Possible Mechanisms That Protect the Fetus from Maternal Rejection

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Abstract

There is no other foreign tissue transplant that has such a strongly parasitic relationship with its human host as the fetus. Although the fetus contains paternal genes, is completely tolerized by its maternal host in almost all pregnancies. This presents an immunological paradox and has generated a lot of attention from leading researchers in the reproductive and immunology fields. This paper reviews the leading explanations for this paradox; that it is attributed to a detailed mechanism of the maternal and fetal immune system in which tryptophan suppresses T-cells from attacking specific paternal cells, while maintaining a strong immune response against other foreign antigens during pregnancy. Other opinions contribute fetal tolerization to the maternal immune systems strong bias of Th2 cells and a decrease of Th1 cells. Researchers suspect that women suffering from recurrent miscarriages are unable to tolerize their fetus, and consequently, their immune system attacks the fetus several weeks after implantation and aborts the pregnancy. Other medical implications include preeclampsia, which is attributed to immunological issues. Doctors are now trying to understand how these mechanisms work to provide treatment for women who cannot naturally tolerize their fetus, and for patients suffering from preeclampsia.

Introduction

The immune system is incredibly complex in its means of maintaining health and protecting the body against foreign invasion. It is a network of cells, tissues, and organs that work together to defend the body against "invaders" known as antigens. If the body recognizes a cell as being "non-self", it triggers an immune response against the antigen. The immune response includes different cells that the body stores in preparation for attack (Storey, Jordan, 2008).

All immune cells begin as immature stem cells in the bone marrow. They respond to cytokines (which are proteins involved with immune system cell communication) and other signals to develop into B cells, T cells, and phagocytes. B cells' main role is to secrete antibodies. When B-cells encounter an antigen, they create plasma cells for that antigen, which then secretes hundreds of identical antibodies that are specific to that antigen. Antibodies, also known as IG- immunoglobin, are highly specific proteins found in body fluids that identify antigens and connect to them with its specific shape and mark them for destruction. They neutralize the antigen and prevent it from attacking a host cell. Phagocytic cells then destroy the antigen (Storey, Jordan, 2008).

Another type of immune cell is called a T-cell. There are two different types of T cells; Helper T cells (CD4's) contribute by directing immune responses, and Killer T cells (CD8's) attack infected cells. The Major Histocompatibility Complex (MHC) are proteins on cell surfaces and code for the specific unique proteins that the cell contains. MHC protein bind to the surfaces of antigenic cells and help T-cells distinguish other cells as being self or nonself (Adar, et. al. 2015).

This leads to the concept of transplantation. If foreign tissue is implanted in the body, the T-cells will recognize the tissue's MHC as being nonself and will therefore attack it. A fetus has the distinction of being a tissue alloantigen in the mother's body. This is because it is impossible for a mother and child to be genetically identical since the fetus inherits a set of genes from each parent so the paternal genes are going to be considered foreign to the maternal immune system (Mellor, Munn, 2007). Furthermore, if the fetus is a boy, then they are certainly genetically different due to the presence of the Y chromosome in all males (Simpson, et. al. 1997). Consequently, one would assume that the maternal immune system would identify the fetus as being a foreign tissue and reject it. However, nature proves that this is not the case. Additionally, pregnant women do not seem to be more susceptible to infection. This proves that the maternal immune system is functioning and carrying out all other appropriate immune responses (Sacks, et. al. 1999). The purpose of this review is to explore this unusual relationship, and by surveying the recent literature, gain insight into the complexities of the immune system and explain this seemingly paradoxical relationship. The first to have raised the question of the maternal-fetal immunological paradox was Peter Medawar. His initial 1953 lecture and essay on this topic led to extensive research till this day. Retrospectively, scientists give him the distinction as the father of reproductive immunology. Upon doing pioneering research on skin graft rejection, Medawar wondered why a fetus is different than any other foreign transplant if the body clearly tolerizes its presence. He proposed three possible explanations; the mother and fetus have a physical anatomical separation, the antigenic immaturity of the fetus, and the immunological inertness of the mother (Billington, 2003).

