-MMc) has become exciting and is being investigated, with preliminary results regarding its negative and beneficial effects.

Chimerism has been well studied in animal models. The first chimeric mouse was made in the 1960s through the aggregation of eight-cell-stage embryos. Chimerism has been found to occur as a result of bidirectional cell exchanging in dizygotic twins in twin cattle calves (7). It has been shown to be associated with a masculine appearance and behavioral development in chimeric individuals with the XX/XY karyotype in sheep (8). These individuals are sterile chimeric females with masculine behavior and dysfunctional ovaries. These observations suggest that chimerism may be important for understanding the behavioral biology. Certain species have unique reproductive traits in primates. It has been shown that FMcCs in maternal tissues of Rhesus monkeys can be measured for several years after birth (9). There are reports of natural chimerism in mammals such as mice, dogs, and cats (10,11). A dog with ambiguous genitalia was found to have XX/XY chimerism (12). In mice, the F-MMcCs were also common in all tissues (13,14). It has been reported that fetal cells migrate to the damaged areas of the heart muscle in pregnant mice and provide cardiac differentiation (15). It has been suggested that FMcCs are more common in damaged mouse lung and brain regions caused by smoking or excitotoxic lesions, and this may be due to the protective effect of cells (16,17). Reciprocal chimeric cell exchange in the placenta in mice suggests that the knowledge of these cells to cross the blood-brain barrier and migrate to sites of tissue damage may be similar in humans.

The most common form of genetic chimerism in humans is hermaphroditism, which occurs when ovarian and testicular tissue are seen in the same individual. Generally, these individuals have indeterminate and

variable external genitalia. Some cases with true hermaphroditism karyotype (46,XX/XY) have also been reported, accounting for approximately 10% of total hermaphrodite cases. These cases are mostly mosaics of cells with 47,XXY karyotype resulting from chromosome failure (18). Before embryonic sex differentiation, it may be in the form of fertilization of a separately fertilized egg with a second polar cell or parthenogenetic division of an egg fertilized by two sperm (19). Due to the overall rarity and variable nature of this condition, it is possible that many cases of hermaphroditism go undiagnosed or occur later in life. Therefore, most of the reported cases are younger patients with worse phenotypes.

4.1. Autoimmune diseases

Microchimerism studies have been carried out mostly in AD among human diseases. About 5% of the human population is affected by AD. Thereis a clear gender predisposition to these diseases. Approximately 78% of affected individuals are women (20,21). Several hypotheses have been proposed to explain the reasons for the gender difference such as hormonesor stronger immune responses in women. The first study that investigated naturally acquired microchimerism in autoimmune disease was a prospective,blinded study of FMc in women with Progressive systemic sclerosis (PSS). Levels of fetal DNA were significantly higher in women with PSS compared with healthy women (22). In addition, chimerism causes some AD to be seen more frequently in women following pregnancy and pathologies similar to chronic graft-versus-host disease (cGVHD). AD typically result in tissue destruction and pathological findings similar to cGVHD. This has led to the investigation of Mc in host tissues. Systemic lupus erythematosus (SLE) is characterized by extensive organ complications and the production of antinuclear antibodies that result in similarity to cGVHD (22). The FMcCs have been reported in all tissues of a woman with two sons who died from complications of SLE (23). The McCs localize to areas of inflammation. These findings suggest that Mc plays a role in the etiology of AD.

Mc has been extensively investigated in rheumatic and autoimmune thyroid diseases. The relationship between chimerism and rheumatic diseasesis well known. It has been reported that FMc is more common in the blood and various tissue samples of women diagnosed with systemic sclerosis compared to controls (24,25). In contrast, it has been suggested that the frequency of McCs is not different between women with systemic sclerosis and controls, and that Mc does not play a role in the pathogenesis of the disease (26). On the other hand, higher frequency of FMcCs was reported in the blood of women with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) compared to controls (27). It is assumed that FMcCs are associated with the pathogenesis of SLE. It has been shown that the disease

may be associated with the presence and proliferation of FMcCs transmitted to the mother during pregnancy. A positive relationship was found between the amount of FMcCs and multiple births in these patients, and an inverse relationship in healthy women. However, patients with lupus nephritis (LN) were found to have a higher amount of FMcCs than the healthy control group, and the amount of this cells were significantly higher in patients with LN than in patients without kidney damage (28). This suggests that these cells may play a role in LN. However, it was also reported that there was no significant difference in the frequency of F-MMc in patients with SLE compared to healthy controls (29). These findings suggest that diseased allelic genes acquired via microchimerism may contribute to the etiology of disease in the host and Mc cells may help facilitate the autoimmune response.

Findings on this subject show that Mc is a part of the immune system and has passed on 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 women than in women with cancer, suggesting that these cells have the potential to be involved in immune surveillance. At the same time, persistence of fetal cells after birth without any apparent maternal immune rejection demonstrates this. It is known that the number of FMcCs increases in AD. Maternal microchimeric cells (MMcCs) that migrate to the fetus can adapt or integrate with the immune system and organ systems of the fetus. Infectious diseases can accelerate routine cell exchange between mother and fetus. When the fetus is exposed toinfective agents, the mother's cellular defense system becomes more active to protect the fetus. It is not known whether maternal cells, together with fetal cells, or alone due to allogeneic similarity, attack antigens.

