The collection of essays reviews, explores, and reports state-of-the-art autoimmunity issues with a cause and effect relationship. It provides a comprehensive presentation of immunity and autoimmunity and their connection to related diseases, current trends, data and possible future developments in health sciences. As such, it represents a unique resource for medical educators, medical practitioners and academics.

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TABLE OF CONTENTS

CHAPTER EIGHTEEN

PREGNANCY INDUCED AUTOIMMUNE DISEASES

NAZAN YURTCU

Introduction

Autoimmune diseases have been seen in approximately 8% of the population, and about 80% of these patients are women (Fairweather and Rose 2004). The interaction between autoimmunity and reproduction has two sides. On the one hand, pregnancy may cause de novo autoimmune diseases, especially after pregnancy; and on the other hand, pregnancy may change the course of autoimmune disease regarding its severity and exacerbations (Borchers et al. 2010). After vaginal or cesarean deliveries, and induced abortion, maternal risk of autoimmune disease development is increased and continues to have increased incidence in post-reproductive years (Bianchi et al. 1996). Considering the clinical similarities of chronic graft-versus-host disease and the complex nature of autoimmunity manifested by some autoimmune diseases; persistent fetal microchimerism, the maternal acquisition of intact cells of fetal origin without any apparent rejection may play a role in autoimmune disorders (Shrivastava et al. 2019). Microchimerism is a common phenomenon going on with the presence of genetically distinct cells in the individual and can be seen in 70% of healthy women. Although microchimerism probably occurs in small quantities, microchimeric cells have remarkable effects on women's health (Gammill and Nelson 2010).

Fetal microchimerism as a phenomenon was hypothesized to be responsible for the de novo autoimmune diseases' occurrence; however, published data regarding the pregnancy-related autoimmune diseases are still controversial and debated. This chapter discusses pregnancy-induced autoimmunity and its effects on women's health in the light of studies investigating microchimerism and related conditions.

Microchimerism

Long-term clinical experience points to a causative factor in patients who developed autoimmunity after pregnancy. Recently, an answer to this causality seems to have been found with the discovery of bi-directional cell trafficking that ends up with the permanence of maternal cells in the offspring and fetal cells in the mother even decades after childbirth. These events lead to two types of microchimerism: fetal microchimerism – the presence of fetal cells in the maternal circulation – and maternal microchimerism – the presence of maternal cells in the fetal circulation –, respectively (Johnson and Bianchi 2004; Nijagal and MacKenzie 2013; Jeanty et al. 2014; Johnson et al. 2020). Microchimerism accounts for less than 1% of the total cell population. The significance of maternal and fetal microchimerism lasts a lifetime in health and disease. Whether microchimerism is beneficial to the individual is not fully demonstrated. However, since fetal and maternal microchimerism is commonly seen in healthy individuals, it seems that we can deduce that microchimerism has a possible benefit to the host. The type, persistence, and amount of microchimerism are influenced by pregnancy complications, obstetric features, infection exposures, and additional factors (Fugazzola et al. 2011; Gammill and Harrington 2017; Ichinohe 2010). Cell migration starts in weeks 4-6 of pregnancy and increases in parallel with the gestational week. In the second trimester, 1-6 cell/ml can be detected in the maternal blood, and this number is much higher near birth. This progressive increase is followed by feto-maternal hemorrhage at the time of delivery (Fugazzola et al. 2011).

The easiest way to detect and examine fetal microchimerism is to take women with a previous male pregnancy as a subject, due to the presence of the Y chromosome. The following two ways generally detect fetal microchimerism. The first is the sex-determining region Y (SRY) gene amplification of the Y chromosome. This is the most widespread technique used with a sensitivity high enough to detect one male cell per million female cells. The second is fluorescence in situ hybridization (FISH) analysis done by using X and Y chromosomes' specific probes. Human leukocyte antigen (HLA) typing is based upon the identification and quantification of non-hereditary, non-shared, maternal-specific HLA polymorphisms, and can be used for the identification of both female and male lineage fetal cells. With these techniques, fetal microchimeric cells were found to be a prevalent occurrence in pregnancy. The number of these cells increases gradually during pregnancy, reaching a peak at birth,

and their level decreases postpartum (Yan et al. 2005; O'Donoghue 2008; Fugazzola et al. 2012).

