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INVITED REVIEW

Fetal-placental antigens and the maternal immune system: Reproductive immunology comes of age*

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Abstract

Reproductive physiology and immunology as scientific disciplines each have rich, largely independent histories. The physicians and philosophers of ancient Greece made remarkable observations and inferences to explain regeneration as well as illness and immunity. The scientific enlightenment of the renaissance and the technological advances of the past century have led to the explosion of knowledge that we are experiencing today. Breakthroughs in transplantation, immunology, and reproduction eventually culminated with Medawar's discovery of acquired immunological tolerance, which helped to explain the transplantation success and failure. Medawar's musings also keenly pointed out that the fetus apparently breaks these newly discovered rules, and with this, the field of reproductive immunology was launched. As a result of having stemmed from transplantation immunology, scientist still analogizes the fetus to a successful allograft. Although we now know of the fundamental differences between the two, this analogy remains a useful tool to understand how the fetus thrives despite its immunological disparity with the mother. Here, we review the history of reproductive immunology, and how major and minor histocompatibility antigens, blood group antigens, and tissue-specific "self" antigens from the fetus and transplanted organs parallel and differ.

KEYWORDS
AIRE, antigens, fetus, historical perspective, immunology, placenta, pregnancy

1 | INTRODUCTION

Since Peter Medawar famously asked how the fetus manages to thrive despite its semi-allogeneic relationship to the mother,[1] scientists have compared the fetus with a transplanted graft because of the paternal half of its genetic makeup and the intimate relationship between maternal and fetal tissues. Work of reproductive immunologists over the past 70 years has revealed that while transplanted tissues must overcome or evade a host immune system, viviparity and immunity co-evolved rather than competed. Nonetheless, the pathophysiology of transplantation remains a useful comparator to understand how the fetus and maternal immune system coexist and further, how the fetus and placenta coopt maternal immune cells to promote implantation, placentation, and fetal growth.

Our grasp of the immunology of pregnancy has itself evolved, and questions were launched only after fundamental discoveries in each field occurred separately. In this article, we review the relationship between pregnancy and the maternal immune system by paralleling the

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histories of reproduction and of immunology, outlining how reproductive immunology emerged as a scientific field of its own (Figure 1). We discuss how the recent histories of reproduction and transplantation immunology are inextricably linked, and how fetal antigens both correspond and differ with those relevant to transplantation.

2 | EARLY PERCEPTIONS OF REPRODUCTION AND IMMUNOLOGY

Since ancient times, how animals reproduce has marveled scientists and philosophers. Philosophers and physicians of ancient Greece embraced preformationism, one of the earliest documented theories of how reproduction and embryological development occurrs. In this theory, animals reproduce via "animalcules" (or for humans, "homonculi")—miniature versions of offspring that were thought to preexist in semen. According to Pythagoras (c. 570 – c. 495 BC), animalcules circulate throughout the male body to gather specific traits of the father to be passed on. The idea that the "seed" or "vitality" of the next generation came from the male dominated for much of ancient history; the mother's womb was believed merely to serve as a vessel for growth of the tiny offspring.

Hippocrates' (460–370 BC) ideas on reproduction challenged this view: he asserted that *two* seeds are required for regeneration, one each from the male and the female.[2] He argued that only this could explain the resemblance of children to *both* parents. Later, Aristotle (385–323 BC) pointed out additional flaws of preformationism: first, the notion that animalcules circulate to gather characteristics of the father contradicts obvious anatomical and physiological differences between men and women. Second, if homunculi are preformed, they must be so *ad infinitum*; yet Aristotle believed that infinity only exists in theory. Instead, he offered another view—an idea that turned out to be fundamentally correct: he reasoned that offspring form according to a "plan" that both parents contributed. This plan is what we now know as the genetic code.

Meanwhile, the first documented observation of physiological immunity (from the Latin *immunus*, meaning "exempt from public service") came from Thucydides' description of the Plague of Athens (429–426 BC). Interestingly, Thucydides was an Athenian general and historian who made a number of critical scientific observations. The "plague" he described was more likely smallpox than the bubonic plague; nonetheless, his observations proved foundational. He noticed that "… the disease did not attack the same person a second time, or at any rate not fatally.". He also commented that some who recovered even believed that they would be protected from other diseases. Shrewdly, Thucydides thought this notion callow, unknowingly giving testimony to immunological specificity.[3]