It is assumed that the fetal immune system does not give an immune reaction due to allogeneic genetic similarity to the mother's cells. Indeed, there is evidence that MMc is a common perception in newborn mice. In immunocompromised mice, MMcCs have been detected in hematopoietic organs (bone marrow, spleen, liver, lymph nodes, and thymus) and other organs (heart, brain, lung) (30,31). There is a link between the development of schizophrenia in children born to mothers who had measles and influenza infections during pregnancy. However, it has been reported that there is a relationship between the amount of maternal antibodies against the herpes simplex virus in the mother during pregnancy and the increased risk of psychosis in the child's adulthood (32). According to the results of the study; The immune cells of the fetus may be reactive to maternal antigens and trigger a counter-reaction. This appears to be an effective mechanism in the initiation or exacerbation of AD.

The suppression of Hashimoto's thyroiditis and graves diseases during pregnancy and their exacerbation after birth suggest that the changes that

occur during pregnancy facilitate the pathogenesis of these diseases. Women with thyroid and nodular goiter or follicular adenoma have FMcCs more frequently than controls. This shows that these cells may potentially play a role in the etiology of Hashimoto's thyroiditis and Graves' diseases. Primary biliary cirrhosis (PBC) is an autoimmune liver disease. The frequency of McCs is increased in these female patients compared to other liver patients. This shows that Mc is involved in the etiology of PBC and other liver diseases. Juvenile idiopathic inflammatory myopathy disease shows similar pathology to cGVHD and Mk is thought to be a potential in its pathogenesis. Individuals with juvenile dermatomyositis disease have been shown to have ahigher frequency of MMcCs in blood and muscle tissue compared to healthy controls (33). MMc causes Type 1 diabetes by the autoimmunity mechanism. In these patients, it was reported that MMcCs were increased in blood and pancreatic tissue compared to controls and was found significantly more frequently in patients' pancreatic beta cells (34,35). The role of mother cells in pancreatic tissue is unknown, and they may be present at the onset of the disease or may have been established later or migrated to the tissue in response to active autoimmunity.

People are born with the general image of the world within himself. The information that the baby carries the genes carries the accumulation of all the information in the evolutionary process, not only from the current parents, but also from the first ancestors. It is thought that some of the informationthat has come from the first creation of man has been transferred to future generations through ancestral inheritance. The collective consciousness consists of patterns or images that Jung called "archetypes" (36). These images are transmitted from person to person. These images are not only the product of human history, but also contain pre-human evolution. Archetypes are the state of human beings having tendencies similar to the behavioral patterns developed by their ancestors in the past. This transition is thought to occur via both MMcCs and FMcCs. MMcCs unconsciously and together withspecialized cells transmit information to the fetus. FMcCs can also pass through the mother's body and return to the fetus through breastfeeding, where they receive ancestral information from collective unconscious sources. In this way, it is suggested that the transfer of unconscious information to the offspring may have been achieved by maternal-fetal cell transfer. With the migration of MMcCs, bio-psycho-social information, immune information, traumas, myths and archetypes may be transferred to the next generation. During the formation of the zygote, information may not have been recorded due to inappropriate genetic codes between the mother and father. F-MMc path may be preferred to minimize information loss. In line with all this information, it may be that human psycho-social informationis not transmitted by chromosomes, and this information and ancestral

background information may be copied from mother to offspring via FMcCs and passed on to new generations.

4.2. Cancer

There may also be times when every physiological function in the human body does not go right. McCs that function within physiological limits can also go outside this limit in some adverse conditions. The findings have shown that FMcCs may be involved in rejuvenating the source of precursor stem cells, repairing maternal tissues, controlling cancer cells or developing cancer. 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. Negative changes in the micro-niches of these stem cells can direct them in different undesirable directions. MMcCs, which are transferred to the fetus and participates in the structure of its tissues, may also function as a source of stem cells for the production of new cells. It is known that a limited number of MMcCs migrating to the fetus is true, but this limit/number can reach several times under the influence of chronic inflammatory destruction. 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. Aftera while, they can transform into cancer cells due to the pluripotent properties of MMcCs under this stress of destruction and remodeling. In our unpublished study; we detected 18% maternal stem cells in breast sarcoma cancer tissue of a male patient with breast cancer (BrC). Here, the reason for the high density of MMcCs in cancer tissue comes to mind, and what are the mother cells doing here? Are they to fight cancer or are they precursors of cancer cells? It seems possible that McCs with high transformation propertiesmay 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 directionof changes in the microenvironment.

McCs may play a role in the onset of cancer. The first opinion on this subject was reported in 1996 (37). In the following years, it has been suggested that these stem cells may be a driving force in cancer development and progression, tissue repair and diseases. McCs have been found frequentlyin breast, thyroid, cervix, lung, hematological cancers and tumors such as melanomas. Initially, these foreign stem cells were assumed to be protective against these diseases. It has been thought that FMMcCs may play a role in the progression of cancer in malignant tumors, but they may also be positively effective in the fight against the development of cancer. It has beensuggested that FMcCs are found in injured tissue areas and that these cells may originate from the bone marrow or may be locally grown stem cells (38).

