Immunology of Pregnancy

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To my wife Anette for her unconditional love and support
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PREFACE

Immunology of Implantation: 
An Introduction

Gil Mor

Pregnancy Represents an Allograft

Cases of recurrent abortions, preeclampsia or babies born with hemolytic diseases of the newborn still puzzle us with the question “Why did your mother reject you?”

Although, after looking at the complexity of the maternal-fetal immune interaction and the cases of successful pregnancies, the question now becomes: “Why didn’t your mother reject you?”

Medawar, in the early 1950s, recognized for the first time the unique immunology of the maternal-fetal interface and its potential relevance for transplantation. In his original work, he described the “fetal allograft analogy” where the fetus is viewed as a semiallogeneic conceptus that evaded rejection. The approaches over the next 50 years have followed the methodology and development of transplantation immunity or more recently tumor immunity, unveiling new hypotheses and redefining old concepts.

The objective of this book is to review some of the significant events involved in human implantation related to the interaction between the maternal immune system and the fetus. The volume focuses on the main aspects of reproductive immunology, both from basic sciences and clinical points of view. Although there are still gaps in our knowledge, the advances accomplished in the last five years have proved the importance of understanding the role of the immune system during pregnancy. This not only represents a fascinating field for research, but it has the potential for new areas of treatment and diagnosis.

Defining Immunology of Pregnancy

Colbern and Main in 1991 redefined the conceptual framework of reproductive immunology as maternal-placental tolerance instead of maternal-fetal tolerance, focusing the interaction of the maternal immune system on the placenta and not on the fetus. The embryo in early development divides into two groups of cells, an internal, the inner cell mass, which give rise to the embryo and an external layer, the embryonic trophoblast that becomes trophoblast cells and later the placenta. The cells from the placenta are the only part of the fetus to interact directly with the mother’s uterine cells, and therefore the maternal immune system, and are able to evade immune rejection. The fetus itself has no direct contact with maternal cells. Moreover, the fetus per se is known to express paternal major histocompatibility complex (MHC) antigens and is rejected as allograft if removed from its cocoon of trophoblast and transplanted to the thigh muscle or kidney capsule of the mother.

This book we will focus on the interaction between trophoblast cells and the maternal immune system.

Types of Immune Response

The immune system eliminates foreign material in two ways: natural/innate immunity and adaptive immunity. Natural immunity produces a relatively unsophisticated response that prevents access of pathogens to the body. This is a primitive evolutionary response that occurs without the need of prior exposure to similar pathogens. For example, macrophages and granulocytes engulf invading microorganisms at the site of entry. Adaptive immunity is an additional, more sophisticated response found in higher forms such as humans. Cells of the innate immune system process phagocytosed foreign material and present its antigens to cells of the adaptive immunity for possible reactions. This immune response is highly specific and normally is potentiated by repeated antigenic encounters.

Adaptive immunity consists of two types of immune responses: humoral immunity, in which antibodies are produced and, cellular immunity, which involves cell lysis by specialized lymphocytes (cytolytic T cells). Adaptive immunity is characterized by an anamnestic response that enables the immune cells to 'remember' the foreign antigenic encounter and react to further exposures to the same antigen faster and more vigorously and by the use of cytokines for communication and regulation of the innate immune response.

Cytokines: Th-1 and Th-2 Type

Immune cells mediate their effects by releasing cytokines and thus establishing particular microenvironments. T helper lymphocytes (Th) that originate from the thymus play a major role in creating a specific microenvironment for a particular organ or tissue. Following an immune challenge, immune cells produce cytokine, the type of which determines their differentiation into T helper-1 (Th-1) or T-helper 2 (Th-2) lymphocytes. For example, Th-1 lymphocytes secrete interleukin-2 (IL-2) and interferon-γ (INF-γ) setting the basis for a pro-inflammatory environment. Conversely, the Th-2 lymphocytes secrete cytokines such as IL-4 and IL-10 which are predominately involved in antibody production following an antigenic challenge. The actions of the two types of lymphocytes are closely intertwined, both acting in concert and responding to counter regulatory effects of their cytokines. For example Th1 cytokines produce pro-inflammatory cytokine that while acting to reinforce the cytotoxic immune response, also down-regulate the production of Th-2 type cytokines.