Some 2000 years later, the first intentional exposure to disease for preventative purposes—variolation—was documented. Variolation was used to prevent smallpox in 16th century China, India, and the Ottoman Empire; its origins remain obscure, however, and this practice may have been used for hundreds of years prior.[4] From its use in Asia, variolation spread into Europe and the United Kingdom, and became accepted medical protocol by the 18th century. Unfortunately, lack of standardization meant that it sometimes led to fulminant infection and death, although it still did so less commonly than natural infection. The scientific basis for variolation was not understood, but it set the stage for Jenner's development of the

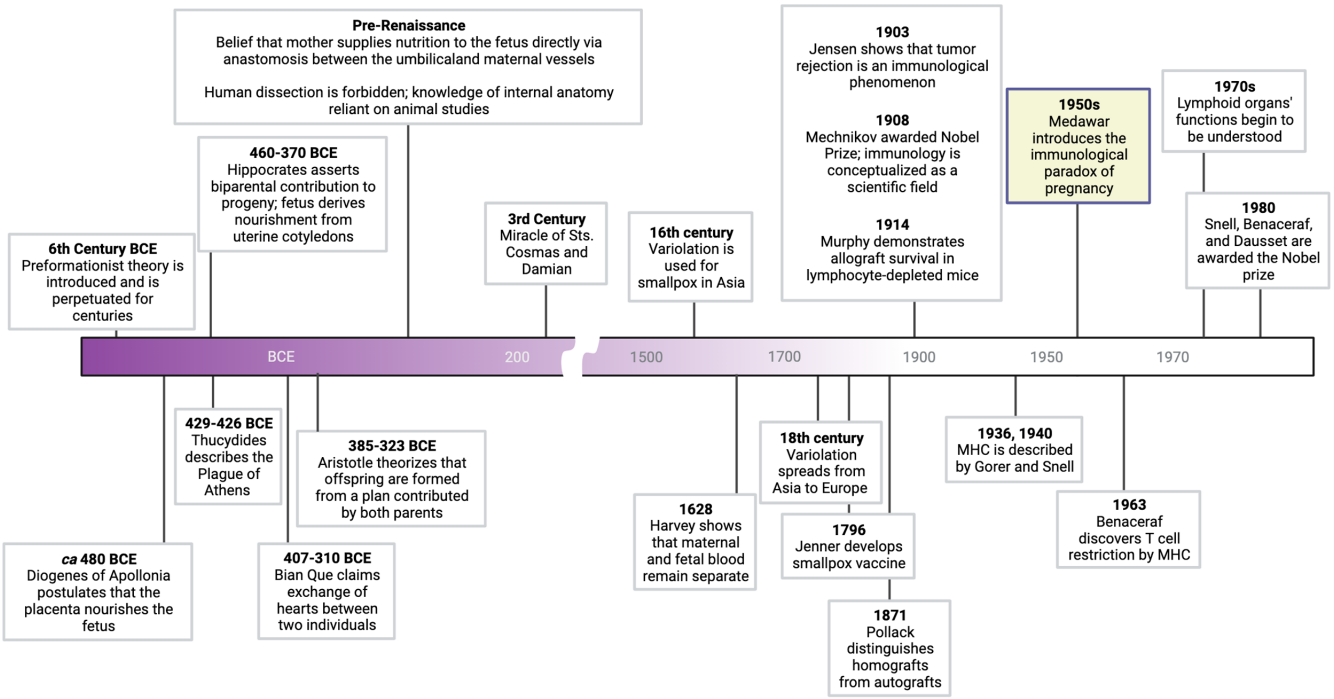

FIGURE 1 Timeline of seminal theories, observations, and discoveries in immunology and reproductive physiology that led to the development of reproductive immunology as a scientific field

vaccine using the cowpox virus. Pasteur and others then developed additional vaccines against other debilitating, life-threatening diseases, and advanced the understanding of their effectiveness.

While protection from disease by the growing practice of vaccination was realized at the time, how it drove immunity was not. At the time, the major theoretical basis explain physiology, health, and illness was the four humors: blood, yellow bile, black bile, and phlegm. This idea dominated our understanding of physiology from ancient Greek times to well into the second millennium AD. The ancients thought the thymus to be the "seat of the soul" and was described by Galen as an "organ of mystery" that purified the nervous system[5]; its function as the source of T cells was not comprehended until the 1970's.[6] Bone marrow was thought to nourish bone (Hippocrates, Galen) or consist of waste (Aristotle),[7] and the spleen to be the source of black bile.[8] Remarkably, the lymphatic system was correctly described to contain fluid, and both the spleen and lymph nodes to enlarge in pathological states.[9] Clearly, however, there was little understanding of the functions of these organs, and understandably, no awareness of immune cells.

