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T cell recognition and immunity in the fetus and mother

Cody A. Koch^{1,2} and **Jeffrey L. Platt^{1,2,3,4}**

¹ *Transplantation Biology Program, Mayo Clinic College of Medicine, Rochester, MN 55905*

² *Department of Immunology, Mayo Clinic College of Medicine, Rochester, MN 55905*

³ *Department of Surgery, Mayo Clinic College of Medicine, Rochester, MN 55905*

⁴ *Department of Pediatrics, Mayo Clinic College of Medicine, Rochester, MN 55905*

Abstract

All multicellular organisms protect themselves from invasion by allogeneic organisms and cells by mounting immune responses. While protective, allogeneic immune responses present a threat to successful reproduction in eutherian mammals in which the maternal immune system is exposed to the semi-allogeneic fetus. Thus, successful reproduction in eutherian mammals depends on mechanisms that control the potentially hostile maternal immune system without hindering immune responses to potentially deadly infectious organisms. Three general mechanisms have been proposed to explain successful reproduction in mammals; (i) the formation of an anatomical barrier between mother and fetus; (2) expression of allogeneic antigens at a very low level by the fetus; (iii) and hindrance of the maternal immune system responding to fetal antigens. These mechanisms explain in part how the fetus evades the maternal immune system; however, they do not explain fully the survival of the fetus. We hypothesize that site-specific immune suppression may play an important role in successful eutherian reproduction in conjunction with other mechanisms. Site-specific immune suppression at the fetal-maternal interface would protect the fetus while allowing peripheral maternal immune responses to continue unabated.

Introduction

The immune system allows multi-cellular organisms to differentiate self and non-self, preventing parasitism by foreign cells and defending against infectious organisms. While one might envision that highly disparate, xenogeneic, cells are easily recognized and destroyed by the host immune system, allogeneic and semi-allogeneic cells which closely resemble the host might be more difficult to recognize and destroy. However, all multi-cellular organisms mount rigorous allograft reactions.

Allograft reactions may incidentally cross react with reactions against microorganisms. However, allograft reactions provide distinct advantages. Thus, allograft reactions protect against invasion and expansion of allogeneic cells. Such invasion clearly threatens colonial organisms; yet such invasion of allogeneic cells could also threaten motile animals [1].

Correspondence: Dr. Jeffrey L. Platt, M.D., Transplantation Biology, Mayo Clinic, Medical Sciences Building 2-66, 200 1st St SW, Rochester, MN 55905, Phone: (507)538-0313, Fax: (507)284-4957, E-mail: platt.jeffrey@mayo.edu.

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In any case the powerful allogeneic response would seem to be a potential barrier to pregnancy yet, it is not. Here we discuss the mechanisms and how the barrier posed by alloimmunity may be overcome in pregnancy.

Fetal evasion of the immune system during pregnancy

The overwhelming success of the fetus in evading immune rejection by the mother has puzzled investigators for decades. Medawar [2] proposed three general mechanisms for such evasion. First, the maternal immune system might not be capable of responding to fetal antigens due to mechanisms that induce anergy or tolerance in responding maternal cells. Second, an anatomical barrier might form between mother and fetus preventing access of maternal immune cells to fetal antigens. Third, fetal cells might suppress the expression of alloantigens. These three mechanisms, while valuable from a heuristic perspective, do not fully explain how the fetus evades rejection by the mother. Thus, we previously proposed a fourth mechanism in which the fetus generates site-specific immune suppression [3]. Thus, the effector functions of maternal immune cells would be blocked at the maternal-fetal interface protecting the fetus while allowing the cells to mount immune responses to microorganisms and other foreign cells.

Maternal immune responsiveness to the fetus

The maternal immune system is capable of recognizing fetal alloantigens during pregnancy. Woodruff [4] found that fetal tissues transplanted to pregnant female rats rejected the transplants as quickly as organ allografts. Similarly, fetal tissue transplants were second-set responses if the mother had been previously immunized while fetuses would survive despite such immunization. Beer and Billingham [5] found that the uterus is not an immune-privileged site, as skin syngeneic to the fetus are implanted on the uterus is rejected with similar kinetics to nulliparous females.

The maternal immune response changes during pregnancy. Tallon et al. [6] found that CD4⁺ T cells decrease in the 2nd and 3rd trimesters while CD8⁺ T cells decrease during the third trimester. Watanabe et al. [7] found that peripheral blood CD8⁺ T cells decreased during the 1st trimester while CD4⁺ T cells decreased in the 3rd trimester with both populations increasing to baseline four months postpartum. Vacchio et al. [8] found that the CD4⁺ T cell population in the spleens increases during allogeneic pregnancies but not syngeneic pregnancies. Carter et al. [9] found that cell numbers in the spleen and para-aortic lymph nodes draining the uterus are decreased during pregnancy in mice.