However, it has been reported that FMcCs have cancer-forming potential and can act as cancer stem cells (39).

McCs are more common in women with papillary thyroid cancer (PTC) and breast cancer, as in autoimmune diseases. This suggests that FMc may contribute to the etiology of these diseases. It has been found that the rate of FMcCs in the neoplastic thyroid tissue of women with PTC is 47.5% (40), and the rate of FMcCs in the blood is lower than the neoplastic thyroid tissue (41). In the light of these findings, it has been suggested that fetal cells protect the host with their cytotoxic role against preneoplastic cells and may prevent new tumor or tumor progression by acting as a protector against cancer cells (42). It has been reported that FMcCs are found in BrC patients and controls, but McCs is less in the unaffected breast tissue of patients (43). These findings may indicate potential beneficial effects of Mc in contrast to autoimmune diseases. It may support the hypothesis that McCs may be involved in immune surveillance, migrate to damaged or diseased tissue, and be involved in tissue repair. However, more research needs to be done for this. The frequency of FMcCs in the blood of women with breast cancer was reported to be lower compared to controls, but was generally higher in women who subsequently developed colon cancer (44). It has been reported that FMcCs are significantly lower in women with BrC compared to healthy women (45). It has been reported that in women with FMcCs, survival time is prolonged following diagnosis if they have any type of cancer (44). This suggests that Mc may contribute differently to each type of cancer. In addition, it can be said that the immunological and repair roles of McCs may contribute to better survival of women regardless of cancer type. At the same time, more research is needed to determine whether fetal cells have a protective or pathogenic role in women with cancer.

FMcCs are known to play a role in the formation and proliferation of lung cancer in mice. In a study we conducted in patients with lung (LC) and bladder cancer (BlC); A significant difference in the frequency of McCs was reported between patients with LC and BlC (46). FMcCs are found approximately four times higher in patients with BlC than in patients with LC, suggesting that BlC may be associated with McCs. Similarly, in another study, it was reported that FMc was found to be 4 times higher in patients with colon cancer compared to patients with BrC (47). 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. As a matter of fact, the density of FMcCs in the circulating blood of healthy women was found to be significantly higher than that of women with BrC. This suggests that

aggregation of FMcCs in cancer tissue is involved in the development of cancer. In particular, it is not known whether FMcCs can 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 damaged tissues as well as previously suggested for some autoimmune diseases and cancers. In addition,it has been reported that FMcCs can be differentiated by environmental and developmental factors in the mature thyroid follicles of the mother. However, it has been reported that the presence of MMcCs in the cancer stroma may be actively associated with a new vascularization and the formation of cancer (48,49). All these information and findings are believed to be an important alternative way to explain the etiology of Mc diseases. It also shows that their pluripotent McCs can develop into cancer stem cells. Therefore, we can suggest that Mc may have a role in the development of cancer.

It has been reported that MMcCs differentiate to participate in the production of fetal tissues and organs, and some survive as maternal stem cells to differentiate and repair future tissue damage (50). FMcCs in mammary tissue are mature and formed cells that are passed back to the fetus through lactation. If FMcCs in the mother's breast are not transferred to the fetus by breastfeeding, they wait and multiply in the breast tissue. When these alloimmune cells are few in number, they are not recognized as foreign cells by the mother's immune system, so there is no immunological reaction against them. 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 these reactions can transform these stem cells into cancer cells. It has been reportedthat some fetal cells escape from maternal immune surveillance mechanisms and play a role in the pathogenesis of some autoimmune diseases resembling chronic graft-versus-host responses as seen in allogeneic graft recipients (51,52). It is also known that fetal immune cells can be reactive to maternal antigens, thus triggering a vaccine-shock reaction. Recent research shows that Mc plays a role in the development of autoimmune diseases and these diseases may actually be an alloimmune disease, not an autoimmune disease. It is known that the amount of FMcCs in the blood and tissues of women with autoimmune disease is higher than in healthy women. At the same time, it is seriously considered that FMcCs may be involved in the formation of cancer in the mother. Therefore, their McCs may serve as potential cells in cancerization or as targets of immune response.

In the studies; whether FMcCs are involved in tissue repair or contribute to cancer growth has not been definitively determined. These cells have been hypothesized to be involved in chronic inflammatory responses that cause tissue damage or in repairing damaged tissue or gaining resistance to

infections. Why are McCs frequently observed in cancerous patient tissuesbut not in healthy control subjects? The frequency of FMcCs in LC tissues has been reported to be several times higher than in the surrounding healthy tissue. At the same time, FMcCs have been shown to accumulate in the LC tissue of post-pregnancy women even years later (39). Disease may developas a result of loss of control of genetic regulatory genes that control normal cell proliferation and differentiation of these cells as a result of mutations or microenvironmental changes. In other words, it would be fair to say that as a result of genetic or epigenetic changes or changes in micro-environmental niches, these cells can act like cancer stem cells and cause cancer.