Similarly, the embryological development and purpose of the placenta remained mysterious throughout most of written history. The Greek philosopher-physicians thought the placenta was something of an alter ego or an external soul to the child. (Some communities retain similar beliefs today, which must continue to be respected when considering the use of the placenta for scientific purposes.) Diogenes of Apollonia (*ca* 480 BC) was the first in recorded history to postulate that the fetus derives nourishment from the placenta; others believed that nutrition was obtained from the amniotic fluid.[10] Hippocrates, on the other hand, held the more widely believed view that the fetus feeds and respires through suckling of uterine cotyledons; this theory may have included the belief that the umbilical vessels were connected to the uterus and in turn, the breasts.

Until the Renaissance, both church and government forbade dissection of cadavers, which hindered progress in human medicine for millennia. Physicians relied instead on dissection of animals to understand internal organs, and thus sometimes failed to appreciate major differences between the reproductive systems of animals and humans. This is infamously depicted in da Vinci's depiction of the fetus in the womb, which, reminiscent of Hippocrates' opinions, shows a human fetus with a bovine cotyledonary placenta —presumably the only resource available to him (Figure 2).[11]

Interestingly, da Vinci correctly concluded from these dissections that fetal and maternal vessels remain separate—an issue that contradicted centuries of belief that they fuse, and one that would not be resolved for another 100 years. Using the scientific method for the first time, J.C. Arantius (1530–1589) and William Harvey (1578–1657) showed, independently, that maternal and fetal blood remain separate—first by exsanguination of dogs, and then by perfusion of the human placenta.[12] We now understand from an immunological standpoint that intermixing of maternal and fetal blood would precipitate a significant and dangerous immune response in some patients.

Because of the disseminated nature of the immune system, the lack of appropriate technology, and the inability to link distinct organs with immunologic function, advances in gross anatomy and microscopy had a lower impact on immunologic discovery than in other areas. Thus, immunology remained undesignated as a scientific field until Mechnikov received the Nobel Prize in 1908 for his observations on phagocytes.[13] Nonetheless, physicians long savored the idea that grafting and transplantation could save life and limb. The Chinese physician Bian Que (407–310 B.C.) is said to have cured two patients, one of low "intellectual ability" and one of low "willpower", by exchanging hearts between the two, and legend tells that the two men woke up "as good as new" (Bian Que is also credited to have invented anesthesia). Later, the Catholic Sts. Cosmas and Damien posthumously appeared to a church verger and replaced his cancerous leg with that of a deceased Moor, a "miracle" that inspired numerous Gothic- and Renaissance-era paintings (Figure 3).

These accounts may or may not have been actual attempts at transplantation. Regardless, neither physicians nor laymen could have been aware of why these or similar operations would have invariably failed. But because the stakes were high, surgeons persisted. What must have been persistent failure of homografts—grafts between two individuals—was either overlooked or disregarded until the late in the 19th century. In 1871, George Pollack (St. George's Hospital in London) made the seminal observation that in the same patient, autografts could be successful but homografts would fail. Unfortunately, Pollack's report escaped noticed by the scientific community—as did other important observations. In 1903, Carl Jensen, a veterinary surgeon at the Royal Veterinary and Agricultural College in Denmark, reported that failure of tumors transplanted between mice is an immunological phenomenon. This conclusion was discounted, however, as no antibody was evident; at the time, this was the hallmark of immunity.[14] Further, lymphocytes were thought to be stationary—counter to the idea that they could infiltrate tissues. Eventually, however, the role of lymphocytes was brought to light by James B. Murphy (Rockefeller Institute), who showed that allogeneic tumors survived indefinitely in lymphocyte-depleted mice.[15] In the 1930's, Leo Loeb further showed that the rate at which homografts disappeared correlated with the genetic distance between the donor and recipient.[14] Under Loeb's influence, Brown, and Padgett showed that identical twins accepted each other's skin grafts.[14]

Clarence Little, who founded the Jackson Laboratory, promoted the idea that if sufficiently inbred, grafts between mice could be interchanged.[16] Soon afterward, Peter Gorer and George Snell solidified this idea using congenic mice, narrowing down the major histocompatibility complex (MHC) genes as the locus responsible for inter-strain graft failure in congenic mice.[17,18] Experiments by Baruj Benaceraf revealed that T cells are restricted by the MHC, finally explaining involvement of lymphocytes in graft rejection.[19] This was followed by Jean Dausset's discovery of the human MHC locus (human leukocyte antigens, HLA).[20] Together, Snell, Benaceraf and Dausset received the Nobel prize "for their discoveries concerning genetically determined structures on the cell surface that regulated immunological reactions."