The dimensions of the T cell compartment can be dramatically changed during pregnancy. Tafuri et al. [10] found that H2-K^b-specific TCR transgenic T cells constituted 46% of the splenic T cell population if the mother was carrying an H2-K^b-bearing fetus and 80% of the splenic T cell population if the fetus was syngeneic to the mother. Not only did the H2-K^b-specific T cells in the spleen decrease in the presence of an H2-K^b-bearing fetus but the expression levels of CD8 on the cells decreased during pregnancy returning to normal shortly after birth. In contrast, Zhou et al. [11] found that the splenic T cell population specific for H2-K^b increases three-fold when H2-K^b expression on trophoblast is driven by the HLA-G promoter during allogeneic but not syngeneic pregnancy. Jiang et al. [12] found that H-Y specific T cells are decreased 40% at 18 days gestation and were increased 50% by five days after birth. Jiang et al. [12] also found that the H-Y specific T cells do not respond to the H-Y antigen during pregnancy and the response cannot be rescued by IL-2. While the results in the studies presented above conflict, they do reveal that maternal T cell responses specific for the fetus change during pregnancy, suggesting that maternal T cells recognize fetal alloantigens. However, the mechanism(s) causing changes to the maternal T cell compartment during pregnancy remain unclear.

Immune barrier between mother and fetus

The trophoblast separates mother and fetus. The barrier formed by the trophoblast is complex with multiple different cell types. Once a fertilized egg implants in the maternal uterus the fetal trophoblast invades maternal vasculature to form an intervillous space through which maternal nutrients pass to the growing fetus. Shortly after the initial invasion of trophoblast, fetal blood vessels form fetal villi that are in direct contact with the maternal circulation and are covered with differentiated trophoblast cells called syncytiotrophoblast. Trophoblast cells resist immune attack. For instance, Zuckerman et al. [13] found that murine trophoblast cells resist lysis by CD8⁺ T cells whereas fetal fibroblasts do not. The differentiated cells of the trophoblast are also frequently renewed so any immune injury that does occur might be quickly repaired. The cytotrophoblast lies beneath the syncytiotrophoblast, protected from the maternal circulation, and serves as the only mitotically active trophoblast cell population renewing the syncytiotrophoblast population throughout gestation [14].

Maternal-fetal chimerism

Medawar hypothesized that the fetal-maternal barrier prevents the maternal immune system from contacting fetal cells bearing alloantigen [2]. Some fetal cells do enter the maternal circulation and can persist for years and even decades in the mother. Studying human pregnancies, Thomas et al. [15] found fetal DNA in the maternal circulation as early as the 4th week of gestation. Lo et al. [16] found fetal DNA in 26 of 51 pregnancies cases studied. Since the analysis was limited to blood cells (understandably), one might expect to observe chimerism in most if not all pregnancies if a sensitive assay is used.

Fetal DNA was once thought to derive from shedding of fetal trophoblast cells. However, fetal hematopoietic cells have also been shown to enter the maternal circulation. Walknowska et al. [17] detected male hematopoietic cells in pregnant females. Bianchi et al. [18] detected fetal mononuclear cells circulating in mothers as long as 27 years after birth. Even more interesting than persistence of these fetal cells is the likelihood that these cells originated from multipotent stem cells of the fetus that colonized the mother. Srivatsa et al. [19] found fetal cells in thyroid specimens of women years after pregnancy, in some cases giving rise to differentiated tissue such as thyroid follicles.

Immunological implications of fetal maternal chimerism

Chimerism can induce allogeneic tolerance [20]; while fetal-maternal chimerism appears not to do so. Tafuri et al. [10] did observe that pregnant mice were tolerant to P815 mastocytoma cells MHC-matched to the fetus; however, this tolerance abated shortly after birth. Thus, the role of fetal-maternal chimerism and tolerance in the survival of the fetus remains unclear.

Expression of fetal antigen during pregnancy

Fetal cells might evade detection and thus destruction by the maternal immune system by down-regulating the expression of fetal alloantigens. The only trophoblast cells in humans to express classical MHC class I molecules are the interstitial trophoblast cells that are in contact with the maternal decidua [21,22]. Trophoblast cells in contact with the maternal circulation do not express either MHC class I or MHC class II molecules [22]. While the lack of expression of classical MHC molecules might help to explain the survival of the fetus, it cannot completely explain the ability of the fetus to evade destruction by the maternal immune system. Shomer et al. [23] induced the expression of allogeneic MHC class I molecules on trophoblast using transgenic technology and found that the maternal immune system did not reject the fetus. Rogers et al. [24] similarly induced the expression of MHC class I molecules on trophoblast without detriment to the fetus, even in the presence of defects of the Fas/FasL pathway. Thus,

some mechanism(s) other than immunological ignorance also protects the fetus from the maternal immune system.