Each of the different components of the immune system interacts, at different stages and circumstances, with the trophoblast. Our objective is to understand the type of interaction and its role in the support of a normal pregnancy.

In the following pages I will summarize some of the main hypotheses proposed to explain the trophoblast-maternal interaction.

Maternal Immune Response to the Trophoblast

The Pregnant Uterus as an Immune Privileged Site

Implantation is the process by which the blastocyst becomes intimately connected with the maternal endometrium/decidua. During this period, the semi-allogenic fetus is in direct contact with the maternal uterine and blood-borne cells; however, as I pointed above, fetal rejection by the maternal immune system, in the majority of the cases, is prevented by mechanisms yet undefined. A number of mechanisms have been proposed to account for the immune-privileged state of the decidua. The different hypothesis can be summarized in five main ideas: (i) a mechanical barrier effect of the trophoblast, (ii) suppression of the maternal immune system during pregnancy, (iii) the absence of MHC class I molecules in the trophoblast, (iv) cytokine shift, and more recently (v) local immune suppression mediated by the Fas/FasL system. I will discuss some of these hypotheses in brief and refer to the chapter where it is discussed in detail.
Mechanical Barrier

The concept of mechanical barrier was proposed to explain the lack of immune response in organs such as the brain, cornea, testicles and kidneys. We refer to these tissues as immune privileged sites where an immune response represents a dangerous condition for the tissue. Immune privilege sites are also organs or tissues of the body which, when grafted to conventional (nonprivileged) body sites, experience extended or indefinite survival. Whereas foreign grafts placed at nonprivileged sites are rejected promptly. The pregnant uterus is an example of an immune privilege site.

The first reasonable explanation of immune privilege was proposed by Peter Medawar in the late 1940s. Medawar proposed that organs such as the anterior chamber of the eye and the brain resided behind blood:tissue barriers. The existence of a mechanical barrier, (in the brain the blood brain barrier [BBB]), prevents the movement of immune cells in and out of the tissue. This barrier created a state of "immunologic ignorance" in which antigens within were never detected by the immune system without. The pregnant uterus was proposed to have a mechanical barrier formed by the trophoblast and the decidua, which prevented the movement of activated T cells from the periphery to the implantation site. Similarly, this barrier would isolate the fetus and prevent the escape of fetal cells to the maternal circulation.

Challenging the mechanical barrier effect theory are studies showing that the trophoblast-decidual interface is less inert or impermeable than first envisioned. Evidence for traffic in both directions across the maternal-fetus interface includes the migration of maternal cells into the fetus and the presence of fetal cells in the maternal circulation. This is the case of almost all the immune privilege tissues, including the brain's BBB. Conclusive evidence has shown that immune cells circulate through all parts of the brain, indicating that immune cells are not deterred by mechanical barriers.

The studies described by Adams and Lee Nelson in this book further demonstrate the bi-directional traffic across the maternal-fetal interface.

Systemic Immune Suppression

The second theory postulates the existence of nonspecific immune suppression during pregnancy. Numerous factors produced and isolated from the maternal placenta interface or from the serum have been associated with immunosuppressive activity. Some studies have suggested that human placental lactogen, human placental protein 14, and pregnancy associated plasma protein-A may have immune-depressant activity on lymphocytes. Soluble suppressor activity has also been identified in supernatants and cytosol fractions from placental explants and uterine secretions (for review see ref 6). Although all these studies have shown an immunologic effect, it is important to keep in mind that many of these factors have only been partially purified and their action has been tested using in vitro assays for lymphocytes or NK cell activity. These assays are very sensitive to impurities, and upon further purification many of these factors have lost their "immunosuppressive" effects.