Methods

Research was compiled from original journal articles, accessed through Touro's online library (www.tourolib.org) which has a subscription to the EBSCO and ProQuest databases. Key phrases such as maternal fetal immunology, rejection of fetus, and

tolerization of fetal allograft were searched to find relevant information. These were the basis for this comprehensive review of the topic.

Discussion

The first to have raised the question of the maternal-fetal immunological paradox was Peter Medawar. His initial 1953 lecture and essay on this topic led to extensive research till this day. Retrospectively, scientists give him the distinction as the father of reproductive immunology. Upon doing pioneering research on skin graft rejection, Medawar wondered why a fetus is different than any other foreign transplant if the body clearly tolerizes its presence. He proposed three possible explanations; the mother and fetus have a physical anatomical separation, the antigenic immaturity of the fetus, and the immunological inertness of the mother (Billington, 2003).

T cell Awareness of Fetal Presence

In response to Medawar's first hypothesis, research was done to test if the maternal immune system is aware of the fetus's presence. The trophoblast is a tissue layer that surrounds the embryonic cells. It supplies that embryo with nutrients, and its outer layer separates the fetal and maternal circulatory system throughout the entire pregnancy (Bonney, Matzinger, 1997). Researchers performed an experiment to discover if there are fetal MHC molecules at the extraembryonic tissues and if so, if the paternal genes are present in equal proportion to the maternally inherited genes. They implanted an embryo with paternal (foreign) and maternal (identical) MHC class 1 genes in a mouse and tracked them. On day 13 of gestation, fetal cells had low levels of MHC class 1 genes, yet equivocally high levels of both paternally and maternally derived genes were present at the interface of the extraembryonic and uterine tissues . Since the paternally derived genes are present in high numbers at the interface, it is unlikely that the paternal antigens are not accessible to the maternal immune cells. This study proves that the maternal tolerance cannot be contributed to a lack of paternal gene expression or to a lack of contact between the mother's immune system and fetal cells (Philpott, et. al. 1988).

Another study which strengthens this point was done on mice in which H-2K females were mated with H-2B males. For comparison purposes, they also mated these females to H-2K synergic mice and a third party, H-2s bearing mice. When tested mid-pregnancy, mice bearing H-2B conceptuses had reduced numbers of T cells with high expression of the clonotype and 6-9 times more clonotype positive cells that were missing CD4 and CD8 than the control mice. This reaction proves that the maternal T cells are exposed to and recognize the paternal alloantigen (Tafuri, et al. 1995).

They tested the mice further to determine if the T cell changes were still present after delivery of the fetus and found that the T cells were restored to the same levels as the control mice. However, that could just indicate that there is only tolerization when the paternal alloantigen is present in the body. To test this, after delivery, they introduced grafts of the H-2KB gene and the mice rejected it. They have also tried transplanting paternal grafts and have found that the mother's immune system only accepted it if the MHC peptide complexes on the graft were identical to that of the fetus. After the pregnancy, however, the maternal immune system did reject the graft. This study proved that pregnancy induces a transient state of tolerance for the paternally derived genes of the fetus (Tafuri, et. al. 1995).

These studies indicate that Medawar's first two hypotheses were wrong. The maternal tolerance is clearly not due to lack of exposure, and must be contributed to some mechanism which occurs during pregnancy that protects the fetus from rejection. As for his argument that the fetal antigenic cells are immature, we do see that fetal cells may lack high levels of MHC expression during gestation. However, he was assuming that the only exposure the maternal immune system has is from the fetal cellsf. As the above experiments proved, the trophoblast, which is definitely in contact with the mother's immune cells, had MHC genes at high levels from the beginning of gestation. Thus, it cannot be that the tolerization is due to antigenic immaturity.

Another study was done to test Medawar's third hypothesis which is that the mother is in an immunological tolerant state. They found that the T cells in the spleen and lymph node displayed characteristics that were typical of functionally unresponsive T cells and are not typical for antigen-experienced T cells (Zhou, Mellor, 1998). Researchers conclude from this data that maternal T cells are exposed to the paternal alloantigen's and this exposure somehow induces a tolerant state. Scientists are now focused on trying to figure out what exactly causes this tolerant state. However, it is clear that the mother's immune system is not suppressed, because it is responsive to all other antigens. Therefore, it would be inaccurate to describe the maternal immune system as being inert.