The discovery of the MHC coincided with those of acquired immunity and transplantation tolerance by Peter Medawar. Medawar

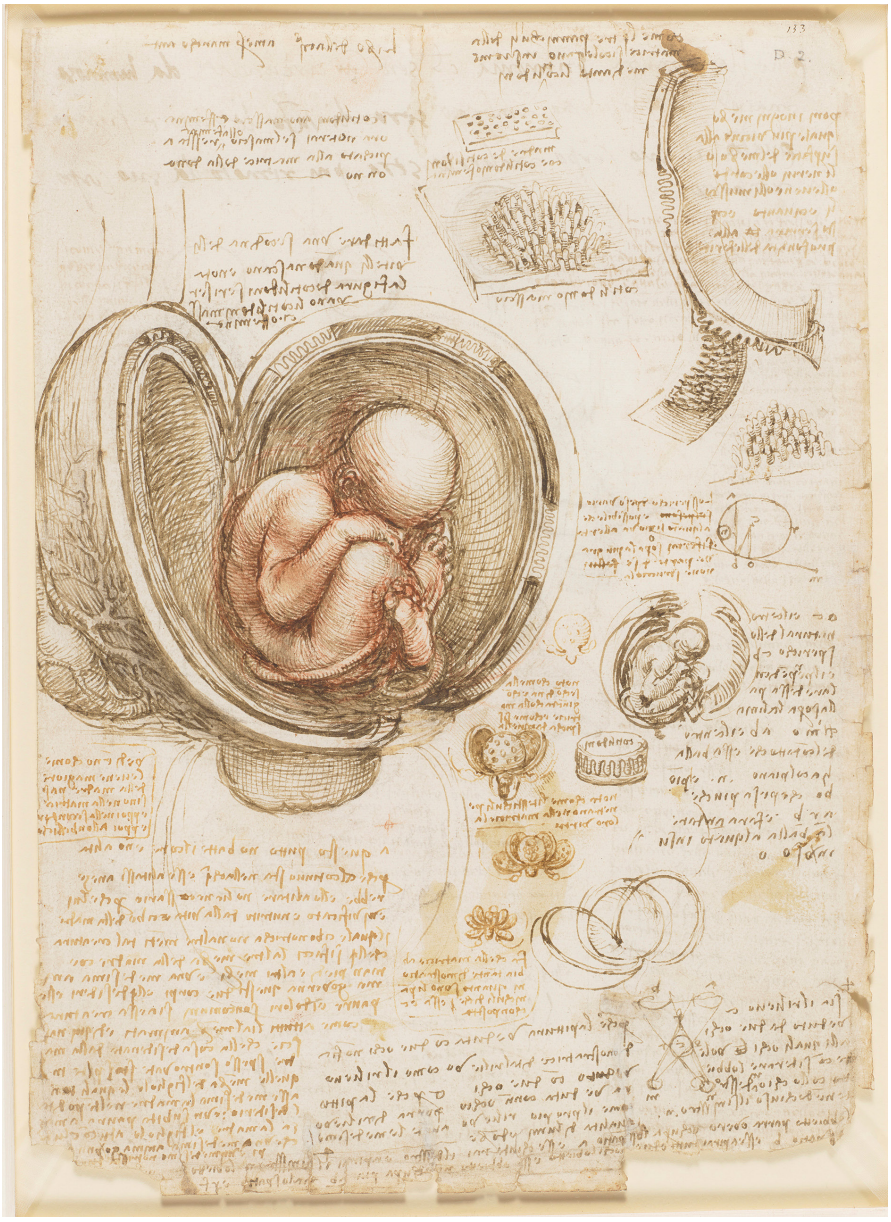

FIGURE 2 Fetus in the Womb, by Leonardo da Vinci. Da Vinci depicts a cotyledonary placenta characteristic of ruminants in the central drawing as well as in smaller studies to the lower and upper right. Used with permission, Royal Collection Trust/© Her Majesty Queen Elizabeth II 2022

was trained as a zoologist but was commissioned by the Medical Research Council in London to study why skin grafts so often fail, in the hopes for improved treatment of World War II burn victims.[21,22] Prompted by a colleague and Brown and Padgett's discovery about transplantation in twins, Medawar tested the idea that monozygotic and dizygotic cattle twins could be distinguished by skin grafting. The results were startling, however: twin cattle who were clearly dizygotic as assessed by phenotyping usually *accepted* each other's grafts—even when of opposite sex.[23]

