Review paper

Why the mother's immune system does not reject her fetus

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Abstract

Fetal antigens are allogeneic to the mother's immune system and should theoretically elicit an immune response. The fact that this does not occur and that the fetus thrives for so long in the mother without undergoing rejection by her immune system is a scientific mystery. There are five main theories that could explain the fetus's success in evading the mother's immune system. These are the mother's overall immune suppressed state, maternal tolerance to fetal antigens, down-regulation of fetal antigens, the presence of a barrier between maternal immunity and the fetus, and local immune suppression at the site of the placenta. None of these mechanisms can fully explain this phenomenon despite the varying degrees of evidence in support of each. The last mechanism (local immune suppression) seems to be the most plausible one according to current thinking. The actual explanation of this paradox may well lie in a combination of several different factors rather than a single account.

Key words: immune system, fetus, pregnancy.

Introduction

The primary purpose of the body's immune system is to safeguard against invading foreign pathogens. An essential prerequisite to performing this task is the immune system's ability to recognize the body's own antigens as "self" and all other antigens as "non-self". This distinction (between self and non-self) is what guides the immune system in its decision as to whether or not to respond against any given set of antigens. In fact, many pathogens have evolutionarily adapted to mimic the body's unique antigenic signature so as to evade detection by the immune system; such capacity has rendered these pathogens especially virulent. The ability to distinguish self from non-self materializes during the early developmental stages of the immune system. Gaining tolerance to self is a process that is realized and honed both centrally and peripherally. The process of negative selection occurs centrally and serves to identify and remove "autoreactive lymphocytes", that is, lymphocytes that bind strongly to self antigens and hence may initiate autoimmune reactions if not removed. Peripheral tolerance mechanisms are also in place; these serve to suppress the action of any autoreactive lymphocytes that might have escaped the central tolerance mechanism. Together, these mechanisms ensure that the body's immune system is geared towards reacting against non-self-only antigens.

The mystery of why the mother in all mammalian species, including humans, tolerates the fetus without mounting an immune response against it has intrigued researchers for years. One half of the genetic makeup of the

fetus is foreign to the mother's immune system because it is derived from the father. Hence, theoretically, the mother's immune system should identify the fetus as non-self and mount an immune response against it. There have been many key discoveries related to maternal-fetal immunological interactions that have helped shed light on this scientific quandary. No unifying mechanism to date, however, exists to adequately explain this naturally occurring paradox. Theoretically speaking, five possible mechanisms could explain, at least in part, the ability of the fetus to evade the mother's immune system. First, the mother's generally immune-suppressed state during pregnancy may help cushion the fetus from any serious immunological sequelae. Second, the immune cells of the mother may undergo tolerance to fetal antigens in a similar manner to that in which they acquire tolerance to self antigens. Third, an anatomic barrier around the fetus may be present that prevents the maternal immune cells from reaching fetal tissues and afflicting harm. Fourth, fetal cells might somehow be able to suppress the expression and presentation of their own antigens, preventing the immune system from detecting the fetus. The fifth possible mechanism involves the creation of a local area of immune suppression around the fetus. While various degrees of evidence exist in support of each of these arguments, no single explanation has emerged to fully account for this phenomenon.

The mother's immune-suppressed state

Many specific changes occur in the mother's immune system during pregnancy. For example, it has been found that $CD4^+$ T cells decrease during the second and third trimesters whereas $CD8^+$ T cells decrease only during the third trimester [1]. Others have found that $CD4^+$ T cells decrease in the third trimester whereas $CD8^+$ T cells decrease during the first trimester and that both return to baseline levels four months postpartum [2]. Also, other researchers have found that cell numbers in the spleen and paraaortic lymph nodes draining the uterus are decreased during pregnancy in mice [3]. It has also been found that the mother's immune armament during pregnancy shifts to Th2-type responses (i.e. those geared towards antibody-mediated immune reactions) rather than Th1-type responses (those geared towards cell-mediated immunity). This is why cellular autoimmune diseases, such as rheumatoid arthritis, are commonly attenuated during pregnancy whereas antibody-mediated autoimmune diseases, such as systemic lupus erythematosus, often worsen [4]. This pregnancy-related change alone may afford the fetal cells some protection from the mother's immune system. In fact, investigators have found that artificially inducing increased IFN-γ secretion, thus creating a Th1-type cytokine environment, in pregnant mice led to fetal loss [5]. Further evidence for the Th2 environment's beneficial effects on the fetus's well-being and the Th1 environment's detrimental effects on fetal well-being exists. For example, peripheral blood mononuclear cells from human females with a history of recurrent spontaneous abortions have been found to produce 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 [6].

In addition to these specific changes, the pregnant female is also known to be in a relatively suppressed immune state. For example, maternal leukocytes are known to be relatively functionally impaired during pregnancy and the risks of bacteriuria, bacteraemia, and certain infections also rise [7]. Despite this overall immune-suppressed state, the pregnant mother is still able to mount immune responses (with a competent immune system) against a wide range of pathogens. On the other hand, the specific changes to the immune system that occur during pregnancy do provide important insight into the adaptation of the mother's immune system to tolerance of the fetus. Nevertheless, these variables do not exhibit 100% concordance with fetal survival or demise. Hence, these changes, while they may be important contributors, cannot fully account for the fetus's successful evasion of the mother's immune system.