Progesterone has been suggested to have immunosuppressive effects. Progesterone, in vitro, was described to be highly suppressive of mitogen activation and cytotoxic T-cell generation. Similarly, progesterone was shown to blunt an inflammatory response in an in vivo rat model. Other studies have shown that progesterone inhibits cytotoxic and natural killer cell activity as well as prostaglandin F 2α synthesis. It has also been shown that progesterone activates regulatory T cells of a suppressor phenotype by induction of a 34 kDa protein from lymphocytes.

The concept of systemic immunosuppression has been studied by numerous investigators and for many years became an accepted explanation. Indeed, as described above, a wide array of materials in human serum have been found to have profound in vitro immunosuppressive activity. However, from an evolutionary point of view, it is difficult to conceive pregnancy as a stage of immune suppression. In cultures where a pregnant woman is exposed to poor sanitary conditions, a suppressed immune system would make fetus survival impossible. Furthermore, there are recent studies clearly demonstrating that maternal antiviral immunity is not affected.
by pregnancy. The obvious observation that HIV+ pregnant women do not suffer from AIDS-like disease argues against the existence of such nonspecific immune suppression.

**Lack of Expression of HLA Antigens**

The third, more recently postulated theory is based on the fact that polymorphic class I and II molecules have not been detected on the trophoblast. Dr. Schust's chapter discusses the subject in greater detail. Major histocompatibility complex (MHC) class I antigens are expressed on the surface of most nucleated cells and serve as important recognition molecules concerned with vertebrate immune responses. In humans, these antigens are also known as human leukocyte antigens (HLA). HLA class I genes are located on the same chromosomal region (6p.21.3). They have been subdivided into two groups, namely the HLA class Ia and the HLA class Ib genes, according to their polymorphism, tissue distribution and functions. HLA-A, -B and -C class Ia genes exhibit a very high level of polymorphism, are almost ubiquitous expressed among somatic tissue and their immunological functions are well established: they modulate antiviral and antitumoral immune responses through their interaction with T and NK cell receptors. In contrast, HLA-E, F and G class Ib genes are characterized by their limited polymorphism and their restricted tissue distribution. Their roles are still poorly understood. The human placenta does not express HLA-A and HLA-B class I antigens but expresses HLA-G and HLA-C molecules. Where are those genes expressed? Dr. Schust's review discusses this question.

**Cytokine Shift**

The proliferation, invasion and differentiation of trophoblast cells during implantation is a tightly controlled process coordinated by a system of intercellular signals mediated by cytokines, growth factors and hormones. An extensive array of cytokines is produced at the trophoblast-maternal interface that contributes to the well being of the feto-placental unit. Furthermore, these cytokines to a great extent regulate maternal immune responses, which play an important role for a successful pregnancy outcome.

It is now recognized that cytokines have extremely diverse biological effects which may involve cell growth, differentiation and function. Their role in regulating human placenta development and implantation has been much discussed in recent years. The field of cytokines and implantation could be divided in two aspects, one is their role as regulators of the immune response and second as factors controlling trophoblast cell growth and implantation. This subject is extensively reviewed by Dr. Shigeru Saito, Dr. Surendra Sharma, Dr. Jan-S. Krüssel and Dr. Aydin Arici.

**Local Immune Suppression**

The last main hypothesis that we will discuss in this review is the "specific antipaternal suppressor/regulatory mechanism" observed during pregnancy. The first set of observations pointing towards the importance of local immune regulation was from Rossant and colleagues. Their observations were done using the *Mus musculus*:*Mus caroli* system (for more details in the model see ref. 16). They have shown that the transfer of *M. musculus* eggs into *M. caroli* is always successful; in contrast, there is almost a constant time schedule for failure of *M. caroli* embryos in the *M. musculus* uterus. In such a case, cotransferred adjacent *M. musculus* embryos do survive, whereas all the *M. caroli* embryos die from almost the same program. A strong immune infiltrate consisting of CTL and NK cells is observed around day 9.5. By day 13, the embryos are all completely reabsorbed. It was later shown that *M. caroli* embryos can survive until delivery, provided that *M. musculus* placenta was used. These results suggested that an important part of the placenta in *M. caroli* origin was responsible for provoking death and resorption of *M. musculus* embryos. This model was the first to describe these immunologically-mediated abortions and revealed the "immunological" role of the placenta. Furthermore, we consider that one of the
great merits of this model was to bring to focus the importance of local immunoregulatory events.