Indoleamine 2,3-dioxygenase (IDO) Mechanism

There is a mechanism discovered by Drs. Mellor and Munn which is currently the most well accepted explanation for this immunological contradiction. They attribute this tolerance to the fetus shutting off the mother's natural defenses. Their hypothesis is that the embryotic cells in the placenta, known as syncytiotrophoblasts, produce an enzyme called indoleamine 2,3-dioxygenase (IDO) which destroys an amino acid, tryptophan, that is necessary for the maternal T cells to protect the maternal body effectively (Munn, et. al. 1998).

In order to test this hypothesis, an experiment was done in which they had four groups of female mice. Two groups (A and B) were mated to mice that were genetically identical to them and two groups were mated to mice that were genetically different (C and D). Levels of IDO were first assessed in all groups. IDO transcription were present in all mice from 7.5 to 9.5 dpc (days post coitus). At later gestation times, such as on days 10.5 and 13.5, IDO was present in the placenta but not in the uterus or embryonic tissue. This data proves that IDO is only found in synctytiotrophoblasts and not in other tissue (Munn, et. al. 1998).

1-methyl-tryptophan, a pharmacologic agent that inhibits IDO enzyme activity was then inserted under the skin of mice from groups A and C. Groups B and D were used as a control. On 6.5 dpc, mice from all groups were carrying normal numbers of concepti and development was normal as well. However, from 7.5 to 8.5 dpc, the number of concepti in mice from group C (mice that were mated with allogenic males and treated with the IDO inhibitor) decreased significantly and there was hemorrhaging around the concepti that were left. At 8.5 and 9.5 dpc, all concepti showed signs of inflammation and deterioration. After 9.5 dpc, no concepti that were treated with the IDO inhibitor remained. To contrast, the concepti from groups A and B, fetuses whose parents were genetically identical, all survived and showed signs of normal development. This is despite group A having received treatment of the IDO inhibitor. Group D, which included the mice mated with synergetic partners, were not given IDO inhibitor and the pregnancy progressed normally and all concepti survived (Munn, et. al. 1998).

To test if a single paternal MHC class 1 difference will also lead to rejection, the scientists altered one gene and mated the mice. They found that the mice treated with IDO inhibitor all lost their concepti. The results of this experiments clearly indicate that IDO is an important factor in preventing the maternal immune system from rejecting the fetus (Munn, et. al. 1998).

A closer look at this data sheds some light on the mechanism that is likely to be responsible for protecting the fetus from rejection. Data showed that fetal rejection happened very early on in gestation, which does not give enough time for B cells to have produced the appropriate antibodies. This leaves it to T cells to have taken the active role in rejecting the fetus. Furthermore, it would be impossible to attribute the fetal loss to toxic effects of 1-methal-tryptophan, because the synergetic mice that did receive the inhibitor displayed no symptoms, indicating that it must have been an immunological effect of the inhibitor. This groundbreaking study indicates that it is the fetal allograft that protects itself from being rejected (Munn, et. al. 1998).

Many studies have since been done to test this hypothesis. Due to obvious ethical considerations, it is impossible to do complete experiments on humans, because of the rejection results that will likely occur. However, another research group tested for presence of the IDO enzyme in the human placenta. They first detected IDO at around week 14 and then levels increased rapidly and remained high throughout the pregnancy. When studying pregnancies with retarded intrauterine development, the IDO levels were significantly lower. This suggests that IDO enzyme is protecting the fetus from the maternal immune system (Sedlmayr, et. al. 2002).

Because tryptophan is an amino acid and cannot be synthesized by the body, the body's only source of it is from dietary intake. When placing golden hamsters on a high tryptophan diet, experimenters found that there was reduced embryonic survival and it influenced pregnancies adversely. This seems to link tryptophan levels with maternal rejection of the fetus (Meier, Wilson, 1983).

