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A REVIEW ARTICLE: POSSIBLE DISEASES THAT OCCUR DUE TO THE PRESENCE OF CHIMERAS IN THE HUMAN BODY

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Abstract

The existence of chimerism in human beings could potentially have various implications. The present review centers on the phenomenon of chimerism, with a particular emphasis on microchimerism, which represents a relatively unexplored avenue for elucidating variances in health and behavior. Male microchimerism in women is a phenomenon that is believed to occur due to fetomaternal exchange during pregnancy. This condition can be detected in women through the use of polymerase chain reaction molecular techniques that target Y-chromosomal markers. As a result, the examination of chimerism in human diseases has primarily concentrated on conditions that exhibit a higher incidence in females, such as autoimmune disorders and cancers affecting females. In this paper, we present an analysis of chimerism in various human diseases and explore potential behavioral implications. Comprehending the frequency of chimerism and its correlated health ramifications will furnish indispensable insight into human biology and direct innovative methods for managing illnesses.

Keywords: **Autoimmunity, Microchimerism, Chimera, Chimerism, Autoimmune diseases, Blood transfusions.**

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INTRODUCTION

Background

The phenomenon of chimerism refers to the existence of cells originating from a single individual within another individual. Chimerism is primarily attributed to pregnancy and blood transfusions. The attribution of a pathogenic role to chimeric cells has been observed in several autoimmune diseases. Nevertheless, information regarding the prevalence of chimeric cells in healthy organs is limited. To obtain a comprehensive understanding of the potential pathogenicity of chimeric cells in autoimmune disorders, it is imperative to ascertain the frequency of chimeric cells in non-autoimmune affected organs.

1| Chimerism

A Chimera is an organism composed of multiple genetically distinct cell populations that have arisen from different zygotes resulting from sexual reproduction. Microchimerism pertains to the simultaneous presence of two distinct cell populations that differ genetically and originate separately within an individual or an organ, such as the bone marrow. The occurrence of this phenomenon at a low concentration can be ascribed to the migration of cells from the fetus to the mother. Microchimerism pertains to the presence of a limited quantity of cells (or DNA) that have their origin in an individual with a distinct genetic makeup (Shrivastava et al.,2019).

The various instances of chimerism are typically categorized into three main groups: (a) artificial occurrences, which arise subsequent to a blood transfusion or bone marrow transplant; (b) Tetragametic occurrences refer to the phenomenon in which two oocytes are fertilized by two spermatozoa, followed by the fusion of the resulting embryos, resulting in the formation of a singular organism.; and (c) transplacental occurrences, which result from the exchange of blood between a mother and her child, with twin chimerism representing a unique case within this category. The phenomenon of transplacental microchimerism is characterized by a bidirectional transfer of cells between the mother and the fetus, whereby the mother may harbor fetal microchimerism and the child may harbor maternal microchimerism. Fetal cells, including mesenchymal stem cells, leukocytes, nucleated erythrocytes, trophoblasts, and hematopoietic progenitor cells, have been detected in maternal peripheral blood samples collected during pregnancy or postpartum. (Evans *et al*., 1999; Ando and Davies, 2004).

The predominant instances of chimerism that have been identified are denoted as "microchimerism." The aforementioned term refers to a subordinate cellular cohort that constitutes a minority, comprising less than 1% of the overall cellular population. The detection of mixed chimerism in a given sample is dependent on the sensitivity of the employed methods, as there is no established minimum threshold for microchimerism generation in an organism. The field of chimerism research employs four principal methodologies to detect, measure, and differentiate distinct cellular subsets within singular specimens. The examination of cells subsequent to a blood transfusion. The field of transplantation encompasses the transplantation of solid organs and bone marrow. Both of these modalities have the potential to result in chimerism, albeit through distinct mechanisms (Johnson et al., 2020).

2| Chimerism in health

Cells from one person might appear in another individual in a process known as

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chimerism. These cells may be incorporated into the parenchyma or they may circulate. Chimerism has gained popularity since it was originally described as occurring in donated organs in 1965, particularly in connection to transplantation. Important questions include how chimerism is created, such as via rejection-related damage, and if it may increase recipient tolerance (Medawar, 1965; Koopmans and Kremer, 2009).

Lagaaij et al. (2001) provided evidence for the existence of endothelial cells originating from the recipient in kidney transplants. Numerous investigations have shown chimeric tubular epithelial cells in transplanted kidneys. The phenomenon of chimerism has been observed in various transplanted organs. Transplanted livers have been found to contain chimeric endothelium, duct epithelium, and hepatocytes. Furthermore, transplanted hearts have exhibited the presence of chimeric cardiomyocytes and smooth muscle cells, whereas transplanted lungs have displayed chimeric bronchial epithelium and type II pneumocytes (Gao et al., 2001; Kleeberger et al., 2003; Mengel et al., 2004).

It is interesting that various studies have documented varying amounts of chimera cells in solid organs after transplantation, ranging from instances of no chimerism to cases of low or even high levels of chimeric cells (Glaser et al., 2002; Laflamme et al., 2002; Quaini, 2002).

The phenomenon of chimerism has been observed in the non-pathological organs of females, even in the absence of autoimmune disorders. The findings of our study suggest that the presence of chimerism may not be inherently linked to pathological conditions. Extensive research has been conducted on the presence of chimeric cells in the maternal bloodstream during and post-partum. Chimeric cells have been observed in the bloodstream of nearly all expectant mothers (Krabchi et al., 2001; Birch et al., 2005).

It is probable that a majority of these cells are obtained from gestations that have not been identified. The entry of fetal cells into the circulation appears to occur specifically during the termination of a pregnancy, with a discernible distinction between induced abortions and spontaneous terminations such as spontaneous abortion or delivery. The incidence of chimerism appears to be notably higher, and a greater quantity of chimeric cells are detected, among females who have undergone an induced abortion (Bianchi et al., 2001; Khosrotehrani et al., 2003; Yan et al., 2005).