More recently, evidence exists for specific immune suppression directed towards the paternally encoded histocompatibility antigens. Here, the maternal T cells that recognize paternal antigens on the trophoblast are selectively abrogated. The role of decidual T cells during pregnancy is discussed by Dr. Lucia Mincheva-Nilsson.

The Role of the Innate Immune System in Pregnancy

During normal pregnancy, several of the cellular components of the innate immune system are found at the site of implantation. Furthermore, from the first trimester onwards, circulating monocytes, granulocytes and NK cells increase in number and acquire an activated phenotype. This evidence suggests that the innate immune system is not indifferent to the fetus and may have a role not only in host protection to infections, but also as important players in the feto-maternal immune adjustment.

Vikki Abrahams, Ulrike Kaemmerer, Ali Ashkar and I discuss the possible roles of cells of the innate immune system during pregnancy.

Furthermore, Dr. Abrahams' chapter presents evidence supporting the hypothesis that the trophoblast can function as an immune cell, capable of recognizing and responding to bacterial antigens.

Apoptosis and Implantation

During implantation, the uterine endometrium undergoes morphological and physiological changes to accommodate the embryo. This process of accommodation implies that the embryo has to degrade the endometrial extracellular matrix (ECM) to invade the uterus in species with hemochorial placentation. Apoptosis has been observed in endometrial epithelial cells at the embryo implantation site, and it is believed to be due to loss of contact with ECM. Those apoptotic cells are removed either by trophoblast or by maternal macrophages.

Apoptosis marks unwanted cells with "eat me" signals that direct recognition, engulfment and degradation by phagocytes. This clearance process, far from being the end, represents an active and coordinated event, which will send specific signals to the remaining cells either for survival or death. If the wrong message is sent by macrophages to the wrong cell type, it may have profound consequences for the normal physiology of the tissue.

Dr. Shawn Chavez discusses in detail the regulation of apoptosis in trophoblast cells.

Summary

Important reproductive events, including implantation, trophoblast invasion, placental development and immune protection are regulated by immune cells and their products (cytokines) produced at the maternal-fetal interface.

The maternal-fetal immune interaction is very complex, and it is difficult to perceive the whole process based on one mechanism of action. Clearly there are multiple mechanisms of peripheral and local tolerance induction during pregnancy that prevent fetal rejection while maintaining a strong and active immune surveillance against viral or bacterial infections, which may endanger the successful outcome and the survival of the species.

Some of these mechanisms are discussed in this book. In addition the chapters of Drs. Romero, Lockwood, Krüssel, Kwak-Kim and Richman present a clinical view of the role of the immune system in normal pregnancy and how its alterations may lead to complications of pregnancy.
References

CHAPTER 1

Evolution of the Mammalian Reproductive Tract and Placentation

Susan Richman and Frederick Naftolin

Abstract

Phylogenetic analysis suggests that the internalization of reproduction and the development of hemochorial placentation have been accompanied by conservation of primitive genitourinary genes. The products include the renin-angiotensin system and the innate immune system. This explains what might otherwise be considered an ectopic presence of these systems in the mammalian reproductive tract and the interaction of the allograft embryo and maternal host.