The contribution of fetal cell microchimerism to disease states is still controversial. There are currently three hypotheses formulated. According to the first hypothesis, fetal microchimeric cells trigger a chronic inflammatory response and cause tissue damage, leading to a condition similar to graft-versus-host disease. The second hypothesis suggests that fetal microchimeric cells have a protective role in damaged tissue repair, viral infection control, and cancer surveillance. The last hypothesis states that fetal microchimeric cells are a random by-product of pregnancy that has no biological significance (Boddy et al. 2015).

Fetal microchimerism and autoimmune disease

Fetal microchimerism is a natural outcome of a normal gestation and originates in a mixture of maternal and fetal cells detected in maternal tissues. Although in the pertinent literature, there is no consensus on the implications of fetal microchimerism on the development of autoimmune disorders, according to several studies in humans and animal models, a potential role of fetal microchimerism in the initialization of an autoimmune process has been continually suggested due to the higher prevalence of autoimmune disease in females and a peak incidence in fertile age. Microchimerism studies were first conducted at the peripheral blood level. Besides, autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis, primary biliary cirrhosis, thyroiditis, rheumatoid arthritis, Sjögren's syndrome, and systemic sclerosis, were examined primarily (Samura 2010; Fugazzola et al. 2012; Johnson et al. 2020; Somers 2020).

Sjögren's syndrome

Sjögren's syndrome is a rheumatic disease that is autoimmune in origin, affecting the exocrine glands. It resembles chronic graft-versus-host disease clinically and pathologically. Some histological patterns are similar in both chronic graft-versus-host disease and Sjögren's syndrome in which microchimerism researches were recently executed (Kuroki et al. 2002; Lambert et al. 2005). The strong female predilection of Sjögren's syndrome, especially with an increased incidence after childbirth, suggests the role of pregnancy in the development of this syndrome. So, fetal microchimerism could be a part of Sjögren's syndrome's pathogenesis. The Y-chromosome-positive fetal cells can be detected with the usage of

the Y-chromosome-specific gene in the minor salivary gland tissues (Carlucci et al. 2001; Mijares-Boeckh-Behrens et al. 2001; Endo et al. 2002).

Systemic lupus erythematosus

Although the relationship between fetal microchimerism and systemic lupus erythematosus is up-to-date, there are few experimental and clinical data suggesting the role of male fetal cells in systemic lupus erythematosus development (Hilary S. Gammill and Nelson 2010; Kinder et al. 2017). da Silva Florim et al. suggested that fetal microchimerism, represented by a high number of male fetal cells in the venous blood of systemic lupus erythematosus patients, may have an essential part in the systemic lupus erythematosus pathogenesis. They noted that the conflicting findings discovered by different researchers could probably be based upon the sensitivity of assays used in the detection of the microchimeric cells, race, or disease severity (da Silva Florim et al. 2016).

Systemic sclerosis

Fetal microchimerism levels were found to be higher in women with systemic sclerosis, and a particular HLA connection of mother and child can increase the later systemic sclerosis risk in the mother (Bloch et al. 2011; Cristofaro et al. 2018). In some women with systemic sclerosis, male DNA levels were at the highest quartile of fetal microchimerism seen in normal pregnant women with male babies. This situation continued even though women with systemic sclerosis gave birth to their sons decades before (Lambert et al. 2005).

Autoimmune thyroiditis

Fetal microchimerism has been inclusively researched in autoimmune thyroid diseases. The hypothesis that fetal microchimeric cells contribute to the autoimmune thyroid disease pathogenesis was further corroborated by the higher microchimeric cell numbers in the thyroid gland of women with Hashimoto's thyroiditis and Graves' disease, compared to healthy women (Klintschar et al. 2006; Lepez et al. 2011; Fugazzola et al. 2012). Postpartum activated residual fetal cells in the maternal thyroid gland due to maternal immune suppression is still a favorite explanation for postpartum autoimmune thyroid disease exacerbation (Galofre and Davies 2009).

Conclusion

Autoimmune diseases are considerably heterogeneous and composed of more than 80 disorders in which self-tissue destruction is seen due to pathologic immune responses. The female predisposition to them, especially after pregnancy, has increased research focused on microchimerism. This can occur as a natural event in all types of pregnancies, with a potential to remain lifelong in the host. In the fetal type, fetal embryonic or fetal cells can migrate through the placenta into the maternal circulation. These cells can have the ectodermal, endodermal and mesodermal lineages of an embryo. This situation reveals that the founder chimeric cells can behave like the stem cells. Although there is no solid consensus on the role of fetal microchimerism in the development of autoimmunity after pregnancy, increasing evidence with sophisticated laboratory techniques will aid an understanding of the exact function of fetal microchimerism in the states of health and autoimmune disease.

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