TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 11
Number 2 *Spring 2018*

2018

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Devora Krumholtz
Touro College

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Devora Krumholz graduated in January 2018 with a B.S. degree in Biology

Abstract

Many basic multicellular organisms possess some form of immune response to protect themselves against the invasion of foreign objects. It was not until British scientist, Peter Medawar proposed a fundamental question that changed the way researchers studied the maternofetal relationship. A fetus, being genetically different from its mother should be rejected by the maternal immune system, however, it is not. Researchers have since discovered and developed several mechanisms that aim to explain how the maternal immune system prevents fetal rejection. The formation of a mechanical barrier, general and local suppression of the maternal immune system, and a shift in cytokine concentration during pregnancy have been suggested as reasons Forthcoming discoveries in the field of reproductive immunology may further one's understanding of immune regulation during pregnancy, in addition to other applications, such as, the immune responses regarding organ transplants. Although the proposed mechanisms mentioned above helped improve the understanding of how fetal rejection is avoided, many scientists concur that additional research is required to adequately explain the prevention of fetal rejection.

Abbreviations:

Ab- Antibody
Ag- Antigen
APC- Antigen presenting cell
MHC- Major Histocompatibility Complex
IDO- Indoleamine 2,3-dioxy-genase
Ig- Immunoglobulin
IL-2- Interleukin 2
IFN-γ- Interferon Gamma
TNF-β- Tumor Necrosis Factor Beta

Introduction and Background

The National Vital Statistics Reports presented data from a study conducted regarding the total number of births registered in the United States, in 2015. The results showed that there were 3,978,497 births recorded, only 1% less than the total number of births registered in 2014 (Martin, et al. 2017). Many women, worldwide, have successfully given birth to babies, which interests researchers in the field of immunology. During a lecture in England, in 1953, a British immunologist named Peter Medawar asked, "how does the pregnant mother contrive to nourish within itself, for many weeks or months, a fetus that is an antigenically foreign body (Betz, 2010)?" Since then, researchers have been asking the same question (Anonymous, 1999)?

Methods

The research discussed in this paper was compiled from various published articles, taken from Touro's database, including Proquest Science, EBSCO, and PubMed to research why a mother does not reject a genetically different fetus growing inside of her.

Discussion

A. The immune system targets foreign objects

The human body's immune system is a complex network of biological structures intricately designed to protect the body against foreign objects. Foreign objects may be anything the body does not recognize as self, which may include, bacteria, viruses, parasites, and tumors. When a foreign object enters the body, there is a cascade of events carried out by the body's immune system. First, the body must identify the foreign object as "non-self", destroy the pathogen, and lastly, create memory cells to ensure that the foreign object does not attack again (Gilley, et all. 2009).

1. Recognizing "non- self" Objects

One of the main roles of the immune system is to recognize a pathogen and induce a response to eradicate it. Immune system cells such as white blood cells or leukocytes aid in carrying out the tasks. In order to initiate any immune response, an antigen (Ag) must be recognized by special receptors. T-Lymphocytes, killer T cells and helper T cells, play a crucial role in the recognition of Ag. T-cells recognize foreign Ag by the presentation of peptides by the major histocompatibility complex (MHC). The two classes of MHC are MHC I and MHC II. Major histocompatibility complex class I generally presents an intracellular viral Ag to cells that contain CD8+ proteins. These Ag will be destroyed by Cytotoxic T-Lymphocytes, while MHC Class II generally presents extracellular bacterial Ag to cells that contain CD4+ proteins. These Ag are recognized by Helper T-Lymphocytes and will be destroyed with the help of Ab. (Joyce, 2001). CD8+ and CD4+ are cell surface molecules that bind to their respective MHC on an antigen-presenting cell (APC). One of the most common cells that act as an APC are macrophages. (Miceli, Parnes, 1991).

2. Destroying a Pathogen

After the body recognized a pathogen as "non-self," the immune system will try to rid the body of the foreign object. There are two main types of pathogens that will elicit two different responses. The first type is when bacteria enter the human body; helper T cells will release certain cytokines and chemokines. These are certain chemicals that act as chemoattractants for other leukocytes to aid in an inflammatory response. Secondly, will produce Plasma cells, a derivative of lymphocytes, make antibodies (Ab) that will help destroy the pathogen. Antibodies are a Y shape structure, consisting of glycoproteins called immunoglobulins (Ig). There are 5 main isotypes of Ig with different roles, which include: IgG, IgE, IgM, IgA, IgD. Each Ab will bind to a

specific antigen, comparable to the interaction with a lock and a key (Author Unknown, 2016).

In order to help T cells produce Ab, B- lymphocytes will produce specific Ab to help destroy pathogens. Antibodies produced by B cells will circulate the body via the bloodstream and can bind to foreign objects. After a B-cell recognizes a pathogen, the cell matures into a plasma cell, which produces large quantities of Ab. Antibodies have 3 main functions in the immune system. The first role is neutralization, which is when an Ab binds to the surface of the pathogen, thus denying any entry into the normal body cells. The second role is to activate other defense cells that are in the body that can elicit an inflammatory response, for example, phagocytes. The third role is to activate a complement system, which attracts defense cells to the infection site and destroys the pathogen (Author Unknown, 2016).