Maternal tolerance to fetal antigens

The question of whether or not the mother's immune system is capable of recognizing the fetal antigens as non-self and mounting an immune response against them is an essential piece in this scientific puzzle. Evidence conclusively supports that the mother's immune system is, in fact, capable of recognizing the fetal antigen as non-self and thus mounting an immune response. It has been found, for example, that fetal skin tissue transplanted onto female rats pregnant with that same fetus was rejected at the same rate as allogenic grafts [8]. So why is the fetus itself not rejected by the mother? Mixed chimerism is a state in which haematopoietic cellular elements of both the host and donor coexist in the same individual. This has been shown to effectively induce tolerance of the host to transplanted allogenic grafts from that donor [9-14]. An interesting proposition would be that a similar type of mixed chimerism accounts for the mother's apparent tolerance to the fetus. Indeed, fetal DNA has been detected in human females during pregnancy [15, 16]. The significance of this finding is still in doubt given the conflicting evidence regarding maternal tolerance of fetal antigens. While some evidence points to a maternal tolerance of fetal tissue during pregnancy, other evidence negates this claim. For example, Tafuri et al. showed that pregnant mice were tolerant to mastocytoma cells MHC-matched to the fetus but

only during pregnancy [17]. Hence, while chimerism mediates tolerance in the case of allograft transplantation, its true existence and role, if any, in inducing maternal tolerance to fetal tissue has yet to be defined.

Another possible mediator of fetal survival of the mother's immune system is regulatory T cells (Treg cells). These cells are normally responsible for the peripheral suppression of autoimmune T cells. They may, however, also play a role in peripherally suppressing maternal cells that are reactive against fetal tissue. It has been found that adoptive transfer of Treg cells from non-abortion-prone mice crosses to abortion-prone ones decreases the rate of spontaneous abortions in the latter group [18]. Also, the depletion of Treg cells in pregnant mice has been found to significantly decrease the number of viable offspring [19]. It has been found that in human pregnancy, $CD4^+CD25^{high}$ Treg cells localize preferentially to the decidua compared to peripheral blood [20]. The same authors also found a significantly lower proportion of Treg cells in the deciduas of females with spontaneous abortions. Normal human pregnancy is characterized by low peripheral NK cell activity, and increased NK activity seems to play a role in spontaneous abortions of unknown aetiology.

Barrier separating the fetus from the mother's immune system

The third possible mechanism to explain maternal tolerance to the fetus is that of a barrier preventing the mother's immune system from reaching the fetus. The layer separating the mother from the fetus is the trophoblast. It has been found that murine trophoblast cells resist lysis by $CD8^+$ T cells whereas fetal fibroblasts do not [21]. This provides some support for the existence of a physical barrier separating the fetus from the mother's immune system. The importance of this barrier to fetal evasion of the mother's immune system, however, is questionable at best. The finding of fetal cells circulating in the mother's blood, both during and after pregnancy, obviates the vitality of such a barrier in sheltering fetal antigens from the mother's immune system.

Suppression of fetal antigen presentation

The fourth possible mechanism explaining maternal tolerance to fetal antigens revolves around the ability of the fetus to down-regulate its antigens to avoid immune detection by the mother. It has been shown that trophoblast cells in contact with the maternal circulation do not express either MHC class I or MHC class II molecules [22]. The significance of this in preventing fetal rejection by the mother, however, is in serious doubt. Several investigators have induced the expression of allogenic MHC class I molecules on trophoblast using transgenic technology and found that the maternal immune system still did not reject the fetus [23, 24]. Also, ample evidence exists to assert the maternal immune system's ability to effectively mount responses against fetal antigens. This implies that fetal antigens are, in fact, mature enough to be recognized by the mother's immune system as non-self. Hence, as before, this mechanism is unlikely to, at least fully, account for the fetus's survival of the maternal immune system.

Local immune suppression

The fifth possible explanation for maternal tolerance of the fetus is local immune suppression around the fetus permitting it to survive. This is an attractive explanation as it accounts for the fetus's survival while accommodating for a functioning maternal immune system and a mature set of allogeneic fetal antigens. Evidence has emerged to support the role of tryptophan (an essential amino acid) or, more likely, its catabolites in preventing fetal rejection by the mother. Pregnant mice that were given an inhibitor of indoleamine 2,3-dioxygenase, an enzyme that catabolizes tryptophan, aborted their fetuses [25]. Depletion of tryptophan has been found to inhibit T cell proliferation by arresting the cells in the mid-G1 phase of the cell cycle [26]. Also, tryptophan catabolites have been shown to hinder the activation and proliferation of T cells, B cells, and NK cells [27, 28]. Despite the delineation of the role of tryptophan in pregnancy viability in mice, its role in human pregnancy has yet to be studied.

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 [29]. Ample evidence points to the presence of apoptosis at the trophoblast throughout pregnancy [30-32]. This may provide an immunological, rather than physical, barrier to the mother's immune system around the fetus. Also, $CD3^+$ T cells have been shown to undergo apoptosis when cultured with human trophoblast as a result of the expression of FasL [33]. This provides further evidence for this "immunological barrier" theory. This mechanism of local immune suppression seems to be the most favoured explanation of fetal survival in current thinking. Most of the research currently investigating the fetus's evasion of the mother's immune system is centred around this hypothesis. Despite this enthusiasm, the evidence has not yet conclusively shown that fetal survival is entirely attributable to local immune suppression.

In conclusion, despite the many pieces of evidence relating to immunosuppression in pregnancy, none has been shown to be sufficiently necessary, and hence accountable, for the maternal immune system's tolerance towards the fetus. Another complicating factor in this area is the applicability of findings obtained from animal experimentation to humans.

This is a significant issue since a great portion of the research in this area is not performed on humans due to ethical constraints. Of all the broad possible mechanisms that could account for the maternal immune system's tolerance of the fetus, the localized immune suppression theory seems to be the most credible. The eventual answer to this mystery may indeed involve a combination of different factors rather than any one explanation.

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