It has been reported that FMc plays a role in the pathogenesis or progression of cervical cancer (53). Measurable frequency of McCs has been reported in cancer samples such as uterine, melanoma, glioblastoma, and meningioma (54,55). Although, FMc is common in endometrial tissues, it hasbeen reported to be less common in type 1 endometrial cancer tissues compared to controls. It has been suggested that the presence of lower amounts of FMcCs in women with uterine cancer indicates a good prognosis for cancer subtype and stage (56). Melanoma tissues in humans and mice have been reported to contain more chimeric cells than other tissues (57). Among brain tumors, glioblastoma cases were reported to have a higher frequency of FMcCs compared to women with meningiomas (58). In addition, it was reported that Mc prolongs the average survival time in women with glioblastoma and that high McCs frequency may have a positive effect on the disease. However, the effect of chimeric cells in brain tissue on brain function and cognition also needs to be investigated.

4.3. Psychiatric Diseases

Infectious diseases can increase routine microchimeric cell migration between mother and fetus. In order to protect against infectious agents, MMcCs transferred to the fetus do not return, they can settle in various tissues and organs of the fetus. Various opinions have been put forward aboutthe functions of these cells, which settle in the tissues and do not return. The most well-known effect in this regard is that the intelligence and behavior of the fetus are affected. The best-known evidence for an increased risk of mental disorders in the children of mothers who contracted infections during pregnancy; it is a strong relationship between schizophrenic children and maternal respiratory tract infections (59,60). Prenatal difficulties and related changes in immune and endocrine markers may cause postnatal neuro- developmental disorders. Maternal health during pregnancy, for example; may be affected by stress or infections. These conditions lead to increased levels of cytokines and glucocorticoids, potentially leading to an increased frequency of MMcCs in infants. After migrating to the fetal brain, MMcCs

can act as maternal modulators, significantly disrupting the physiological development of the brain. 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) (38).

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 (61). The rubella epidemic in 1964 increased the frequency of patients with schizophrenia from 1% to 20% (62). In many animal studies, it has been reported that prenatal or early postnatal infections cause autistic features or acute and permanent neurological behavioral abnormalities similar to schizophrenia in offspring (63,64). 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 (65,66). In epidemiological studies, it was reported that autism increased 200 times in children of mothers who had measles infection (32). Prenatal infections may also be a possible risk factor for autism spectrum disorders, given that infections such as measles, cytomegalovirus or toxoplasma gondii have teratogenic effects onthe central nervous system. Of these risk factors, influenza infection in pregnant rodents has been reported to cause human-like behavioral disorders and histological abnormalities in offspring (67). The common response to these pathogens is maternal immunity. As a matter of fact, it has been reported that exposure to environmental pollutants that cause high immune responses such as maternal autoimmune diseases, allergies, asthma and acute stress increases the risk of schizophrenia (68,69). It has been observed that psychiatric diseases enter the healing process with the stages of autoimmune diseases. All these evidences point to the important role of neuroinflammation and immune system in the pathophysiology of schizophrenia (59). However, there are numerous reports supporting the hypothesis that immune activation is a risk for the onset of schizophrenia in adulthood (70,71). Increasing clinical cases of schizophrenia after bone marrow transplantation also significantly confirm the understanding of the importance of the immune system in schizophrenia.

Many MMcCs that migrate to the fetus to fight infectious diseases cannot return to the mother's body, appropriate agents differentiate these cells and can be transformed into stem cells. This causes alloimmunity. Because the DNA of the cells involved in the construction of tissues and organs is

different. If MMcCs, which gain physiopathological features, participate in the development of the brain, they cause the formation of 2 different DNAs in the brain. In this case, there will be two different neuromeditor receptor groups in the brain tissue. The production of each DNA is individual. In this case, the rules of chaos physics begin to work, and the architecture of the brain changes as the initial conditions change. Mild neurological symptoms have been detected in babies born with altered brain architecture (59). It is known that Mc plays a role in the history of autoimmune diseases, and may also be a factor in the development of schizophrenia and postpartum psychosis (71,72). We must now accept that MMcCs cause autoimmune diseases and that these cells are involved in the etiology of alloimmune diseases and should be treated accordingly (also in psychiatric diseases).