How could this be explained? Medawar ingeniously considered prior findings by Owen that dizygotic twin cattle share circulating blood via chorionic vascular anastomosis.[24] He further looked to Burnet and Fenner's theory that animals can acquire tolerance to each other's antigens if exposed early enough, during embryonic life.[25] Reflecting on these contributions, Medawar and colleagues reasoned that sharing of blood must also mean sharing of antigens, and further, that there must be a period during fetal life in which immunological tolerance to foreign antigens can be acquired. He tested the idea directly by inoculating mouse fetuses with genetically dissimilar cells, then transplanting tissue from the donor. This celebrated experiment confirmed the hypothesis and laid the foundation for the sub-discipline of immunological tolerance to antigens.[26]

Medawar went on to contribute significantly to the science of transplantation, immune tolerance, cancer immunology, and senescence and ageing. He also had much to say about pregnancy, fetal cells and antigens, and their similarity to cancer cells. In both his musings and his science, he launched the field of reproductive immunology, wondering, after having discovered that mature individuals could not sustain a graft without prior actively acquired tolerance, how, during pregnancy, the mother can tolerate the fetus for a full nine months?[1] Medawar proposed three possibilities: the fetus could be sequestered from the maternal immune system; the mother could

FIGURE 3 Verger's dream: Saints Cosmas and Damian performing a miraculous cure by transplantation of a leg. Oil on wood painting attributed to the Master of Los Balbases, ca. 1495. Wellcome Collection; Public Domain

be immunologically suppressed; or the fetus could be antigenically immature—immunologically invisible to the mother.

All three mechanisms Medawar proposed to keep the fetus safe from the maternal immune system turn out to be true, but only partially. To understand how the fetus and maternal immune system, it remains useful to keep in mind the mechanisms of transplant rejection, and how the fetal-placental unit differs. In the following section, we compare the basic mechanisms of homograft transplantation and failure, to implantation, and placentation, with a focus on antigens that mediate graft failure, and how these same antigens coming from the fetus are tolerated by the maternal immune system in pregnancy.

3 | SELF, NON-SELF, AND DANGER IN TRANSPLANTATION AND PREGNANCY

As the field of immunology grew, the Self/Non-Self model of immunology dominated our understanding into the 1990's. We now know this model to be fundamentally flawed, as it asserts that the immune system is indiscriminately triggered by any non-self entity. Janeway explained that the immune system distinguishes between "non-infectious self" and "infectious non-self" by recognizing conserved pathogen-associated molecular patterns (PAMPS) borne by pathogens.[27] Matzinger expounded on this idea, pointing out that immune theory must also account for survival of both "harmful self" (e.g., cancer), and "harmless non-self" (e.g., commensal bacteria, the fetus).[28] Matzinger's Danger theory states that the immune system should, at least leave certain foreigners, such as the fetus, alone; at best, it should promote the establishment and growth of self, the fetus, and transplants.[29]

3.1 | Early processes in transplantation: inflammation

How does transplantation and pregnancy fit into these fundamental tenets of immunology? Both pregnancy and transplantation involve

the entry of a foreigner past a first line of defense, for example, implantation of the embryo beneath the uterine epithelium. In transplantation, tissue damage is caused iatrogenically, unavoidably, and often extensively. Upon death or brain death of donors, organs hastily release an abundance of danger-associated molecular patterns (DAMPs), such as high-mobility group box 1, heat shock proteins, nucleic acids, extracellular adenosine triphosphate, uric acid, and reactive oxygen species. DAMPs ligate pattern recognition receptors (PRR)—the same receptors that recognize PAMPs—on epithelial, stromal, and resident immune cells. Ischemia and reperfusion of the organ further exacerbate DAMP release.[30] Extensive PRR ligation quickly triggers inflammation and, importantly, maturation of antigen presenting cells in the host, as well as passenger antigen presenting cells in the donated tissue.