The utilization of the Y chromosome in cells derived from tissues has been employed to exhibit the existence of tissue chimerism in transplanted organs that originate from female donors and are transplanted into male recipients. The assertion was made that the aforementioned chimeric cells of the Y chromosome were derived from the recipient. The objective of the study was to investigate the potential presence of chimeric cells in solid organs prior to transplantation, which may have originated from pregnancies involving male offspring or blood transfusions. Research conducted across various mammalian species has established that the process of blood exchange during pregnancy can potentially aid in the transmission of a limited number of cells (Bianchi et al., 1996; Davies, 2012).

3| Sources of chimeric cells

Chimeric cells can arise from three significant sources, namely: chimeric cells originating from gestation, blood transfusions, and transplants. Pregnancy has the potential to induce chimerism through multiple mechanisms, whereby diverse cell lineages may be transmitted throughout gestation. The role of chimerism in prenatal diagnostics will also be

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given due consideration. The induction of chimerism can be achieved through the utilization of blood transfusion. The present discourse aims to expound upon intriguing findings derived from multiple research endeavors that have explored the destiny of chimeric cells following the process of blood transfusion. The field of transplantation encompasses the transplantation of solid organs and bone marrow. Both types of transplantation have the potential to result in chimerism, albeit through distinct mechanisms (Koopmans and Kremer, 2009).

The identification of numerous instances of chimerism was initially accidental, as they were discovered through the observation of inconsistencies in blood types during standard testing procedures. The identification of mixed red cell populations was first reported as an outcome of chorion blood vessel anastomoses during fetal development in cattle, as documented by Owen in 1945. The phenomenon of having both type A and type O red cell populations in humans was initially reported by Dunsford et al. (1953) in a blood donor. It was hypothesized that this condition was due to chimerism from a twin. The process of conducting agglutination testing in blood banks involves the utilization of reagent antibodies that are introduced to the red blood cells of an individual. The purpose of this is to determine whether the cells express the corresponding antigen, which is then identified through visual agglutination. The effectiveness of visual interpretation is predominantly restricted to the examination of the antigenic makeup of primary erythrocyte populations (Mujahid and Dickert, 2015). In addition, it has been reported that the gel column agglutination method, a traditional technique utilized in the field of blood banking, can detect mixed-field agglutination responses in individuals with a minor cell population of 10% (Hong *et al*., 2013).

3.1| Pregnancy

The placental barrier serves as a partition between the fetal and maternal circulations, enabling the exchange of metabolic and gaseous substances. The concept of a placental barrier was initially proposed by John and William Hunter in the 18th century. Their observation of the injection of liquid wax into the uterine artery and its failure to emerge in the fetal circulation served as the basis for this fundamental concept. The placental barrier may experience occasional breaches, allowing for minute amounts of fetal blood and cells to enter the maternal bloodstream, resulting in chimerism (Ramsey, 1985; Koopmans and Kremer, 2009).

3.2| Blood transfusion

In addition to pregnancy, the transfusion of blood products represents another plausible origin for chimeric cells. Lee et al. conducted a comprehensive investigation in 1999 on the survival kinetics of particular donor leukocyte subsets in immunocompetent recipients following blood transfusion. Blood specimens were procured from a cohort of eight female patients who underwent elective surgical procedures prior to receiving transfusions. The specimens were collected on multiple occasions, including days 1, 3, 5, 7, and 14 post-transfusion. Additionally, blood samples were obtained from a separate group of 10 female trauma patients up to 1.5 years following transfusion. The isolation of WBC subsets from frozen whole blood was carried out through the utilization of magnetic beads coated with CD4, CD8 (T cell), CD15 (myeloid), and CD19 (B cell) antibodies. The quantification of white blood cells from donors was performed through the utilization of quantitative polymerase chain reaction targeting the male-specific sex determining region (SRY) sequence. The study observed that male donor leukocytes were cleared at a rate of 99.9% within 24 hours after transfusion in all

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eight elective surgery patients who had received either one or two units of non-leukodepleted male red blood cells (RBCs). Surprisingly, a significant rise in Y chromosome-positive donor leukocytes was detected in six out of eight recipients during the 3-4-day period following transfusion. None of the women in this study exhibited the presence of donor leukocytes in their circulation between 7 to 14 days following transfusion (Lee et al., 1999).

Remarkably, a significant proportion of trauma patients who received 3-14 units of male red blood cells (RBCs) displayed a sustained presence of cells originating from the donor, as observed in 70% of cases. Two patients with the most extensive duration of observation, spanning 18 months, exhibited persistence of donor cells up to the final time-point. Five patients demonstrated donor cell survival for a duration of up to six months. Among these patients, one individual exhibited negative results for male donor cells at the one-year follow-up, while the remaining four patients continued to exhibit positive results at the final sampling time point. The study found that a range of 0.5% to 10% of the circulating white blood cells in the recipients were of donor origin, and this phenomenon was observed across multiple lineages of donor leukocytes, including CD4, CD8, CD15, and CD19. The results indicate that the samples obtained from the two remaining patients exhibited a negative outcome for donor cells within a timeframe of 4 to 6 months post-transfusion (Lee et al., 1999).

3.2| Transplantation

Solid organ or bone marrow transplantation is a known mechanism for the generation of chimeric cells, alongside pregnancy and blood transfusion transplantation. Following transplantation, recipients are considered chimeric as they possess tissues of varying genetic composition, as per the definition of the term. The term chimerism may present a challenge in certain contexts due to its multifaceted manifestations. One common medical procedure involves the transfer of bone marrow or solid organs from a donor to a recipient, resulting in the recipient becoming a chimera. In the context of solid organ and bone marrow transplantation, it is noteworthy that the recipient's circulation contains peripheral cells that originate from the donor, thereby rendering the recipient chimeric, albeit in a distinct manner. Thirdly, it is observed that the epithelial or endothelial cells of the donor organ are replaced by recipient-derived cells, resulting in a chimeric graft (Koopmans and Kremer, 2009).