When F-MMcCs cannot produce stem cells to survive, schizophrenia may recover after the first attack, as these cells in the schizophrenic patient's brain are reduced. If these cells produce new stem cells, then schizophrenia will become chronic. Migration of F-MMcCs may explain the concept of hallucinations. In other words, neuromediator-receptor production will be individualized if there are two different DNAs in the brain tissue. Even if dopamine produced by schizophrenic brain cells reaches the nomadic cells, it will not be able to bind to the receptor due to the different resonance frequency. Therefore, the nomadic cell receptors will continue to demand continuous dopamine due to dopamine starvation and will be constantlyproduced and released. Therefore, there will be relative abundance of dopamine in the environment. In this case, dopamine will activate the auditory receptors and the schizophrenic patient will hear it as a sound (71). Indeed, vibrational frequency is known to change the behavior of Drosophila melanogaster flies. We can compare the vibration frequency to the radio frequency switch that starts our car. Although all keys and slots are similar in appearance, one key cannot start another car because the radio frequency is different. The resonance frequencies of the neuromodulator receptor pair produced by each DNA are also different. For this reason, it is thought that psychotic behaviors seen in the mother after birth can be seen. In our recent study; It has been reported that there is a significant difference in the number of FMcCs between women with postpartum depression and healthy women, and the frequency of these cells is significantly higher in sick women than in healthy controls (72). MMc may be a biological process that marks one's own offspring, perhaps inadvertently leading to greater investment and evolutionary consequences for survival. In addition, increasing maternal exposure to fetal cells during pregnancy may play a role in actively promoting processes that support the child's postnatal care, from maintaining maternal health to increased breastfeeding. F-MMc may have been chosen to have different roles in the evolutionary process, including psychological manipulation, promoting maternal interaction with their children to facilitate

survival (73). It is believed that Mc can be an important alternative in explaining the history of psychiatric disorders. Thus, numerous studies have known that prenatal infections show behavioral abnormalities in offspring, both acute and persistent, resembling autistic or schizophrenia. It has been reported that current studies will provide valuable information on the effects of the immune system on the brain and behavior and represent a more important potential step in schizophrenic patients (74).

FMc is significantly more common in women with preeclampsia and in the female liver. This suggests a possible role of Mc and Fc in liver diseases. Biliary atresia (BA) is a neonatal liver disease in which MMcCs are found in the liver tissue of infants affected by the disease. The findings suggest that chimerism has an immunological role in the pathogenesis of BA. Mc has been observed in mouse and human heart tissue. Indeed, the presence of FMcCs in the heart tissue of two women with boys has been reported. Although, the role of Mc in cardiac conditions is unknown, it may be related to the integration of fetal cells into maternal tissues. The plasticity of McCs indicates the capacity to differentiate and integrate in various tissue types. It will be important for future studies to further investigate this plasticity and understand the tissue-specific effects of chimerism.

5. Conclusion

Mc is a subject we know the least about today, and there is still uncertainty about the relationship F-MMc may play in disease. The interesting thing is that he defined a male Mc in women who did not have male children. It is not known whether these male cells originate from the mother's sibling's DNA, from male abortion, from missing twins, from a history of transfusions or from sexual intercourse. However, in mice, it has been reported that stem cells of previously born siblings are passed from mother to new baby through breastfeeding and/or blood. This shows that the stem cells of the siblings are transferred to other siblings through the mother. We are all born Mc because we carry the stem cells of our mother and previously born siblings. In addition, Mc has also been seen in dizygotic twins. A better understanding of their individual interactions with the host body is required to determine the pathological role of allogeneic McCs. It is hypothesized that McCs shared between mother and offspring may be a mechanism involved in the pathogenesis of diseases.

6. Referances

[1] Bianchi, DW., Fisk, NM. (2007) Fetomaternal cell trafficking and the stem cell debate: gender matters. Journal of the American Medical Association, 297(13), 1489–1491. doi:10.1001/jama.297.13.1489.

[2] Sarkar K, Miller FW. (2004). Possible roles and determinants of microchimerism in autoimmune and other disorders. Autoimmun Rev, 3, 454-63. DOI: 10.1016/j.autrev.2004.06.004.

[3] Hassiotou F, Hartmann PE. (2014). At the dawn of a new discovery: The potential of breast milk stem cells. Adv Nutr. 5, 770-8. doi: 10.3945/an.114.006924.

[4] Hassiotou F, Heath B, Ozal O, et al. (2014). Breastmilk stem cell transfer from mother to neonatal organs. The FASEB Journal. 28, 216-264. DOI: 10.5152/TurkArchPediatr.2021.21006.

[5] Aydın MŞ, Yiğit EN, Vatandaşlar E et al. (2018). Transfer and integration of breast milk stem cells to the brain of suckling pups. Sci Rep, 8, 14289. DOI:10.1038/s41598-018-32715-5.

[6] Hanson LA. (2000) The mother-offspring dyad and the immune system. Acta Paediatr, 89, 252-8. https://doi.org/10.1111/j.1651-2227.2000.tb01325.x.

[7] Ron M, Porat B, Band MR et al. (2011). Chimaerism detection in bovine twins, triplets and quadruplets using sex chromosome-linked markers. Animal Genetics, 42(2), 208–211. DOI: https://doi.org/ 10.1111/j.1365-2052.2010.02099.x.

[8] Kenny DE, Cambre RC, Frahm MW et al. (1992) Freem artinism in a captive herd of Rocky Mountain bighorn sheep (Ovis canadensis). Journal of Wildlife Diseases, 28(3),494–498. DOI: 10.1016/ j.anireprosci.2004.09.008.

[9] Jimenez, DF., Leapley, AC., Lee, CI., et al. (2005) Fetal CD34+ cells in the maternal circulation and long-term microchimerism in rhesus monkeys (Macaca mulatta). Transplantation, 79(2), 142–146. DOI: 10.1097/01.tp.0000144468.71962.aa.