In the absence of pathogens and foreign antigens, the DAMP-initiated, "sterile" inflammatory response normally resolves with wound repair; exceptions may occur in cases of autoimmune disease. However, as explained below, various types of donor antigens, including blood group antigens, MHC, and minor histocompatibility antigens, dictate the ensuing adaptive response, and ultimately the outcome, of transplantation.

3.2 | Inflammatory processes and introduction of antigens in pregnancy

Pregnancy in women—and all animals with invasive (hemochorial or endotheliochorial) placentation—unavoidably involves introduction of foreign material (sperm, seminal fluid), a barrier breach (implantation into uterine epithelium), and expression of foreign, paternally-inherited antigens. In addition, the fetus and placenta express tissue-specific antigens that the mature, gravid female lacks. From the start, however, the maternal immune reaction to fetal antigens differs fundamentally from that of transplanted organs.

Sperm lack MHC molecules and therefore cannot serve as a direct target of T cells. However, sperm cells do possess highly cell-specific antigens that females mostly lack. Further, other cellular and soluble seminal fluid constituents contain both MHC and minor histocompatibility antigens.[31,32] In men, vasectomy, trauma, or infection are associated with tissue damage, breach of the blood testes barrier, production of DAMPs, and leakage of antigenic sperm proteins into the circulation. Despite these antigens belonging to self, they are perceived as foreign, and anti-sperm antibodies develop and can trigger autoimmune-mediated infertility.[33]

Scientists have long held that sperm-specific antigens are not only responsible for inciting anti-sperm antibodies in males, but also have the potential to do so in females. Anti-sperm antibody responses in women are associated with infertility, but this occurs in only rarely.[34] On the other hand, insemination represents the initial introduction of paternal (sperm) antigens into the female genital tract, and there produces a strong, but physiological, inflammatory response. This response likely serves multiple functions: to protect against incidental pathogens transferred during coitus, to clear excess sperm that does not reach the oviduct, and to prime the adaptive immune system for tolerance.

Directional motility allows sperm to vacate the vaginal canal quickly to avoid the pathogen-averse acidic environment, and possibly also to avoid prolonged opportunity for an anti-sperm immune response to develop.[35] Sperm reaching the uterus enter uterine glands where they rapidly recruit inflammatory cells and induce production of cytokines and prostaglandins. This reaction of endometrial tissue to sperm and seminal fluid is conserved across species,[36] attesting to its importance. Interestingly, sperm and/or seminal fluid components co-opt the same pattern recognition receptors used by DAMPs and PAMPs to signal danger, including TLR2 and TLR4.[37–40] Expression of these receptors may be regulated by ovarian steroids, supporting a physiological role for inflammation-induced insemination. Thus, the signals for activating these receptors arise not from tissue damage during coitus, but intrinsically from semen. Ultimately, excess sperm are phagocytosed neutrophils.[37]

Studies in mice and women also show that sperm and seminal fluid also prompts an adaptive immune response, with influx of macrophages, dendritic cells, and effector (CD45RO+) CD8+ T cells.[41] This reaction, which is likely delayed relative to the rapidly induced innate response, may establish incipient events of antigen-specific immune tolerance to gestational antigens.[42] Antigens in the seminal fluid can be presented by dendritic cells,[43] priming maternal T cells to differentiate into regulatory T cells (TReg), which are indispensable for tolerance to embryonic antigens.[44,45] Seminal fluid helps mediate these events, and although it is not required for successful pregnancy, data in women suggest that in vitro fertilization outcome is improved with exposure to seminal fluid around the time of embryo transfer.[46] Thus, despite the foreign antigens and inflammatory responses introduced during mating, the immunological events following coitus appear to promote tolerance, not immunization, to sperm-associated antigens.

3.3 | Implantation

Several days after fertilization, the semi-allogeneic blastocyst positions itself in uterus for implantation. Trophoblast cells of the trophectoderm attach to and penetrate the epithelium, allowing the embryo to deeply invade the endometrium. This process generates prostaglandins, leukotrienes, histamines, cytokines, and chemokines, and vascular leakage—in other words, more inflammation.[47–49] This inflammatory reaction is beneficial and possibly required for implantation: use of anti-inflammatory medications in women is associated with increased risk of miscarriage.[50,51] Conversely, mild endometrial wounding promotes implantation in women undergoing assisted reproduction technologies.[52]