4| Possible implications of chimerism

The potential implications of chimerism in human beings are numerous. At the outset, it is conceivable that the chimeric cells may coexist within the host organism without provoking an immunological reaction. The prevalence of chimeric cells in the bloodstream of asymptomatic individuals provides evidence to support the plausibility of these cells assuming an innocent bystander role.

Moreover, chimeric cells could potentially contribute to the development of transplantation-related pathologies. According to the definition, an individual who undergoes organ transplantation is considered a chimera. Additionally, chimerism of the graft itself can also occur, potentially leading to improved graft tolerance. The notion has been proposed that the substitution of donor cells with recipient cells within the graft leads to a greater degree of self-identity, ultimately resulting in enhanced tolerance of the graft. Conversely, the introduction of donor cells into the recipient's peripheral circulation could potentially impact the peripheral tolerance of the donor towards the graft's cells. Furthermore, it is plausible that

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chimeric cells could be implicated in the onset of autoimmune disorders. The potential impact of chimerism on the immune system is a well-established phenomenon. It is plausible that in specific scenarios, this mechanism may become disrupted, leading to an immune reaction triggered by chimeric cells that could potentially result in a breakdown of self-antigen tolerance. The deleterious function of chimeric cells is substantiated by empirical evidence indicating that chimerism is more prevalent in individuals afflicted with autoimmune disorders (such as systemic sclerosis) as compared to those who are in good health (Koopmans and Kremer, 2009).

5| Possible effects of chimera cells in humans

Inquiries have been raised pertaining to the potential harm that chimerism may cause. Numerous research studies have explored the existence of chimeric cells in diseases that are mediated by the immune system (Klintschar et al., 2001).

The investigation of chimeric cell phenotype in immune-mediated diseases remains incomplete, despite certain studies conducted on systemic sclerosis patients which revealed the presence of T cells among the chimeric cells. It is conceivable that solely chimeric cells exhibiting a specific phenotype, such as chimeric T cells, possess the capability to cause disease, while others, including the CD34+ cells identified during gestation, are inert observers (Artlett et al., 2002).

5.1 | Autoimmune diseases

Autoimmune diseases are typically regarded as intricate immune disorders that exhibit pathological immune responses targeted towards self-tissue. The incidence of certain autoimmune disorders is more prevalent among women during their reproductive years (Harel and Shoenfeld, 2006; Shrivastava et al.,2019).

Microchimerism in human disease has been a primary focus in the studies of autoimmune diseases. Autoimmune diseases affect around 5% of the human population, with a notable gender disparity as approximately 78% of those affected are female. (Jacobson, 1997; Lepez et al., 2011; Wang and Gershwin, 2015). In addition, it is noteworthy that a number of autoimmune disorders exhibit a higher incidence rate among women in the postpartum phase, and exhibit a comparable pathology to chronic graft-versus-host disease (cGVHD), an extensively researched condition in the field of transplantation medicine that arises due to chimerism (Furst, 1979; Lambert et al., 2001). Taken together, these characteristics indicate that microchimerism may play a part in the development of autoimmune diseases. Extensive research has been conducted on the involvement of microchimerism in the development of autoimmune diseases, with a particular focus on rheumatic diseases and autoimmune thyroid diseases (AITD).

Chimeric cells are commonly observed in healthy organs, whereas autoimmune disorders are relatively rare. Currently, there are three prominent hypotheses concerning the potential implication of chimeric cells in the development of autoimmune disorders (Jimenez and Artlett, 2005; Kremer et al., 2007).

The first two hypotheses posit that chimeric cells may have an inductive function through either a graft versus-host or host-versus-graft reaction, commonly referred to as 'detrimental chimerism'. As per the third hypothesis, the involvement of chimeric cells in the repair process, commonly known as "helpful chimerism," is deemed to be of significant importance (Khosrotehrani and Bianchi, 2003).

Merely detecting the presence of chimeric cells does not provide sufficient grounds to infer

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the existence of deleterious chimerism. The findings of some study indicate that the chimeric cells detected in healthy organs did not elicit a host-versus-graft or graft-versus-host response. The occurrence of these reactions necessitates the presence of additional factors, as evidenced by experimental models. Analogously, the manifestation of a disease similar to lupus nephritis in humans, specifically graft-versus-host disease, is contingent upon the induction of chimerism in particular strains of mice. (Via and Shearer, 1988).

An association has been reported in human systemic lupus erythematosus (SLE) between the occurrence of the disease and bidirectional compatibility of HLA class II between parents and offspring (Stevens et al., 2005).

5.1.1| Systemic lupus erythematosus (SLE)

Lupus nephritis is an immune-mediated condition that mostly affects the kidneys. Through the injection of parental T cells into children, lupus nephritis may be replicated in experimental mice models. The etiology of autoimmune illnesses like SLE in humans may be influenced by pregnancy-induced chimerism, although it's probable that only a subset of chimerism is really harmful.

Multiple organs are affected by the severe immune-mediated illness known as systemic lupus erythematosus (SLE). Mostly women experience it throughout their reproductive years. The etiology has been studied in depth, although it is still unclear. It's interesting to note that in experimental animal models, inducing a chimera state by injecting parental T cells in offspring might cause an autoimmune response similar to SLE (Via and Shearer, 1988).