Introduction

Evolution is a conservative process; it more often proceeds through utilization of previously neutral characters than depending upon de novo mutation and selection: novel applications generally arise via utilization of preexisting adaptive mechanisms. Classical evolutionary methodology uses the fossil record, in conjunction with observations of both extant species and ethnographic evidence from surviving societies. For example, the length of human gestation and challenges of delivery such as cephalo-pelvic disproportion appear consequential to the assumption of an upright posture combined with cranial expansion. At the molecular level, this is accomplished by complex combinations of gene duplication, exon shuffling, and transposition. For example, the ancient glycoprotein hormone chorionic gonadotropin (CG) acts as a signal to maternal physiology to begin a series of adaptations to pregnancy. The mammalian gene for CG's beta subunit arose by duplication of the LH beta subunit gene approximately 94 million years ago from the common ancestor of both eutherian mammals and anthropoid primates. During that time span, the gene duplication was apparently followed by a frameshift mutation in the third exon. The major difference in CG gene function from its ancestral LH is in gene expression variants, composition and length of coding region. The translated products differ in the number of sugar chains attached, slowing the clearance of CG molecules from the maternal bloodstream to 12 hours, from 30 minutes in the case of LH. Analogous changes occurring in the structure and function of the excretory apparatus have led to the development of the mammalian reproductive tract and placentation.

Mammalian Reproduction

The development of sexual reproduction fostered genetic variability, which has hastened the pace of evolution. The transition from external to internal fertilization shielded reproduction from a hazardous external environment (predators, toxic chemicals, adverse temperature and pH), which has resulted in the requirement for fewer gametes per successful conception.

Internal fertilization has been accomplished by the enfolding of excretory and reproductive function. This adaptation accompanied the development of nonaquatic, terrestrial life forms, including mammals (Fig. 1).

The higher proportion of live-born young resulting from this system requires a higher investment per oocyte, but furnishes greater overall reproductive success, gene transmission and speciation. In humans, the allocation of resources that might have been devoted simply to generation of innumerable eggs for external fertilization has been replaced by the cyclic modification of the reproductive organs, sexual activity, placentation, gestation, parturition and lactation. All of this developed in the remnants of the ancient excretory tract, with the preservation of many of its mechanisms for interacting with an aquatic external environment.

Secondary Use of Immune Mechanisms for Reproduction

Molecular features of invertebrate immune systems such as the immune effector cells have been retained in mammals. Three genes found in echinoderms encode highly conserved transcription factors; NF-κB, GATA-2/3, and Runt-1, which are rapidly upregulated in response to bacterial challenges. SRCR family genes structurally resemble the mammalian macrophage scavenger receptors. Vertebrates added to this successful strategy by:

1. Internalizing mucosal surfaces and increasing their complexity to form the reproductive tracts—internalized but still aquatic environment.
2. Retaining control over the entirety of embryo development within the female reproductive tract, allowing the young to be born at more advanced stages of development. This, in combination with maternal supervision and protection, facilitates evasion from predators.

Creating this microenvironment for gametogenesis, fertilization and implantation, was accomplished by the aforementioned “internalizing” of the extracorporeal space within the modern reproductive tract. In the process, ancient nonreproductive systems such as the macrophage-cytokine system (innate or nonspecific immunity), which had evolved to interface the genital precursor with the external environment and invading organisms, were modified to accommodate the embryo. Mucosal immunity at body surfaces via TCR (T cell antigen receptor) γδ lymphocytes emerged earlier in evolution than TCR αβ, perhaps due to primitive digestive tract exposure to injury and infection in early jawed vertebrates. The generation of T cells also occurs in gut associated lymphoid tissue, which was the early adaptive immune
system, while the thymus evolved later, and its ontogeny is from pharyngeal pouch endoderm. In humans, the third pouch develops into the thymus, while the second develops into the palatine tonsil. The thymus also utilizes evolutionarily conserved immune-neuroendocrine effectors, as its mesenchyme develops from neural crest cells. T and B cells, MHC and antibody production constitute the adaptive or specific portion of the immune system. Signals from the embryo-host interaction relay the presence of an allograft to the maternal host, triggering the deployment of processes originally designed to protect against microbial or environmental challenges.

A later chapter will describe how hormonal regulation of immunocytes prevents rejection of the allograft embryo; however, the evolutionary relationship between the endometrium and the embryo is a derivative function of the reproductive tract development.