The endometrium responds to inflammation promoted by the implanting embryo in a highly distinct manner. Together with hormonal priming of the uterus, the implanting embryo triggers endometrial decidualization, in which maternal macrophages and dendritic cells immune cells play a compulsory role. Macrophages, which comprise more

than 20% of cells at the implantation site,[53] likely serve to rapidly clear and prevent excessive release of danger signals from maternal cells that die in the process.[54,55] Further, macrophages of the M2 phenotype may promote decidualization through regulation of the Wnt/β-catenin pathway.[56] Dendritic cells are also required for implantation, possibly by promoting angiogenesis through sFlt-1 and TGF-β production.[57]

Finally, the inflammatory process of decidualization negatively feeds back by ultimately shutting down implantation-associated inflammation, thereafter driving an anti-inflammatory profile.[58] This is critical, as excessive inflammation damages the embryo and causes implantation failure.[59] This anti-inflammatory state appears to dominate pregnancy following the implantation period until partrurition.[60]

4 | ANTIGENS IN TRANSPLANTATION AND PREGNANCY

Expression of fetus-derived antigens drives our interest in the question of the fetal semi-allograft; after all, only in the absence of foreign antigen are grafts accepted without immune suppression. The types of antigens carried by transplanted organs and cells determines the nature of the immune response, which can be mediated by antibodies or cytotoxic T cells, with assistance from helper T cells necessary for both. In pregnancy, the maternal immune system also responds via antibodies and T cells specific for fetal antigens, but in healthy pregnancy, with tolerizing rather than immunizing outcomes. As in transplantation, fetal-placental antigens that alert the maternal immune system include blood group antigens, MHC antigens, and minor histocompatibility antigens. In addition, new lines of evidence suggest the importance of maternal tolerance to "former self" antigens—antigens whose expression is restricted to the fetus and placenta, that mother herself expressed through her own former existence as a fetus (Figure 4).

4.1 | Blood group antigens

Hemolytic disease of the newborn (HDN) is perhaps the only definitive instance in which a fetal antigen can elicit a strong, dangerous maternal immune response that culminates in "fetal rejection." Encoded by the *RHD* gene, Rh is critical to membrane structure in red blood cells, and because it is polymorphic, antigenic, and prominently expressed on fetal erythrocytes, is of considerable concern. In transplantation, RhD-positive donor organs can cause delayed hemolysis, and in pregnancy, HDN—particularly in a second, but possibly in a first pregnancy.

In 1941, scientists first documented that erythroblastosis fetalis or HDN resulted from isoimmunization of RhD-negative mothers by RhD-positive fetuses, and subsequent passage of anti-Rh antibodies across the placenta. These findings were facilitated by Erlich's work, which established the role of antibodies in immune reactions.[61] Interestingly, this cause of HDN was realized nearly two decades before the function of T cells was known and Medawar introduced the immunological paradox of pregnancy.[62] Fortunately, as soon as the early 1960's, clinical treatment that essentially prevents the disease became available; Rh-associated HDN remains, however, problematic in underdeveloped countries.[63,64]

Unlike Rh antibodies, which occur only after transfusion or pregnancy, anti-ABO group antibodies form at an early age in