The aforementioned discovery gave rise to the supposition that chimeric cells could potentially play a role in the development of systemic lupus erythematosus in humans and could be detected in the organs affected by the disease. Systemic Lupus Erythematosus (SLE) exhibits a predilection for renal involvement. The present study describes a case of a deceased woman who had succumbed to complications arising from Systemic Lupus Erythematosus (SLE). Prior to her demise, the woman had given birth to two male offspring. The study reports the presence of male cells in all of the woman's histologically abnormal tissues (Johnson et al., 2001).

5.1.2 | Rheumatic autoimmune diseases

The relationship between chimerism and rheumatic diseases has been extensively documented. Numerous studies have investigated females diagnosed with systemic sclerosis, revealing results that suggest a higher incidence and measurement of male microchimerism in peripheral blood and diverse tissue specimens in comparison to control groups (Johnson et al., 2001; Sawaya et al., 2004; Rak et al., 2009).

A study conducted on females diagnosed with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) found a higher prevalence of male microchimerism in the peripheral blood when compared to the control group (Kekow et al., 2013).

The involvement of HLA associations as significant risk factors in autoimmune disorders has led to their extensive investigation in relation to microchimerism. The shared epitope, a five-aminoacid motif encoded by HLA-DRB1 alleles, is present in around 80% of patients diagnosed with RA (Rak et al., 2009).

The onset of RA disease may be influenced by microchimerism, as it has been observed that women with RA have elevated levels of minor cell populations possessing HLA-DRB1*04 and HLA-DRB1*01 in conjunction with the shared epitope. The aforementioned findings

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suggest that the acquisition of disease-associated alleles through microchimerism could potentially play a role in the development of host disease etiology (Rak et al., 2009; Yan et al.,2011).

The implications of Human Leukocyte Antigen (HLA) associations are far-reaching, extending to systemic sclerosis. In this context, the presence of detectable fetal microchimeric T lymphocytes has been linked to a maternal HLA-DQA1*0501 allele. This allele is believed to facilitate persistent microchimerism (Lambert et al., 2000). The data presented collectively indicate that the molecular association between the host and acquired cells plays a role in promoting microchimerism and consequent autoimmune reaction. Nevertheless, further investigations are required to clarify these associations and the corresponding immunological mechanisms.

Autoimmune disorders often lead to tissue damage and bear resemblance to cGVHD. Consequently, research has explored microchimerism in host tissues. Systemic Lupus Erythematosus (SLE) is distinguished by the generation of antinuclear antibodies that exhibit specificity for nuclear constituents of the cell, leading to widespread organ complications and resemblance to chronic graft-versus-host disease (cGVHD) (Johnson et al., 2001).

5.1.3 | Autoimmune thyroid diseases

Autoimmune thyroid diseases (AITD) are a commonly occurring autoimmune disorder that affects a significant proportion of the general population, with estimates suggesting a prevalence of up to 5% (Jacobson and Tomer, 2007). Graves' disease (GD) and Hashimoto's thyroiditis (HT) are the predominant types of autoimmune thyroid diseases (AITD). Hypertension (HT) and Graves' disease (GD) are complex disorders that are influenced by both genetic and environmental factors. However, there is a hypothesis suggesting that fetal microchimeric cells may have a functional role in the pathogenesis of these conditions (Renné et al., 2004; Saranac et al., 2011).

AITD exhibits a notable inclination towards females, as evidenced by a female-to-male ratio of 10:1. Additionally, the illness is inclined to have a higher incidence rate among females aged 30 to 50 years, and is frequently identified in the period subsequent to childbirth (Weetman, 2010).

Approximately 66% of women who develop gestational diabetes experience its onset during the postpartum period, indicating a significant involvement of immunomodulatory occurrences subsequent to delivery (Jansson et al.,1987). The potential activation of fetal microchimeric cells within the maternal thyroid gland subsequent to the loss of maternal immune suppression during the postpartum period may suggest a significant involvement of fetal cells in the development of autoimmune thyroid disease (AITD) (Davies, 1999). Additionally, HT and GD exhibit similarities to Graft vs. Host disease, which arises subsequent to hematopoietic cell transplantation, a medically induced manifestation of chimerism (Lambert and Nelson, 2003).

The presence of fetal microchimerism in autoimmune thyroid diseases (AITD). Research has indicated that fetal cells are more prevalent in the thyroid glands and blood of individuals with autoimmune thyroid disease (AITD) in comparison to healthy controls or those with a benign adenoma or nodular goiter (Klintschar et al.,2006; Lepez et al., 2011).

There exists a possibility that fetal cells may actively contribute to the determination of the maternal immune repertoire. The interaction between fetal immune cells and maternal cells

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during the postpartum period has the potential to trigger the onset of postpartum autoimmune thyroid disease (AITD). The hypothesis is supported by the presence of fetal cells in the thyroid gland, where the autoimmune reaction is occurring (Klintschar et al., 2001; Ando et al., 2002).

Two hypotheses have been proposed regarding the role of fetal cells in graft-versus-host reactions. The first hypothesis suggests that fetal cells may act as effector cells, initiating a graft-versus-host reaction. The second hypothesis proposes that fetal cells may be the target of a host-versus-graft reaction. Following parturition, the cessation of placental immune suppression may trigger the activation of fetal immune cells, which in turn may instigate an autoimmune response predicated on HLA disparities. Hypothesis 1 posits that the autoimmune disease is initiated through the activation of fetal immature T cells, monocytes, macrophages, and NK cells, as well as the production of inflammatory cytokines and chemokines (Evans et al., 1999).

It is plausible that fetal cells may be deemed partially alloimmune, leading to an autoimmune response. The aforementioned phenomenon may manifest as a result of the maternal cells' direct response to fetal cells or due to molecular mimicry between fetal antigens and intrathyroidal maternal antigens, as hypothesized by the second hypothesis (Klonisch and Drouin, 2009; Miech, 2010).