### The Role of the Endometrial Cycle

It is conventional to consider the ovarian and endometrial cycles as the fundamental processes involved in reproductive biology. However, the primary biologic goal is reproduction, and menstruation is merely the avenue of reestablishing reproductive competence. In an evolutionary sense, each complete menstrual cycle signals a lost opportunity to perpetuate the germ line. The superficial endometrium (functionalis) is the nexus of fetal signaling and the adhesion/implantation mechanism. In higher primates, this portion of the endometrium will be shed periodically. This occurs in the absence of signals (hCG, etc.) from the conceptus that drive the corpus luteum's cells to secrete the estrogen and progesterone that decidualize the endometrium and maintain the embryo until its placenta is able to function independently. The complete mechanism of menstruation (shedding of the functionalis) following ovulation remains unsettled; it appears that this process is triggered by the withdrawal of ovarian steroids from the expiring corpus luteum that upregulate production of PGF2α. VEGF secreted by the endometrial stromal and epithelial cells plays a role in the remodeling and regeneration from the basal layer that follows in the subsequent cycle, providing another opportunity to achieve pregnancy.

The unique individual that is at the blastocyst stage will invade the receptive endometrium and become essentially an allograft. This occurs in two steps: adhesion followed by implantation. The yolk sac-placenta provides nourishment until the definitive placenta develops. The maternal host's reaction to invasion by the embryo includes ancestral innate immune reactions to foreign proteins, modulated by estrogen, progesterone, and other signals from the maternal gonad and/or embryo. At this point, immune function is primarily a TH1 response. The human placenta is uniquely aggressive, and capable of invading through the endometrium to the myometrium and beyond, as in the case of placenta accreta/percreta. It is not yet clear what role this characteristic plays in. Balancing the need for minimally encumbered respiratory exchange, against the danger of overzealous invasion leading to maternal exsanguinations or other complications. While the villous cytotrophoblasts are extraordinarily efficient for this respiratory and nutrient exchange, the invasive extravillous cytotrophoblast must be limited to invading only the decidua and superficial myometrium. Without this control, the placenta could implant on muscle that would not provide proper nourishment to the conception and the mother would risk exsanguination from her large pelvic vessels. Potential controlling autocrine/paracrine mechanisms include glycoproteins, cytokines, and growth factors. The proliferative, invasive and migratory activity of the villous cells declines with increasing gestational age, but it has not been established whether this is due to intrinsic cell programming or extrinsic decidual factors.

Immunoregulatory mechanisms are increasingly seen to be key regulators of this invasive behavior. In vitro models of the maternal fetal interface involve co-culture of trophoblast and decidual cell lines on collagen gel matrices. Decidual TBF-B and dermatan sulfate proteoglycan
Figure 2. Adaptational changes on placentation.

IL have been shown to prevent overinvasion when activated by trophoblast proteolytic enzymes such as MMP. During placenta development, lymphocytes are excluded from the maternal-fetal interface, while monocytes and granulocytes gain access.

Endometrial stromal cells and deciduas express insulin, IGF-1, and glucocorticoid receptor, peaking at days 4 and 5 of gestation. This suggests a relationship between the regulation of invasion and the immunologic alterations in the progression of pregnancy, i.e., the barrier may be one and the same: the immune system.

Placentas and Placentation

The most primitive and presumably ancestral placentation is choriovitelline, formed by fusion of the yolk sac and chorion. Placental structural evolution proceeded towards the generation of a larger surface area, which facilitated metabolic exchange accompanying changes in more aggressive invasion of the maternal host. The production of growth factors, cytokines and hormones encourages increased blood flow and nutrient delivery to the feto-placental unit. Interspecies comparisons again demonstrate the recycling of existing pathways for functions common to other systems, such as the FGF signaling and branching morphogenesis utilized in ontogeny of both pulmonary alveoli and placental villi (Fig. 2).