[10] Axiak-Bechtel, SM., Kumar, SR., Hansen, SA. et al. (2013). Ychromosome DNA is present in the blood of female dogs suggesting the presence of fetal microchimerism. PLoS One, 8(7), e68114. DOI: 10.1371/journal.pone.0068114.

[11] Lyons, LA. (2012). Genetic testing in domestic cats. Molecular and Cellular Probes, 26(6), 224–230. doi: 10.1016/j.mcp.2012.04.004.

[12] Szczerbal, I., Nowacka-Woszuk, J., Nizanski, W., et al. (2014). Switonski M. A case of leucocyte chimerism (78,XX/78,XY) in a dog with a disorder of sexual development. Reproduction in Domestic Animals, 49(3), e31–e34. DOI: 10.1111/rda.12318.

[13] Perlman, RL. (2016). Mouse models of human disease: An evolutionary perspective. Evolution, Medicine, and Public Health, 16(1), 170–176. DOI: 10.1093/emph/eow014.

[14] Su, EC., Johnson, KL., Tighiouart, H., et al. (2008). Murine maternal cell microchimerism: Analysis using real-time PCR and in vivo imaging. Biology of Reproduction, 8(5), 883–887. DOI: 10.1095/biolreprod.107.063305.

[15] Kara, RJ., Bolli, P., Matsunaga, I., et al. (2012). A mouse model for fetal maternal stem cell transfer during ischemic cardiac injury. Clinical and Translational Science, 5(4), 321–328. doi: 10.1111/j.1752-8062.2012.00424.x.

[16] Pritchard, S., Wick, HC., Slonim, DK., et al. (2012). Comprehensive analysis of genes expressed by rare microchimeric fetal cells in the maternal mouse lung. Biology of Reproduction, 87(2), 42. DOI: 10.1095/biolreprod.112.101147.

[17] Vogelgesang, A., Scapin, C., Barone, C., et al. (2014). Cigarette smoke exposure during pregnancy alters fetomaternal cell trafficking leading to retention of microchimeric cells in the maternal lung. PLoS One, 9(5), e88285. doi: 10.1371/journal.pone.0088285.

[18] Niu, DM., Pan, CC., Lin, CY., et al. (2002). Mosaic or chimera? Revisiting an old hypothesis about the cause of the 46,XX/46,XY hermaphrodite. The Journal of Pediatrics, 140(6), 732–735. DOI: 10.1067/mpd.2002.124321.

[19] Shin, SY., Yoo, HW., Lee, BH., et al. (2012). Identification of the mechanism underlying a human chimera by SNP array analysis. American Journal of Medical Genetics, Part A, 158a(9), 2119–2123. DOI: 10.1002/ajmg.a.35476.

[20] 20. Lepez, T., Vandewoestyne, M., Hussain, S., et al. (2011). Fetal microchimeric cells in blood of women with an autoimmune thyroid disease. PLoS One, 6(12), e29646. doi.org/10. 1371/journal.pone.0029646.

[21] Wang, L., Wang, FS., Gershwin, ME. (2015). Human autoimmune diseases: A comprehensive update. Journal of Internal Medicine, 278(4), 369–395. DOI: 10.1111/joim.12395.

[22] Nelson, JL. (1998). Microchimerism and autoimmune disease. The New England Journal of Medicine, 338(17):1224–1225. DOI: 10.1056/NEJM199804233381711.

[23] Johnson, KL., McAlindon, TE., Mulcahy, E., et al. (2001). Microchimerism in a female patient with systemic lupus erythematosus. Arthritis and Rheumatism, 44(9), 2107–2111. DOI: 10.1002/1529-0131(200109)44:9<2107:AID-ART361>3.0.CO;2-9.

[24] Ohtsuka, T., Miyamoto, Y., Yamakage, A., et al. (2001). Quantitative analysis of microchimerism in systemic sclerosis skin tissue. Archives of Dermatological Research, 293(8), 87–391. DOI: 10.1007/ s004030100245.

[25] Sawaya, HH., Jimenez, SA., Artlett, CM. (2004). Quantification of fetal microchimeric cells in clinically affected and unaffected skin of patients with systemic sclerosis. Rheumatology (Oxford), 43(8), 965– 968. DOI: 10.1093/rheumatology/keh211.

[26] Lambert, NC., Pang, JM., Yan, Z., et al. (2005). Male microchimerism in women with systemic sclerosis and healthy women who have never given birth to a son. Annals of the Rheumatic Diseases, 64(6), 845– 848. DOI: 10.1136/ard.2004.029314.

[27] Kekow, M., Barleben, M., Drynda, S., et al. (2013). Long-term persistence and effects of fetal microchimerisms on disease onset and status in a cohort of women with rheumatoid arthritis and systemic lupus erythematosus. BMC Musculoskeletal Disorders, 13,14,325. DOI: 10.1186/1471-2474-14-325.

[28] Florim, GMS., Caldas, HC., Pavarino, EC., et al. (2015). Variables associated to fetal microchimerism in systemic lupus erythematosus patients. Clin Rheumatol, 1-4. DOI: 10.1007/s10067-015-3122-8.