5.1.4 | Autoimmune diseases of the liver

PBC (Primary biliary cirrhosis) is a liver disease characterized by cholestasis that persists over time and exhibits a gradual progression in its clinical manifestation. The presence of anti-mitochondrial autoantibodies has been observed to be linked with a reaction against mitochondrial enzymes. Primary biliary cholangitis (PBC) exhibits a higher prevalence in females, with a female to male ratio of approximately 10:1 (Schöniger-Hekele et al., 2002)

Prior research has investigated the occurrence of male microchimerism in females with primary biliary cholangitis (PBC), both in those with a male child (70%) and in the overall female PBC population (18%). The results indicated that the prevalence of male microchimerism in liver specimens was comparable to that of women with other liver diseases serving as controls (5% and 72%, respectively) (Tanaka et al., 1999; Schöniger-Hekele et al., 2002).

The prevalence of male microchimerism in males varies significantly across studies, as evidenced by the findings of Johnson et al. (2020). It is noteworthy that the study conducted by Schoniger-Hekele et al. (2002) reported a higher proportion of female primary biliary cholangitis (PBC) patients with male microchimerism compared to other liver disease patients. However, it is possible that this difference may be attributed to an unaccounted larger proportion of women with male offspring in the PBC group. In a study conducted by Invernizzi et al. (2000), the prevalence of male microchimerism of presumed fetal origin was found to be similar in both primary biliary cirrhosis (PBC) women (36%) and healthy control women (31%) when examining peripheral blood. The potential involvement of maternal microchimerism in the pathogenesis of PBC has been investigated, and a study by Nomura et al. (2004) reported insignificant results regarding any correlation with PBC. Collectively, the aforementioned studies indicate that microchimerism is unlikely to exert an effect on the etiology of primary biliary cholangitis (PBC) and other liver ailments (Johnson et al., 2020).

5.1.5| Sjögren's syndrome (SS)

Sjögren's syndrome (SS) is an autoimmune disorder that is distinguished by the infiltration

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of lymphocytes into the lachrymal and salivary glands, resulting in a marked reduction in the secretion of tears and saliva. The aforementioned condition is correlated with the generation of diverse autoantibodies. Systemic sclerosis (SS) exhibits a higher prevalence among the female population, with a frequency that is over nine times greater in women than in men (Giacomelli et al., 2002; Shrivastava et al.,2019).

The heightened occurrence of Sjögren's syndrome (SS) following childbirth and its correlation with a strong inclination towards females imply a potential association between pregnancy and SS. The aforementioned observations have given rise to the supposition that fetal microchimerism could potentially play a role in the development of both SS and systemic sclerosis. In order to investigate this hypothesis, a number of studies were conducted, wherein DNA was extracted from the minor salivary glands of affected individuals and subjected to analysis for the Y-chromosome-specific gene via a nested PCR test. The Y-chromosome-positive fetal cells were detected in the minor salivary gland specimens through the utilization of in situ hybridization with a DNA probe specific to the Y-chromosome (Endo et al., 2002).

The research conducted by Endo et al. revealed that in the salivary glands, the presence of fetal DNA was identified through PCR testing in 11 out of 20 women diagnosed with SS, whereas only one out of eight normal controls exhibited the same outcome. Furthermore, the presence of fetal cells was unambiguously identified in three out of eight women diagnosed with SS through the application of in situ hybridization (Endo et al., 2002). Therefore, the detection of fetal cells within the salivary glands implies that the pathogenesis of SS may involve anti-maternal GVHD.

5.1.6 | juvenile idiopathic inflammatory myopathies

Juvenile rheumatic diseases are a significant area of investigation in the context of maternal microchimerism-related conditions, much like their adult counterparts. Juvenile idiopathic inflammatory myopathies (JIIM) refer to a diverse set of uncommon connective tissue diseases that manifest as chronic muscle inflammation, leading to gradual proximal muscle weakness (Rider and Miller, 1997; Johnson et al., 2020).

Juvenile dermatomyositis (JDM) is a prevalent condition among juvenile idiopathic inflammatory myopathies (JIIM), characterized by the presence of lymphocytic perivascular infiltrates in both the muscle and skin lesions, which bears resemblance to chronic graft-versus-host disease (cGVHD). The prevalence of maternal microchimerism in peripheral blood and muscle tissue has been found to be higher in individuals with JDM as compared to those who are healthy. Similarly, an investigation into microchimeric HLA-Cw alleles revealed the presence of chimerism in 73% of patients with juvenile idiopathic inflammatory myopathies (JIIM), whereas only 10% of individuals in the control group exhibited such chimerism. (Reed et al., 2000; Artlett et al., 2001; Ye et al., 2012).

The association between the HLA-DQA1*0501 alleles in mothers and the presence of maternal microchimerism in children diagnosed with JDM has been reported in previous studies (Reed et al., 2000; Reed, 2003). The presented data exhibits a significant resemblance to rheumatic autoimmune disorders observed in adults, thereby reinforcing the proposition that HLA genes may play a role in microchimerism and disease vulnerability through an alternative pathway. This is supported by the strong association of the HLADQA1*0501 allele with both JIIM conditions in various ethnic groups and the existence of microchimerism (Lambert et al.,

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2000; Reed & Stirling, 1995).

5.1.7| Type 1 diabetes

The onset of Type 1 diabetes (T1D) typically occurs in the pediatric and young adult population. This has led to the proposition of an etiological mechanism involving autoimmunity triggered by maternal microchimerism. Compared to controls, patients with T1D exhibit elevated levels of maternal microchimerism in both their peripheral blood and pancreas tissue (Nelson et al., 2007; Ye et al., 2014).

Subsequent analysis of maternal microchimeric cells within the pancreas has revealed a prevalent occurrence in both typical and T1D pancreatic tissues. The presence of maternal cells originating from a maternal multi/pluripotent progenitor cell is indicated by their endocrine, exocrine, and vascular endothelial lineage (Nelson et al., 2007; Ye et al., 2014).