Study of placental structure in eutherian mammals suggests adaptive pressure for development of the hemochorial type of placenta over alternative epitheliochorial or synepitheliochorial types. Hemochorial placentae are not found in any animal larger than the human or gorilla. This may be secondary to the potential drawback of such structure in the ready passage of fetal cells to the maternal organism and potential for oxidative stress. Nucleotide sequence data suggests that haemochorial placentation evolved independently in each of the four mammalian
superorders, likely reflecting their separation by the newly emerging continental land masses 100 million years ago. This is classical evolutionary adaptation as described by Darwin after his visit to the Galapagos Archipelago, in which side vent lava flows perform in the same manner as the spreading of the tectonic plates described above (Fig. 3).

The eutherian mammal branch is relatively recent, and there are few placental specific genes that appear to have arisen by gene duplications and deletions. Primate-specific placental adaptations such as early implantation, deep and widespread invasion of trophoblast cells into and remodeling of maternal decidual vessels may be compensation for the biomechanical constraints imposed by bipedal posture. However, it is associated with the most aggressively invasive placenta in nature, that of Homo sapiens.

**Maternal-Fetal Immune Function**

**Placental Evolution**

The ubiquitous challenge of balancing protection against invading foreign organisms with the necessity for the maternal immune system to tolerate the presence of a fetal endograft containing 50% nonself antigens is not unique to primates. Most maternal antibodies misdirected against the fetus are directed against paternally inherited MHC.

Mammalian TATA binding protein, used for promoter recognition during transcription by RNA polymerases in all eukaryotes, is another highly conserved molecule across species. Mice with an engineered version lacking 111 amino acids die in mid-gestation, despite normal transcription function of the enzyme complex, apparently due to structural placental defects that lead to maternal rejection type reactions. Embryonic rescue is possible by utilization of immuno-compromised mothers, suggesting that the TBP-N terminus disrupts a β2m-dependent process that the placenta uses to evade a maternal rejection response. This system is ubiquitous to all vertebrate species, and may have coevolved with the MHC system, as both are linked on chromosome 17.
Placental Contribution and Graft Tolerance

Placental trophoblasts produce many immunosuppressive molecules, such as progesterone, matrix metalloproteinases, and complement inhibitors. Many species have solved this conundrum in a similar fashion, by minimizing the placental expression of major histocompatibility complex genes. This occurs despite the gross structural differences. Vertebrates developed specific immunity, in contradistinction to the generalized defense systems such as mucus, cilia, enzymes, phagocytosis, and acute phase proteins. All vertebrates will reject tissue grafted from nonisogenic individuals of the same species, and exhibit the same degree of plasticity, necessary to keep pace with the short intergenerational intervals and frequency of mutations characteristic of invading pathogens. In parallel with the microorganisms, T and B cell intergenerational intervals are short, between 12 and 24 hours. B cell antibody receptors exhibit $10^8$ specificities, while the corresponding number for T cells is $10^{15}$. Positive and negative selection during thymic maturation reduces the risk of self reactivity in peripheral tissues. This is a central theme in the evolution of multicellular organisms, i.e., species success depends on the resolution of conflict between selection at the level of the multicellular entity versus that of the individual cell.\(^{23}\)

In the case of mammals, fetuses are retained within the reproductive tract for longer periods of time, increasing the temporal challenge to the immune system.\(^{24}\)

Of the MHC molecules, HLA-G has been most extensively studied, being expressed preferentially on extravillous trophoblasts at the maternal-fetal interface. It is one of the three nonclassical human MHC class I genes. Its expression on target cells protects them from natural killer (NK) cell-mediated lysis via inhibitory receptors 1 and 2. The CD94/NKG2-A receptor complex is most utilized by maternal decidual NK cells. HLA-G has been proposed as the ancestral MHC class I gene via sequence homologies.\(^{25}\) These molecules do not present antigens and may send the above noted negative signals to maternal NK cells to avoid fetal rejection. HLA-DR antigen expression has also been sought on human first trimester trophoblasts without success.\(^{26}\)

The low polymorphisms in HLA-G molecules worldwide in human populations and the lack of hypervariable regions at the peptide binding site argue for strong selection pressure for its perpetuation. Conserved intron 2 sequences in all primate species studied thus far suggest that this structure may have appeared as recently as 15 million years ago, when the orangutan diverged from the human lineage.