[29] Kanold, AM., Svenungsson, E., Gunnarsson, I., et al. (2013). A research study of the association between maternal microchimerism and systemic lupus erythematosus in adults: A comparison between patients and healthy controls based on single-nucleotide polymorphism using quantitative real-time PCR. PLoS One, 8(9), 74534. doi.org/10.1371/journal.pone.0074534.

[30] Piotrowski, P., Croy, BA. (1996). Maternal cells are widely distributed in murine fetuses in utero. Biol Reprod.,54(5), 1103-1110. doi.org/10.1095/biolreprod54.5.1103.

[31] 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. DOI: 10.1097/01.lab.0000067500.85003.32.

[32] Khandaker, GM., Cousins, L., Deakin, J., et al. (2015). Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet psychiatry, 2(3), 258-70. DOI: 10.1016/S2215-0366(14)00122-9.

[33] Ye, J., Vives-Pi, M., Gillespie, KM. (2014). Maternal microchimerism: Increased in the insulin positive compartment of type 1 diabetes pancreas but not in infiltrating immune cells or replicating islet cells. PLoS One, 9(1), e86985. DOI: 10.1371/ journal.pone.0086985.

[34] Ye, Y., van Zyl, B., Varsani, H., et al. (2012). Maternal microchimerism in muscle biopsies from children with juvenile dermatomyositis. Rheumatology (Oxford), 51(6), 987–991. doi: 10.1093/rheumatology/ker430.

[35] Nelson, JL., Gillespie, KM., Lambert, NC., et al. (2007). Maternal microchimerism in peripheral blood in type 1 diabetes and pancreatic islet beta cell microchimerism. Proceedings of the National Academy of Sciences of the United States of America, 104(5), 1637–1642. doi: 10.1073/pnas.0606169104.

[36] Jung, CG., Hull, RFC. (1981). The Archetypes and The Collective Unconscious (Collected Works of C.G. Jung Vol.9 Part 1). (ISBN13: 9780691097619).

[37] Nelson, JL. (1996). Maternal-fetal immunology and autoimmune disease: is some autoimmune disease auto-alloimmune or allo-autoimmune? Arthritis Rheum., 39:191–946. DOI: 10.1002/art. 1780390203.

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

[39] Nelson JL. (2009). Naturally acquired microchimerism: for better or for worse. Arthritis Rheum., 60(1), 5-7. doi: 10.1002/art.24217.

[40] Cirello, V., Recalcati, MP., Muzza, M., et al. (2008). Fetal cell microchimerism in papillary thyroid cancer: A possible role in tumor damage and tissue repair. Cancer Research, 68(20), 8482–8488. DOI: 10.1158/0008-5472.CAN-08-0672.

[41] Cirello, V., Rizzo, R., Crippa, M., et al. (2015). Fetal cell microchimerism: A protective role in autoimmune thyroid diseases. European Journal of Endocrinology, 173(1), 111–118. DOI: 10.1530 EJE-15-0028.

[42] Cirello, V., Fugazzola, L. (2014). Positive effect of fetal cell microchimerism on tumor presentation and outcome in papillary thyroid cancer. Chimerism, 5(3–4), 106–108. DOI: 10.1080/19381956.2015.1107254.

[43] Gadi VK. (2010). Fetal microchimerism in breast from women with and without breast cancer. Breast Cancer Research and Treatment, 121(1), 241–244. DOI: 10.1007/s10549-009-0548-1.

[44] Kamper-Jorgensen, M. (2012). Microchimerism and survival after breast and colon cancer diagnosis. Chimerism, 3(3), 72–73. DOI: 10.4161/chim.22770.

[45] Korkmaz, DT., Demirhan, O., Çetinel, N., et al. (2021). Fetal microchimerism and X chromosome aneuploidies in women with breast cancer. International Journal of Medical and Health Research, 7(2), 31-38.

[46] Taştemir Korkmaz, D., Demirhan, O., et al. (2015). Microchimeric Cells, Sex Chromosome Aneuploidies and Cancer. Pathol. Oncol. Res., 21, 1157–1165. DOI: 10.1007/s12253-015-9934-7.

[47] Kamper-Jørgensen, M., Biggar, RJ., Tjønneland, A., et al. (2012). Opposite effects of microchimerism on breast and colon cancer. Eur J Cancer, 2012, 48:2227–2235. DOI: 10.1016/j.ejca.2012.02.006.

[48] Galofré, JC., Duntas, LH., Premawardhana, LD. (2012). Advances in Graves‘ Disease. J Thyroid Res., 2012, 809231. doi.org/10.1155/2012/809231.

[49] Davies, D., Demirhan, O. (2019). Pregnancy-related microchimerism unknown pathophysiological effects. Front Womens Healt, 4, 1-4.DOI: 10.15761/FWH.1000167.

[50] Shi, L., Fatemi, SH., Sidwell, RW., et al. (2003). Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J Neurosci., 2, 297-302. DOI: 10.1523/JNEUROSCI.23-01-00297.2003.