The second type of pathogen that will cause an immune response is infection with a virus. In this case, activated Cytotoxic T- cells are able to directly destroy the pathogen when it displays pathogen peptides on the MHC Class 1. Cytotoxic- T cells, also called Killer T cells release cytotoxins, such as perforin, which creates a hole in the wall of the infected cell. This in turn kills the cell along with the pathogen due to the loss of fluid (Author Unknown, 2016)

B. Fetal Cells and a Mother's Immune System

In order to better explain the interaction between fetal cells and the mother's immune system, one must understand what happens after a sperm fertilizes an egg. Once an egg is fertilized, it rapidly divides to form the blastocyst, a hollow ball of cells comprised of two portions. One is the inner cell mass that will become the embryo, which will develop into a fetus about eight weeks after conception. The second is the outer layer of the blastocyst, which will become the trophoblast. The trophoblast will ultimately occupy the lining of the uterus, thus facilitating embryonic implantation (Urman, Balaban 2001).

C. Immune System During Pregnancy

Based on the roles of the human's immune system, one could assume that a mother's immune system would try to eliminate a fetus. When a mother conceives a child, genetic material from both the mother and the father are incorporated into the fetus, however the mother's mother's side of the placenta is genetically different from the fetus. Therefore, the fetus inside the womb would be considered "non-self" (Lightner, et al, 2008). Peter B. Medawar suggested the "immunological paradox of pregnancy" (Mor, 2007). He proposed that since the fetus is considered "semiforeign," there must be a conflict between the fetus and the mother's immune system. For over 60 years since Medawar posed this phenomenon, there have been many attempts to explain why a mother's immune system does not reject a genetically different fetus.

Accepted Hypotheses

a. Mechanical Barrier

The first hypothesis explains that the fetal tissue is unrecognizable as "nonself" by the mother's immune cells due to a mechanical barrier (Mor, 2007). The uterus of a pregnant mother has a mechanical barrier, consisting of synctiotrophoblasts that envelop the fetus. This trophoblast-immune interaction includes three stages (Fig. 1). During the first stage of attraction, the trophoblast cells secrete chemoattractants that will signal immune cells to migrate to the implantation site. The implantation site refers to the area of the uterus in which the trophoblasts invade. After attraction, the trophoblasts produce cytokines that regulate the differentiation of immune cells. This stage is called recruitment and/or education. Upon completion of these two steps, the response can take place. In this stage, the immune cells from stage two respond to different signals (Swain, 2013). After completion of all three stages, the mechanical barrier is formed. This in turn prevents the movement of activated T cells from the periphery to the implantation site and enables antigens that are inside the barrier to be undetected by the mother's immune system.

b. Suppressed Immune System During Pregnancy

Research done by David Munn and his colleagues at the Medical College of Georgia in Augusta suggests a different hypothesis. They discovered that macrophages, an important immune cell involved in antigen presentation, can disable killer T-cells. This in turn will prevent the T cells from attacking any object that is recognized as non-self (Anonymous, 1999). In order for this to occur, the synctiotrophoblasts in the placenta produces an enzyme known as indoleamine 2,3-dioxy-genase (IDO). The function of IDO is to destroy tryptophan, an amino acid required by T cells to destroy a foreign object. In 1990, Andrew Mellor, a colleague of Munn, concluded that IDO inhibits a mother's T cell response towards a genetically different fetus. On the contrary, if a mother fails to produce IDO, it would cause the mother to miscarry (Gura, 1998).

Munn and his colleagues conducted experiments in to prove their hypothesis. They used two groups of pregnant mice; one group had been bred to genetically identical fathers of the same strain while the second group was bred to fathers from a genetically different strain (Gura, 1998). The experimenters then embedded time release-capsules consisting of either 1-methyl-tryptophan, which is an IDO inhibitor, or a control substance underneath the skin of the pregnant mice. Results showed that only the mice carrying genetically different fetuses that had been given the inhibitor rejected their fetuses (Anonymous, 1999) (Gura 1998). Interestingly, the embryos developed normally until inflammatory cells migrated to the implantation site and caused hemorrhaging around the embryo. Munn proposed "the mother is rejecting the placenta and eventually the embryo chokes off and dies" (Gura, 1998). From the data collected,

Munn and his colleagues concluded that after implantation, an embryo starts making connections with the mother's blood supply. Sequentially, synctiotrophoblasts will start producing IDO, destroying tryptophan and suppressing the maternal immune system (Gura, 1998). However, other researchers have reservations about this hypothesis. In Pregnancy Reconceived, Mor argues that if the maternal immune system is suppressed, it would be nearly impossible for a mother and its fetus to survive. Exposure to any pathogen would be fatal (Mor, 2007).

c. Local Active Suppression in Decidua

In addition to the general suppression of a mother's immune system, researchers have found that an important role in the maternofetal interaction is the local active suppression by cells in the decidua (Chaouat, 1990). The decidua is a mucous membrane lining of the uterus during pregnancy. This lining allows for nutrition and gas exchange before the placenta is functional (Mizugishi, et al. 2007). Cells located in the decidua may inhibit the production of lymphocytes thus leading to the inhibition of the production and expression of receptors for interleukin 2 (IL-2). IL-2 is a cytokine signaling molecule produced by activated T cells and is crucial for the rejection of foreign objects in the body. This type of suppressor cell is trophoblast independent. However, there is another type of cell that suppresses the role of IL-2 in the maternal immune system and these suppressor cells in the decidua are trophoblast dependent. ¬ Both types of suppressor cells have an effect on the production or action of IL-2.