An alternative system that may be employed in the service of fetal immune tolerance is that of Fas/FasL. Activated T cells recognizing placental alloantigens express Fas, bind to the FasL expressed by the trophoblast, and undergo apoptosis.\(^{27}\)

Comparative amino acid sequence analysis of IgE, G and G2 structure confirms the immunologic divergence of mammals from early reptilian species approximately 300 million years ago.\(^{28}\) The mammalian immune system appeared approximately 100 million years ago at the time metatherian (marsupial) and eutherian placental lineages emerged (Fig. 3).

Summary

In summary, the evolution of the human reproductive tract and placentation demonstrates conservative retention of archetypal systems found in simpler species. These have been modified for the complexity of primate reproduction. These modifications include internalization of the excretory apparatus for use in reproduction (Fig. 4).

Accordingly, it is not surprising that the mechanisms involved in interactions between cells and tissues occupying the reproductive tract and the tract itself are the same as those used in interactions between the body and its (internalized) extracorporeal space.
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Figure 4. A summary of the relationship between the lining of the reproductive tract and the developing embryo. Note that the embryo, which is in the uterine cavity, is within the extracorporeal space that has been incorporated by the internalization of the reproductive process, see Figure 1. (Modified from Naftolin et al. Gynecological Endocrinology 1988; 2:265-273.)

References
CHAPTER 2

Toll-Like Receptors and Pregnancy

Vikki M. Abrahams and Gil Mor

Abstract

The maternal-fetal interface represents an immunologically unique site that must promote tolerance to the allogenic fetus, whilst maintaining host defense against a diverse array of possible pathogens. Clinical studies have shown a strong association between certain pregnancy complications and intrauterine infections. Therefore, innate immune responses to microorganisms at the maternal-fetal interface may have a significant impact on the success of a pregnancy. There is growing evidence that trophoblast cells are able to recognize and respond to pathogens through the expression of Toll-like receptors, a system characteristic of innate immune cells. This review will discuss the role of Toll-like receptors at the maternal-fetal interface, the potential for trophoblast cells to function as components of the innate immune system and the impact TLR-mediated trophoblast responses may have on a pregnancy.

Introduction

During pregnancy there is a strong immunological presence at the maternal-fetal interface, particularly by cells of the innate immune system.\(^1\) The role of the immune system at the maternal-fetal interface is thought to facilitate implantation and placental development, whilst promoting fetal tolerance.\(^2\)\(^-\)\(^3\) However, a certain level of host defense at this site is also required. As a consequence, either an inefficient clearance of an infectious agent, or an overzealous immune response may have a significant impact on the pregnancy. Clinical studies have shown a strong association between certain pregnancy complications and intrauterine infections,\(^4\)\(^5\) suggesting that the innate immune response can affect the outcome of a pregnancy. Preeclampsia and intrauterine growth restriction (IUGR) are both thought to be associated with infection\(^6\)\(^-\)\(^8\) and a link between preterm labor and intrauterine infections is now well established. Indeed, infections have been reported as responsible for up to 40% of preterm labor cases.\(^9\) Furthermore, 80% of preterm deliveries occurring at less than 30 weeks of gestation have evidence of infection,\(^10\) suggesting that an intrauterine infection may occur early in pregnancy, preceding such pregnancy complications.\(^4\) Infection, therefore, represents an important and frequent mechanism of disease, yet, the precise molecular mechanisms by which infection can affect a pregnancy remains undefined. While immune cells such as macrophages and NK cells are present the maternal-fetal interface,\(^1\) they may not be the only cells able to respond to infectious agents. In addition to the classical immune cells, placental cells may also have the potential to function as a component of the innate immune system.\(^11\) This review will discuss how trophoblast cells may respond to a pathogen through the system of evolutionary conserved proteins known as Toll-like receptors, and how such responses might impact a pregnancy.

Infections and the Innate Immune

The innate immune system represents the immunological first line of defense against invading pathogens through its ability to distinguish between what is non-infectious self and