[51] Ay, G. (2004). Autoimmune thyroid diseases and fetal microchimerism. Harran Tıp Fak Der., 1(3), 41-47.

[52] Klintschar, M., P, Schwaiger., S, Mannweiler., et al. (2001). Evidence of fetal microchimerism in Hashimoto‘s thyroiditis. J Clin Endocrinol Metab., 8, 2494-2498. DOI: 10.1210/jcem.86.6.7540.

[53] Li, L., Neaves, WB. (2006). Normal stem cells and cancer stem cells: the niche matters. Cancer Res., 66, 4553–4557. DOI: 10.1158/0008-5472.CAN-05-3986.

[54] Broestl, L., Rubin, JB., Dahiya, S. (2018). Fetal microchimerism in human brain tumors. Brain Pathology, 28(4), 484–494. DOI: 10.1111/bpa.12557.

[55] Hromadnikova, I., Kotlabova, K., Pirkova, P., et al. (2014). The occurrence of fetal microchimeric cells in endometrial tissues is a very common phenomenon in benign uterine disorders, and the lower prevalence of fetal microchimerism is associated with better uterine cancer prognoses. DNA and Cell Biology, 33(1), 40–48. doi.org/ 10.1089/dna.2013.2125.

[56] Nguyen Huu, S., Oster, M., Avril, MF., et al. (2009). Fetal microchimeric cells participate in tumour angiogenesis in melanomas occurring during pregnancy. The American Journal of Pathology, 174(2), 630–637. doi: 10.2353/ajpath.2009.080566.

[57] Broestl, L., Rubin, JB., Dahiya, S. (2018). Fetal microchimerism in human brain tumors. Brain Pathology, 28(4), 484–494. DOI: 10.1111/ bpa.12557.

[58] Betts, KS., Williams, GM., Najman, JM., et al. (2015). Therelationship between maternal depressive, anxious, and stress symptoms during pregnancy and adult offspring behavioral and emotional problems. Depress Anxiety, 32, 82–90. DOI: 10.1002/ da.22272.

[59] Penner, JD., Brown, AS. (2007). Prenatal infectious and nutritional factors and risk of adult schizophrenia. Exp. Rev. Neurotherap, 7, 797-805. DOI: 10.1586/14737175.7.7.797.

[60] Piotrowski, P., Croy, BA. (1996). Maternal cells are widely distributed in murine fetuses in utero. Biol Reprod., 54(5), 1103-1110. doi.org/10.1095/biolreprod54.5.1103.

[61] Meyer, U., Feldon, J., Dammann, O. (2011). Schizophrenia and autism: both shared and disorder-specific pathogenesis via perinatal inflammation? Pediatr. Res., 69, 26R–33R. DOI: 10.1203/PDR. 0b013e318212c196.

[62] Patterson, PH. (2011a). Maternal infection and immune involvement in autism. Trends Mol. Med., 17, 389–394. DOI: 10.1016/j. molmed.2011.03.001.

[63] Hyman, SL., Arndt, TL., Rodier, PM. (2006). Environmental agents and autism: once and future associations Int. Rev. Res. Ment. Retard., 30,171-194. https://doi.org/10.1016/S0074-7750(05)30005-X.

[64] Moy, SS., Nadler, JJ. (2008). Advances in behavioral genetics: mouse models of autism. Mol. Psy., 3, 4-26. DOI: 10.1038/sj.mp.4002082.

[65] Brown, AS. (2006). Prenatal infection as a risk factor for schizophrenia Schiz Bull., 32, 200-202. DOI: 10.1093/schbul/sbj052.

[66] Johnson, RT. (1994). Infections during pregnancy Adv. Neurol., 64,153-162. ??

[67] 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. DOI: 10.1016/S2215-0366(14)00122-9.

[68] Demirbek, B., Demirhan, O. (2019). Microchimerism may be the cause of psychiatric disorders. Arch Psychiatr Ment Health., 3, 42- 046. DOI: 10.29328/journal.apmh.1001009.

[69] Demirhan, O., Öztürk, N., Aydın, Z., et al. (2019). Effect of Fetal Microchimeric Cells on the Development of Postnatal Depression. Medical and Clinical Archives, 3,1-6. DOI: 10.15761/MCA.1000149.

[70] Boddy, AM., Fortunato, A., Wilson Sayres, M., et al. (2015). Fetal microchimerism and maternal health: A review and evolutionary analysis of cooperation and conflict beyond the womb. BioEssays, 37(10): 1106–1118. DOI: 10.1002/bies.201500059.

[71] Bayes-Genis, A., Bellosillo, B., de la Calle, O., et al. (2005). Identification of male cardiomyocytes of extracardiac origin in the hearts of women with male progeny: Male fetal cell microchimerismof the heart. The Journal of Heart and Lung Transplantation, 24(12), 2179–2183. DOI:https://doi.org/10.1016/j.healun.2005.06.003.

[72] Aydın, MŞ., Yiğit, E., Vatandaşlar, E., et al. (2018). Transfer and integration of breast milk stem cells to the brain of suckling pups. Scientific Reports, 8,1-9. DOI: 10.1038/s41598-018-32715-5.