Site-specific suppression of the maternal immune system

Given the immune interactions between fetus and mother – the lack of maternal tolerance or ignorance and success of pregnancies in highly sensitized mothers – we have hypothesized that “site-specific” rather than systemic control best explains fetal engraftment. Besides promoting engraftment, site-specific controls allow, in principle, the full action of the immune system toward host defense. Below we discuss some “site-specific” mechanisms that have been proposed.

Fas/FasL

Apoptosis induced by the Fas/FasL pathway is essential to the control of the immune system as evidenced by the severe lymphoproliferation and autoimmunity that results when this pathway is disrupted [25]. The expression of FasL, which induces apoptosis of cells bearing the Fas receptor, is thought to underlie the immune-privilege of the anterior chamber of the eye and testes which express high levels of FasL and delete reactive lymphocytes [26].

The Fas/FasL pathway is also thought to be important for the control of maternal immune responses at the fetal-maternal interface. Apoptosis can be detected at the fetal-maternal interface throughout gestation [27–29]. This apoptosis might reflect the normal turnover of cells in an area of high cellular proliferation and growth; however, it could also represent a mechanism to prevent the maternal immune system from attacking the fetus. The expression of FasL mRNA can be detected at the fetal-maternal interface as early as 6 days post-conception in mice and as early as 12 days post-conception in humans [30,31]. Coumans et al. [32] found that human CD3⁺ T cells undergo apoptosis when cultured with human trophoblast due to the expression of FasL. Vacchio and Hodes [33] studied the role of Fas/FasL in the maternal response to the H-Y antigen using TCR transgenic mice. The authors found that 50% of the H-Y specific T cells were deleted in mothers carrying male fetuses; however, when the mothers were deficient in Fas the deletion of H-Y reactive T cells did not occur. These results suggest that Fas/FasL interactions are necessary for the deletion of maternal T cells reactive to the fetus; however, no increase in fetal abortion was reported. The results of Vacchio and Hodes [33] as well as the fact that *gld* mice, deficient in FasL, and *lpr* mice, deficient in Fas, are still able to reproduce suggests that Fas/FasL is not critical to the survival of allogeneic fetuses.

Tryptophan catabolism

Tryptophan, or its catabolism, is thought to prevent maternal immune responses to the fetus. Munn et al. [34] found that wild-type mice carrying allogeneic pregnancies given an inhibitor of the enzyme indoleamine 2,3-dioxygenase, which catabolizes tryptophan, abort their fetuses while wild type mice carrying syngeneic pregnancies or immunodeficient mice carrying allogeneic pregnancies administered the inhibitor give birth to normal offspring. However, reconstitution of pregnant immunodeficient mice with transgenic T cells specific for fetal MHC molecules resulted in fetal loss.

Indoleamine 2,3-dioxygenase protects the fetus from the maternal immune response by one of two mechanisms. First, indoleamine 2,3-dioxygenase might deplete the microenvironment of tryptophan. Levels of tryptophan in the maternal circulation decrease during human pregnancy compared to non-pregnant controls while the levels of its main catabolite, kynurenine, remain unchanged [35]. Munn et al. [36] found that depletion of tryptophan by macrophages inhibits T cell proliferation by arresting the cells in the mid-G1 phase of the cell cycle. Second, the catabolites of tryptophan produced by indoleamine 2,3-dioxygenase might act directly on

maternal immune cells. Terness et al. [37] found catabolites of tryptophan, including kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid, prevent the activation and proliferation of T cells and B cells. Frumento et al. [38] found that kynurenine and picolinic acid suppress T cell and NK cell activation and proliferation. Fallarino et al. [39] found that tryptophan catabolites induce apoptosis of T cells.

While tryptophan catabolism might be essential in murine pregnancy the role in human pregnancy is less clear. Defects in tryptophan catabolism have not been reported as a cause of fetal loss in humans. Regardless, should tryptophan catabolism play a role in successful human pregnancy the mechanism is likely a combination of both the depletion of tryptophan as well as the direct effects of tryptophan catabolites on maternal immune cells.