The pancreases of T1D patients exhibit a significant enrichment of beta cells in maternal cells. Nevertheless, the precise function of these cells in immune homeostasis during the developmental stage remains ambiguous (Nelson et al., 2007; Ye et al., 2014).

The precise function of maternal cells within pancreatic tissues remains unclear, as the retrospective analysis does not provide insight into the timing of cell grafting. Hence, it is plausible that these cells were present and implicated in the onset of the disease or, alternatively, they may have translocated to the tissue subsequent to active autoimmunity, necessitating additional investigation.

5.2 | Cancer

While fetal microchimerism has been suggested as a potential contributor to autoimmune disorders, it could also provide a favorable impact by enhancing immune monitoring of cancerous cells (Gadi and Nelson,2007).

In contrast to the results observed in autoimmune disorders, the aforementioned findings suggest the possibility of advantageous outcomes and provide cumulative corroboration for the theory that microchimeric cells could play a role in immune monitoring, travel to impaired or diseased tissue, and be enlisted for the purpose of tissue restoration. Fetal microchimerism has been observed to exhibit a protective function in the suppression of tumor development in women with a history of pregnancy who have been diagnosed with breast cancer. The presence of allogeneic fetal microchimeric cells in parous women may potentially offer immune-surveillance against breast cancer. Additionally, it is suggested that parous women who do develop breast cancer may have a diminished supply of acquired allogeneic immunity. Advanced maternal age has been linked to a decreased likelihood of developing ovarian cancer. Based on the evidence that the quantity of microchimeric cells in women who have given birth decreases over time following pregnancy, and that postmenopausal women are at the greatest risk for developing ovarian cancer, it is plausible that fetal microchimerism could have a defensive effect against ovarian cancer (Shrivastava et al.,2019)

Research has demonstrated that microchimeric fetal cells tend to aggregate in lung tumors among women, even after several decades post pregnancy. The incidence of these entities in neoplasms was significantly greater in pulmonary neoplasms than in adjacent non-neoplastic pulmonary tissue. It is possible that fetal cells could be mobilized from the bone marrow and migrate to tumor sites, where they would then perform their functions in immune surveillance and tissue repair. In the context of noncancerous ailments, these cells exhibit a

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dualistic nature, whereby they may either combat or exacerbate the disease. Similarly, in the case of tumor formation, these cells may assume an immune surveillance function, thereby impeding tumor development, or they may adopt the characteristics of cancer stem cells, thereby promoting tumor growth (Sawicki, 2008).

Papillary thyroid cancer (PTC) and breast cancer exhibit a higher incidence rate in females, akin to autoimmune diseases. As such, it is plausible that fetal microchimerism may play a role in the pathogenesis of these conditions. A study conducted on neoplastic thyroid tissue associated with papillary thyroid carcinoma (PTC) found that male microchimerism was present in the tissue of 47.5% of women who had previously undergone male pregnancy. In contrast, no such detection was observed in female controls with PTC and no history of male pregnancy (Cirello et al., 2008).

It has been found through subsequent studies that male cells are present in neoplastic thyroid tissue. However, the prevalence of male microchimerism in the peripheral blood of women with PTC is lower compared to healthy controls, as reported by Cirello et al. in 2010. The presence of peripheral blood male microchimerism and PTC is associated with a decreased incidence of extra-thyroidal extension or lymph node metastasis and improved overall prognosis. The current study postulates that the aforementioned observations may be attributed to the protective role of fetal cells in the host organism, which involves their cytotoxic action against preneoplastic cells and their function as sentinel cells against malignant cells. This mechanism is believed to impede the development of new tumors and hinder the progression of existing ones. A comparative analysis of breast cancer cases and controls has revealed the presence of male microchimerism in 26% and 56% of the respective groups. However, a subsequent case-control investigation has reported a lower incidence of male microchimerism in the unaffected breast tissue of women diagnosed with breast cancer. (Gadi, 2010; Cirello and Fugazzola, 2014; Cirello et al., 2015).

Building upon prior research, a prospective investigation involving 428 Danish women revealed a reduced initial occurrence of male microchimerism in the peripheral blood of individuals who subsequently developed breast cancer (40%) in comparison to controls (70%). Conversely, women who later developed colon cancer exhibited an overall higher initial prevalence of male microchimerism (95%). The study found that individuals with detectable male microchimerism exhibited improved survival rates following the diagnosis of either type of cancer (Kamper, 2012; Kamper et al., 2012).

The hypothesis that emerges from the study suggests that microchimerism could potentially have varying impacts on different types of cancer, and that the immunological and reparative functions of chimeric cells may play a role in enhancing the survival rates of women, irrespective of the type of cancer they are afflicted with. Geck (2013) proposed a hypothesis that reconciles seemingly contradictory findings regarding the presence of chimerism via fetomaternal exchange. The hypothesis posits that the observed phenomenon is indicative of an instance of evolution in progress, wherein the advantageous and disadvantageous consequences of chimerism are undergoing evaluation in an evolutionary trial (Geck, 2013).

Further investigation is required to specifically scrutinize the mechanism of action by which fetal cells exert a protective or pathogenic influence in women afflicted with cancer. Several types of cancer, such as uterine, melanoma, glioblastoma, and meningioma, have been

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observed to exhibit detectable microchimerism in tumor specimens through the use of FISH or PCR methodologies (Huu et al., 2009; Hromadnikova et al., 2014; Broestl et al., 2018).

The prevalence of male microchimerism was found to be higher in cases of glioblastoma compared to women with meningioma, among brain tumors. In addition, it was observed that female patients diagnosed with glioblastoma and possessing microchimerism exhibited a comparatively extended mean survival duration, implying that the higher incidence of microchimerism in such patients could potentially exert a favorable influence on the course of the disease. The occurrence of microchimerism within cerebral tissues raises a number of inquiries, such as the potential impact of chimeric cells on cerebral performance and cognitive abilities, necessitating additional exploration (Broestl et al., 2018).