Another finding which seems to give credence to Mellor and Munns findings is the progressive decrease of tryptophan levels in serum from the beginning of human pregnancy until delivery. This shows a distinct inverse relationship between tryptophan levels and successful pregnancy in humans (Schröcksnadel, et. al. 1996).

In addition to the discovery of the role of IDO enzyme, further experiments indicate that there is another enzyme, Tryptophan 2,3-dioxygenase (TDO), which also contributes to tryptophan degrading activities. While establishing a time course, they have found that on days 9.5 to 12.5, IDO enzyme was at its peak expression. This phase coincides with the days of placental appearance and growth. In this experiment, IDO levels did decrease after this small phase, but tolerization lasted throughout the pregnancy which can indicate that once tolerance is established, it lasts despite continued tryptophan activity. However, on days 5.5 to 10.5, at the early stages of gestation, TDO enzyme was found at high levels. It is clear that during this early stage, IDO enzyme is not there, as 1-methal-tryptophan (an IDO inhibitor) was administered and did not inhibit the tryptophan degrading activities. This study suggests that early tryptophan inhibiting activities is due to TDO enzyme and during placental formation, IDO enzyme is responsible for inhibiting the T cell proliferation (Suzuki, et. al. 2001).

Th-2 Bias Mechanism

Many researchers contribute the tolerization to mechanisms other than the IDO enzyme.

Another mechanism that is now being researched is based on the link between successful pregnancy and a bias of Th2 cells. There are two types of helper T cells, Th1 and Th2. Th1 cell secretes pro inflammatory cytokines such as IFN-y and TNF-a. Th2 cells secrete anti-inflammatory cytokines such as IL-4,

IL-10, and IL-13. IL-4, which is produced by Th2 inhibits the growth of Th1 cells. IFN-y, which is produced by Th1 inhibits the growth of Th2 cells. Dr. Wegmann, hypothesized that in successful pregnancies, there is a strong bias of Th2 cells circulating at the maternal-fetal interphase. Because Th2 is anti-inflammatory, a significantly strong presence of Th2 cells will protect the fetus from th1 cells that cause inflammation and will allow fetal tolerization. In order to test this hypothesis, he injected pregnant mice with IFN-y and found that it resulted in pregnancy loss. This indicates that Th2 cells may promote maternal tolerance (Wegmann, et. al. 1993) .

Similar experiments done on both humans and mice have indicated this mechanism. Several studies showed that in normal human pregnancies there were increased levels of Th2 cell ration bias and at fetal loss there was a Th1 cell ratio bias (Ng, 2002). Furthermore, after examining samples from pregnant women, they found increased expression of IL-4 mRNA and decreased expression of IFN-y mRNA (Tranchot-Diallo, et. al. 1997).

A study of the th1/th2 cell levels in peripheral blood of women showed further links. Researchers examined the blood of women who have a history of recurrent miscarriages which is assumed to have been caused by maternal rejection. Within that group, they had a subgroup of women who were currently in middle of a healthy pregnancy and a subgroup of women who just had a miscarriage. They found that the women in the middle of a normal pregnancy had a strong bias of th2 compared to the women who just had a miscarriage and that the women who just miscarried had a strong bias of th1 cells (Makhseed, et. al. 2001). This implicates that th1/th2 cell ratio may play a significant role in the maternal tolerization of paternal alloantigens.

Nonconcurrent Theory

There have been suggestions that the fetal cells migrate to the maternal circulatory system: the lymph node, spleen, and thymus, where they will proliferate and then inactivate the potentially reactive T-cells. Several studies prove this to be the case with tolerized organ transplants. However, later research proved that it is highly unlikely that fetal cell migration can account for maternal tolerization. They found that, in fact, this scenario of fetal cell migration occurred in 1 out of 5 pregnant mice and at a level of 1-5 fetal cells per every 100,000 maternal cells. Because this event occurs so rarely, it doesn't seem rational to list fetal cell migration as a likely mechanism that protects the fetus from being rejected (Bonney, Matzinger, 1997).