HLA-G

HLA-G, a non-classical MHC molecule, was originally thought to protect the fetus from natural killer cell mediated-damage, but may protect the fetus from T cell-mediated damage as well. Riteau et al. [40] found that cells transfected with HLA-G1 inhibit as much as 95% of T cell proliferation in mixed lymphocyte cultures. Kapasi et al. [41] found that high concentrations of soluble HLA-G suppress cytotoxic T cell responses and generate a Th2-type cytokine environment thought to be important for fetal survival. How HLA-G inhibits T cell responses remains unclear. Some have hypothesized that HLA-G binds to inhibitory receptors on T cells such as ILT-2 or ILT-4 [40]. However, soluble HLA-G has also been shown to induce apoptosis of T cells. For instance, Fournel et al. [42] found that soluble HLA-G causes apoptosis via a Fas/FasL dependent pathway.

Cytokine environment

The cytokine environment surrounding the fetus is essential to successful pregnancy. Pregnancy is associated with the Th2 deviation – thus the observation that cellular autoimmune diseases, such as rheumatoid arthritis, can go into remission during pregnancy, while antibody-mediated autoimmune diseases, such as systemic lupus erythematosus, often worsen [43]. A Th2-type response promotes successful fetal outcome while a Th1-type response induces abortion [44]. For instance, the high rate of abortion following CBA/J and DBA/2 mice matings is thought to be due to a deficiency in the production of Th2-type cytokines [43]. Chaouat et al. [45] found that stimulating IL-10 production using injections of IFN- τ prevents the high rate of fetal abortions in CBA/J and DBA/2 crosses. Clark et al. [46] found that the administration of GM-CSF to CBA/2 females mated with DBA-2 males also prevented spontaneous abortion due to the inhibition of T cell-mediated cytotoxicity directed against trophoblast cells. Hill et al. [47] found that the peripheral blood mononuclear cells from human females with a history recurrent spontaneous abortion produced high levels of IFN- α but not IL-4 and IL-10; in contrast, mononuclear cells from normal pregnant females did not produce IFN- α but did produce IL-10. Guleria et al. [48] found that blockade of the inhibitory T cell costimulatory molecule programmed death ligand 1 during allogeneic pregnancy leads to fetal loss due to increased secretion of IFN- γ creating a Th1-type cytokine environment while no effect was seen in syngeneic pregnancies. While a Th2-type cytokine environment is clearly important for successful pregnancy the mechanism responsible for initiating the response is unknown.

Regulatory T cells

The idea that suppressive or regulatory T cells might play a role in successful pregnancy was first suggested in the late 1970s. Chaouat et al. [49] reported that the adoptive transfer of splenocytes from pregnant mice enhances the growth of transplanted tumors the authors hypothesized growth was owed to “enhancing” antibodies or suppressive cells. Chaouat et al. [50] later reported that splenocytes from pregnant females suppressed lymphocyte proliferation

while splenocytes from non-pregnant females did not. These early experiments suggested that the splenocytes of pregnant females had suppressive effects and that these effects were directed towards cells specific for paternal antigen.

Later, the identification of a CD4⁺CD25⁺Foxp3⁺ T cell population with suppressive properties has prompted interest in role of this cell population in pregnancy [51]. Aluvihare et al. [52] found that the transfer of CD25-depleted lymphocytes to BALB/c *nu/nu* mice results in fetal loss when the mice are mated with allogeneic but not syngeneic males. The authors found that the maternal CD4⁺CD25⁺ T cell population expands regardless of whether the mother is carrying a syngeneic or an allogeneic fetus and that the T cells inhibit proliferation when added to mixed lymphocyte cultures. Darrasse-Jeze et al. [53] found that depletion of regulatory T cells with an anti-CD25 antibody resulted in decreased litter size in allogeneic but not syngeneic matings. Zenclussen et al. [54] found that the high rate of spontaneous abortion that occurs following the mating of CBA/J females with DBA/2 males could be significantly decreased by the adoptive transfer of regulatory T cells from non-abortion prone matings (BALB/c × CBA/J). The authors attributed the decreased abortion rate to increased expression of protective molecules including TGF-β, leukemia inhibitory factor and heme-oxygenase-1 induced by the regulatory T cells. The results of these studies suggest that regulatory T cells play an important role in successful pregnancy; however, the mechanism by which the regulatory T cells might act remains a mystery.

Conclusions

No immunological response is more reliable and more vigorous than the allogeneic response. Yet, the fetus reliably evades alloimmune injury. Unfortunately, generalizations about reproductive mechanisms across species are difficult to make due to vastly different gestation times and placenta anatomy. Thus, discoveries made in animal models need to be verified in humans, but ethical and logistical barriers may make this impossible.

Elucidating the mechanisms important for successful pregnancy will benefit not only reproductive immunology but many other fields as well. Perhaps the fetus represents “nature’s successful transplant” as a human fetus survives in the face of a potentially hostile maternal immune system for 40 weeks without immunosuppressive drugs. Thus, insights into how the fetus evades the maternal immune system will yield valuable knowledge about the basic mechanisms of tolerance and immune evasion.

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