5.3| The wound healing

The initial association of autoimmune disease with persistent fetal cells has been extended by recent investigations in animal and human pregnancy, which indicate that microchimeric fetal cells have a significant impact on the reaction to tissue damage. Fetal cells with microchimeric properties were observed to exhibit the expression of Collagen I, III, and TGF β3 within maternal scars that had undergone healing. The detection of male fetal cells within maternal cesarean section scars postpartum implies that fetal cells may migrate to the site of injury in response to signals produced by maternal skin damage during the surgical procedure. These cells may then participate in the process of maternal tissue repair or undergo local proliferation (Mahmood and O'Donoghue, 2014; Shrivastava et al.,2019).

5.4 | Hermaphroditism

True hermaphroditism is a notable phenotype that is strongly linked to human chimerism, characterized by the co-occurrence of ovarian and testicular tissue during sexual development. Typically, these instances manifest with indeterminate genitalia of fluctuating external severity. True hermaphroditism has been observed in a number of cases with 46,XX/46,XY karyotypes. However, it is noteworthy that these cases only account for roughly 10% of the overall recorded instances of hermaphroditism (Hadjiathanasiou et al., 1994; Niu et al., 2002).

Analysis of the genetic contributions from both the father and mother has facilitated the determination of the source of these instances. Although primarily chimeric, there have been documented occurrences of mosaicism that stem from 47,XXY cells due to nondisjunction incidents (Niu et al., 2002).

The mechanism that underlies the occurrence of 46, XX/46, XY whole-body chimerism has been the subject of several theories, which have been developed in an effort to shed light on it. For the most part, the explanations about this developmental aberration have been concentrated on zygote fusion occurring prior to sex differentiation. These possibilities include the fertilization of ova that have been fertilized in isolation, the fertilization of an ovum and a second polar body, and the parthenogenetic division of an ova that has been fertilized by two different sperm. Hermaphroditism is a disorder that is marked by its infrequency and variability, which may result in a large number of instances that go undetected or manifest themselves later than they should. As a consequence, the majority of reported cases pertain to young patients exhibiting more pronounced phenotypes (Repas et al., 1999; Ramsay et al., 2009; Shin et al., 2012).

5.5 | Role of chimerism cell in behavior

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Research on chimerism has predominantly focused on its involvement in somatic ailments. Nevertheless, the correlation between physiological biology and behavioral characteristics provides a plausible conjecture for the influence of chimerism on individual and social conduct. The existence of chimeric cells in the context of autoimmunity has the potential to cause alterations in hormone levels and consequent behavioral changes as a result of ensuing pathological conditions. Thyroid disorders have been extensively documented to cause alterations in mood and behavior. Contemporary research on human microchimerism has investigated its significant potential involvement in the progression of autoimmune thyroid diseases (AITD). Nonetheless, prior studies have already established the alterations in the endocrine system resulting from such conditions. The presence of hypothyroidism in individuals with Hashimoto's thyroiditis has been observed to be linked with cognitive impairment and depression. Similarly, hyperthyroidism in patients with Graves' disease has been associated with depression, anxiety, and irritability (Grigorova and Sherwin, 2012).

The intricate connection between behavior and the endocrine system involves bidirectional relationships. It is imperative to conduct research on the role of chimerism in endocrine system disorders, as stated by Garland et al. (2016). The rising knowledge of a link between immune dysregulation and the genesis of psychiatric disorders has prompted a heightened interest about the possible involvement of an abnormal immune system in the development and treatment of depression and other severe psychiatric illnesses. This increased curiosity has been spurred by the growing understanding of a correlation between immunological dysregulation and the origin of psychiatric disorders (Gibney and Drexhage, 2013; Arteaga-Henriquez et al., 2019).

It can be postulated that the existing correlations between microchimerism and autoimmune disease imply that this mechanism may operate autonomously from the endocrine pathway. Because of the physiological advantages that men have in terms of strength and endurance, the world of sports and exercise behavior, especially in athletic competition, is generally split into different male and female realms. This is mostly owing to the fact that males compete at a higher level. After the onset of puberty, males typically display a circulating testosterone level that is 15 times higher than that of females. This hormonal difference results in an increased engagement with androgen receptors, which in turn leads to biological improvements in muscle, bone, and hemoglobin (Handelsman et al., 2018).

The phenomenon of maternal microchimerism appears to play a role in the process of parental imprinting and may have unintended consequences for offspring investment and evolutionary outcomes related to survival. Moreover, augmenting the maternal exposure to fetal cells throughout pregnancy may potentially participate in promoting mechanisms that facilitate postnatal care of the offspring, encompassing the preservation of maternal well-being and heightened lactation (Boddy et al., 2015).

Disorders of sex development pose a challenge to the established criteria for female competition eligibility. This includes individuals who present with a 46,XY karyotype and androgen insensitivity, who exhibit a female phenotype. Moreover, individuals with XX/XY chimerism further complicate the process of defining males and females based on genetic testing. Testosterone plays an important part in social conduct, with the possibility for numerous behaviors that are regulated by testosterone to be impacted by bidirectional interactions and Y-

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chromosomal chimerism. These behaviors include those that are connected with a species' ability to survive, reproduce, and establish dominance. Research conducted in the field of developmental psychology has shown that there is a connection between androgens and behaviors that are traditionally associated with males in females. This association has been shown primarily in respect to psychosocial and psychosexual outcomes (Sandberg et al., 2012; Geniole and Carre, 2018).