Clinical Implications

Recurrent Spontaneous Abortions

As the experiments on mice indicated, fetal rejection resulted in the death of concepti. The death was caused by the maternal immune system's rejection of the placenta, which led to severe inflammation and hemorrhaging of the embryo, causing it to choke and die. This scenario can present in human pregnancy as well. Clinicians now wonder if the underlying explanation behind a lot of the miscarriages that occur is really the maternal immune system's rejection of the foreign paternal alloantigen (Mellor, Munn, 2000). Furthermore, if it is indeed the cause of recurrent miscarriages, then discovering the mechanism that induces maternal tolerance has clinical relevance as it is essential for proper treatment.

In order to test the IDO enzyme explanation for fetal tolerization, and to uncover if failure or dysfunction of this mechanism can lead to a miscarriage, researchers tested the cervical mucous, placental villi and decidua tissue. They surgically removed the tissue samples and mucus from women with recurrent miscarriages and divided the group into those that exhibited normal chromosomal groupings and those that did not. They compared the level of IDO enzyme presence to samples from women who had normal pregnancies and delivery. In samples of cervical mucous and decidua tissue they did not find a significant difference among levels of IDO in any group. However, when comparing villi from miscarried pregnancies of normal chromosome analysis and abnormal chromosome analysis, they found that the tissue from the normal chromosome group had significantly higher levels of IDO enzyme than tissue of the abnormal chromosome group. These results suggest that IDO enzyme dysfunction is linked to women suffering from recurrent miscarriages. Further research is necessary to test if IDO enzyme treatment can prevent women from miscarrying by preventing the maternal immune rejection that likely takes place (Obayashi, et. al. 2016).

Similarly, researchers who believe that a Th2 cell bias is responsible for maternal tolerance have studied the connection between helper T cells and recurrent miscarriages. In one experiment, they mated female mice who were deficient in IL-4 and IL-10 with male mice who were genetically different. They found that these mice experienced fetal loss. They treated some of these mice with an intraperitoneal injection of IL-10 and found that it protected the fetuses from resorption. (Sykes, et. al. 2012) Women who are suffering from recurrent spontaneous miscarriages are assumed to have a dysfunction in the immunological response to their fetus. This study implicates that by intervening and manipulating the levels of Th2 cells at the beginning of a pregnancy can protect these women from future miscarriages. Further research is being done on specific treatment methods.

Preeclampsia

Preeclampsia is a pregnancy complication characterized by high blood pressure. The high blood pressure seems to result from abnormal formation of blood vessels in the placenta. ET-1 is the peptide which causes vasoconstriction. Studies have found that

increased level of ET-1 in the plasma correlated with a bias of th1 cells. Upon further examination, this observation can indicate that if maternal tolerance mechanisms do not function normally, preeclampsia can occur.

When comparing women in middle of normal pregnancies to women with preeclampsia, they found that the ratio of th1/th2 was 7.6 in normal pregnancies and 11.6 in preeclampsia pregnancies. This shows that significant increases in levels of th1 are associated with preeclampsia (Kuwajima, et. al. 2001).

The th1/th2 cytokine imbalance that is found in preeclampsia can be explained since th1 cell is a proinflammatory cell and the vasoconstriction can be a result of inflammation of the placenta and umbilical cord (Vargas-Rojas, et. al. 2016).

Conclusion

The mystery of why a mother does not reject her fetus, as she would reject any other foreign object, is the focus of much research and academic debate. There is clear evidence to prove that the maternal immune system is in contact with the fetus and aware of its presence. The fetus is surely expressing paternal genes that are considered foreign to the immune system. Furthermore, the maternal immune system seems to otherwise function completely as normal, indicating that there is a specific mechanism which must protect the fetus. One suggested mechanism is that the fetus secretes IDO enzyme which inhibits a maternal amino acid, tryptophan, which supports the T cells of the immune system. This forces the maternal immune system to tolerize the fetus. Another explanation is that tolerization is due to th2 bias in t cell1/2 ratio. Th2 is an anti-inflammatory cell and can protect the embryotic tissue from a strong immune response. Details of these possible mechanisms has medical relevance for recurrent spontaneous abortions and preeclampsia because both conditions seem to be caused by immunological dysfunctions of the tolerization mechanism. Further research is being done to uncover other details of the mechanism and learn the entire explanation for this immunological paradox.

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