Therefore, local active suppression aids in the prevention of foreign objects attacking the mother's immune system and fetal rejection (Chaouat, 1990.)

d. Cytokine-shift Hypothesis

This hypothesis suggests that during pregnancy, the balance of cytokines within the mother's body shifts. This cytokine shift causes immunological changes in the maternal immune response (Mor, 2007). Cytokines, which are important in cell signaling, are released by Th1 and Th2 helper cells. However, each subgroup facilitates a different immune response. Th1 cells secrete IL-2, Interferon gamma (IFN-γ), and Tumor necrosis factor, Beta (TNF-β) causing a cell mediated immune response, while Th2 cells secrete IL-4, 5, 6, 10, and 13. These are mainly involved in antibody production (Rincón et.al, 1997). Additionally, IL secreted by Th2 cells simulate a humoral immunity and aids in the inhibition of the production of TNF-β and IFN-γ (Kidd 2003). The production of IFN-γ, TNF-β and IL-2 are believed to be damaging to pregnancy. In an experiment studying pregnant mice, these cytokines were injected into the mice and caused fetal loss (Koch and Platt, 2003). Previous research suggests that there is a shift towards a higher production of cytokines released by Th2 during pregnancy and a diminished production of Th1 cytokines (Hoshimoto,et al. 2000).

When a foreign object enters the body of a women who is not pregnant, Th1 cells will secrete pro inflammatory cytokines that will signal for a cell mediated response to occur. However, according to the cytokine-shift hypothesis, the balance of Th1 and Th2 will go towards the secretion of cytokines by Th2, resulting in a suppressed inflammatory response (Mor, 2007).) Many studies have been conducted in an effort to better understand the shift of Th1 to Th2 cytokine secretion during pregnancy. In an experiment conducted by Hoshimoto, et. al. (2009), they gathered thirty female subjects. Group A consisted of ten women who were non-pregnant women with regular menstrual cycles and the other 20 healthy and pregnant women. The pregnant women were separated into two groups, B and C according to weeks of gestation. Group B consisted of 10 pregnant women who were in their first trimester and group C consisted of 10 women in their third trimester. The experimenters took samples of peripheral venous blood and separated the plasma at -80°C until ready for analysis. The results of the experiment showed the correlation between the plasma levels of sCD26 and sCD30 and pregnancy. sCD26 and sCD30 are molecules on the surface of activated Th1 and Th2 cells, respectively. Therefore, plasma levels of sCD26 and sCD30 correlate to Th1 and Th2 responses, respectively.

sCD26 concentrations among group A were significantly higher than group B. Furthermore, the concentration of group B was significantly higher than group C. This indicates that the highest concentration of Th1 cells were among those who were not pregnant, and the lowest concentration was among the pregnant women in their third trimester. Concentrations of sCD30 among groups A and B did not significantly vary, however, compared to the concentration level of group C, they were significantly higher. The researchers concluded that there was a significant decrease in sCD26 levels among pregnant mothers possibly due to the shift from Th1 cytokine secretion. However, sCD30 levels did not differ between non-pregnant women and women in their first trimester, but decreased among women in their third trimester. This decrease may be explained by the increase in water retention as pregnancy progresses. Furthermore, the researchers advise for additional investigation in order to validate the cytokine-shift hypothesis.

Many researchers agree that cytokines play a crucial role during pregnancy. As explained in the research done by Hoshimoto et.al, Koch and Platt mutually agree that a Th2 response is necessary for the fetus to survive in the womb. Results from an experiment with mice showed that there was a 20-50% rate of fetal loss due to a lack of Th2 cytokine production. Furthermore, they applied this idea to humans and suggest that irregularities with Th2 cytokine response may lead to miscarriages. The mechanism that causes the shift between Th1 and Th2 cytokine response in pregnancy is unknown. However, Koch and Platt propose two plausible possibilities. Firstly, there

is a prevention of Th1 cytokine secretion that allows the Th2 response to take over or secondly; there is a specific Th2 response, which inhibits the Th1 response (Koch, Platt, 2003).

Conclusion

This paper attempted to explain the reasons why a mother does not reject her genetically different fetus. Although it was not until the 1950's when Professor Medawar first posed this question, the wealth of knowledge on this topic is rapidly expanding. However, despite the few flaws with the hypotheses, additional research is being studied to resolve the issue.

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