It is noteworthy to consider the potential involvement of male chimerism in the modulation of sex hormone production and function. There is a possibility that localized chimerism leading to the production of testosterone may be adequate in generating discernible characteristics in females. However, additional research is necessary to comprehend the extent of chimerism required to bring about a significant alteration in phenotype. Recent research on disorders of sexual development, such as hermaphroditism, has revealed that females born with atypical genitalia exhibit psychosocial behaviors that are more akin to those of reference males than reference females, suggesting a greater prevalence of masculine personality traits (Johnson et al., 2020).

5.6 | Female-specific diseases

The phenomenon of microchimerism has been gaining attention in the scientific community as a potential area of study for other medical conditions that share similarities with chronic graft-versus-host disease (cGVHD) or have a higher prevalence in females. Pregnancy-related complications represent a distinct category of medical conditions. A correlation has been observed between the occurrence of fetal loss and the presence of detectable microchimerism (Khosrotehrani et al., 2003).

Hence, it is crucial to acknowledge that parity, which refers to the count of pregnancies carried to a viable gestational age, may not be as desirable as gravidity for microchimerism research, as the latter encompasses all pregnancies. The study conducted by Gammill et al. revealed that there is no significant increase in the concentration and prevalence of fetal microchimerism with parity. This finding suggests the potential for dynamic graft-graft interaction (Gammill et al., 2010).

The relationship between preeclampsia and microchimerism is intricate and constantly evolving, as the condition seems to be linked to a distinct source of chimerism. The phenomenon of fetal microchimerism appears to have a pathological association and is notably more widespread in females who experience preeclampsia. Conversely, maternal microchimerism is postulated to have a safeguarding effect and has been detected less frequently in females with preeclampsia and recurrent miscarriage (Gammill et al., 2011; Gammill et al., 2013; Gammill et al.,2014).

The risk of developing preeclampsia at the beginning of a subsequent pregnancy is increased in women who have previously given birth to children of a different father. In contrast, the incidence of preeclampsia is shown to be lower in subsequent pregnancies among women who had already been diagnosed with the condition during a previous pregnancy (Li and Wi, 2000).

The etiology of preeclampsia is postulated to involve exposure to non-shared paternal alleles, which may be further aggravated by fetal microchimerism. Hence, alteration in paternity among females with antecedent preeclampsia could potentially eradicate exposure to a

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provocative antigen. There exists a possibility that the immunological interactions in question may be intensified by fetal microchimerism. Therefore, additional research is necessary to explore whether the sharing of HLA between the maternal and paternal genomes could potentially augment the overall susceptibility to preeclampsia.

6 | Prevalence of chimera

The overall prevalence of human chimerism is a highly elusive piece of information in the field of study. The constraints associated with the present methodologies pose a number of limitations to the study of chimerism on a population level. The complexity of obtaining a comprehensive diagnosis of chimerism is attributed to the restricted sensitivity and the inability to procure a universal sample of chimerism across all tissues in an individual. The utilization of Karyotyping, FISH, and PCR techniques that rely on the detection of Y-chromosomes as a marker of male microchimerism restricts the identification of chimerism to cases that stem from a male contributor. Studies have identified the presence of male microchimerism in women who do not have sons, which is a noteworthy observation. A research investigation was conducted to examine male microchimerism in a cohort of nulliparous Danish girls aged between 10 and 15 years. The study revealed that 13.6% of the participants had male microchimerism in their peripheral blood, which is consistent with the previously reported prevalence of 13% in healthy nulligravid women (Yan et al., 2005; Muller et al., 2015).

The origins of male chimerism remain uncertain, as it is unclear whether it may have arisen from fraternal DNA passed through the mother from an older brother, male miscarriages, vanishing twins, transfusion history, or sexual intercourse (Muller et al., 2015; Peters et al., 2019).

Chimerism has been observed in dizygotic twins as well. The most extensive investigation of chimerism in twins involved the analysis of peripheral blood chimerism in a cohort of 472 individuals. The findings revealed that chimerism was present in 8% and 21% of twin and triplet pairs, respectively (Van Dijk et al., 1996).

A recent study on twins discovered that opposite-sex twins, both male and female, exhibited a higher incidence of thyroid autoantibodies in comparison to monozygotic twins. This finding lends support to the notion that twins may be more susceptible to the prevalence and potential hazards of microchimerism (Brix et al., 2009). The hypothesis that chimerism between twins may arise from twin-to-twin transfusion between dizygotic twins during gestation has been supported by the observation of instances of monochorionic dizygotic twinning (Smeets et al., 2013; Rodriguez-Buritica et al., 2015; Mayeur et al., 2016).

The prevalence of monochorionic dizygotic twin pregnancies that have been recorded is largely attributed to the use of assisted reproductive technology. In comparison to other types of monochorionic twin pregnancies, monochorionic dizygotic twin pregnancies were shown to have similar rates of perinatal morbidity and death, as well as pregnancy loss prior to 24 weeks. This was the conclusion of an in-depth study of monochorionic dizygotic twins.(Peters et al., 2017). The observed genital abnormalities in 15.4% of monochorionic dizygotic twin cases have been attributed to the possibility of intrauterine blood exchange.

A recent investigation was conducted on MRKH syndrome, a condition that primarily impacts the female reproductive system. This medical condition results in the underdevelopment or absence of the vagina and uterus, while the external genitalia remain normal. Individuals who

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are affected by the absence of a uterus, which is a condition that is phenotypically similar to freemartinism in animals, exhibit a lack of menstrual periods. In our study, we observed that male microchimerism in the peripheral blood was less prevalent in adult patients with this condition as compared to healthy controls (Peters et al., 2019).

A crucial aspect to take into account regarding the results obtained in monochorionic dizygotic twin pregnancies is that a considerable number of dizygotic twin pregnancies have been presumed to be dichorionic. Consequently, there is a possibility that researchers are underestimating the overall incidence of this phenomenon. Further investigations are required to obtain a more comprehensive understanding of the correlation between chronicity in dizygotic twin pregnancies and health complications.

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