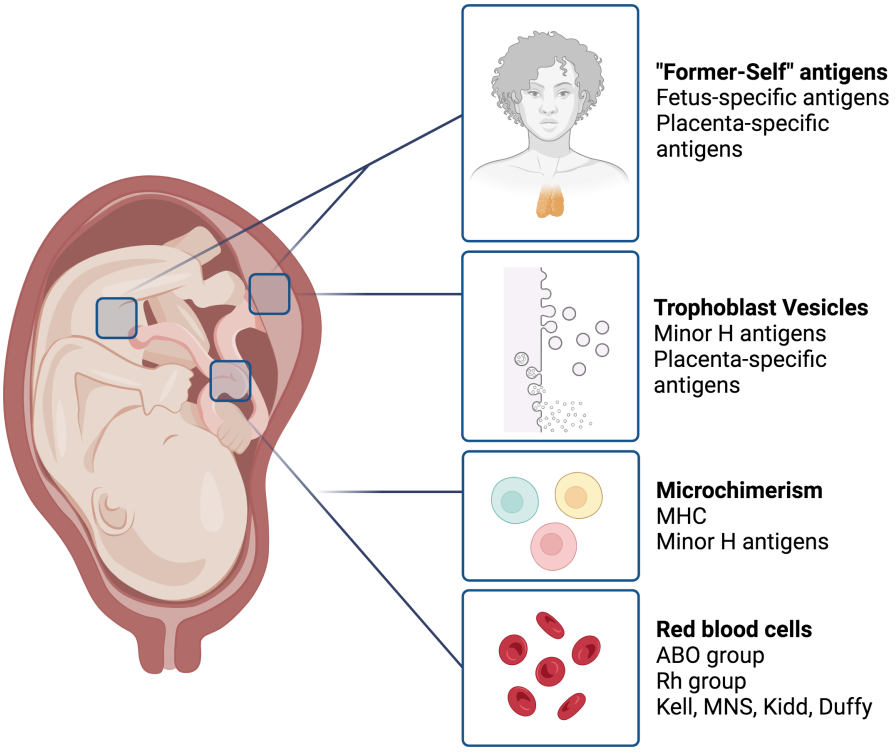

FIGURE 4 Fetal antigens include paternally-inherited MHC and minor histocompatibility (H) antigens, blood group antigens, and fetus/placenta-specific antigens that may be recognized as "former self" by the maternal immune system. These antigens access maternal blood and tissues through fetal microchimerism, placental shedding, and intermixing of maternal and fetal blood at childbirth

response widespread antigens in the environment similar to AB antigens. In transplantation, anti-AB antibodies in incompatible ABO individuals trigger immediate and dangerous hyperacute rejection. Because these antibodies are IgM, they do not cross the placenta from mother to fetus. However, exposure to A or B antigens through transfusion fuels IgG production, which does cross the placenta and can cause mild HDN. This type of HDN is in general not risky for several reasons. First, AB-mismatched transfusions and transplants are entirely preventable. Second, fetal red blood cells express lower amounts of surface AB than adult red blood cells,[65] limiting the number of antibodies that bind. Finally, the fetus expresses A/B antigens more widely,[66] effectively diluting the antibody targets.

While the blood group antigens MNS, Kidd, and Duffy rarely cause HDN,[66] Kell antigens serve as the third most common cause of blood group antigen-associated newborn anemia.[67] Like Rh antibodies, anti-Kell IgG antibodies are associated with prior transfusion and parity, and can cross the placenta.[68–70] Because Kell is expressed early on in erythropoiesis, anti-Kell antibodies do not cause hemolysis but rather suppress growth of fetal erythroid precursors.[71,72] Relative incidence of this complication has risen since treatment for Rh incompatibility became available; fortunately, it remains rare.[73]

4.2 | MHC antigens

The highly polymorphic MHC class I and class II molecules are a substantial barrier to successful transplantation. Alloreactive T cells (those that recognize non-self MHC) occur in individuals at very high rates—up 7% of all T cells—due to degeneracy and/or polyspecificity of T cell receptors for peptide–MHC complexes.[74,75] Because of this, failure to match donor and recipient MHC causes acute rejection of transplanted cells or tissues over days to weeks. In humans, clinicians attempt to match six MHC molecules: the class I molecules HLA-A, -B, and -C; and the class II molecules HLA-DP, -DQ, and -DR. Matching for all six antigens presents a challenge, but the relatively low number of antigens makes it feasible.

At first glance, paternally inherited MHC might seem problematic to pregnancy, particularly as the placenta is awash with maternal blood and lymphocytes for six or more months of pregnancy. JJ Van Rood first reported paternal MHC-reactive antibodies in maternal serum in 1958,[76] and it is now known that as many as 30–40% of women develop antibodies to paternally inherited MHC. This proportion increases with parity and depends on paternal and maternal MHC haplotype.[77,78] Further, cytotoxic T cells against paternal MHC also arise during pregnancy, and can persist for years.[79]

Display of fetal MHC molecules in the placenta was the among earliest questions to arise in reproductive immunology after their discovery and Medawar's findings. The chorion functions as the placental interface between maternal and fetal tissues, and consists of an unbroken outer shell of trophoblast cells and underlying mesoderm.[80] Thus, Medawar's fetal sequestration hypothesis is partially true: these layers establish an immunological barrier in two respects. First, potentially alloreactive fetal class I and class II MHC molecules reside entirely behind the trophoblast barrier. Second, trophoblast cells are equipped with immunosuppressive mechanisms: surface-associated and secreted immunomodulatory mediators.

Faulk and others recognized early on that the syncytiotrophoblast, the layer of trophoblast that is bathed in maternal blood, lacks class I and class II MHC, thereby suggesting a mechanism by which the placenta escapes maternal immunosurveillance.[81–83] Because trophoblast cells (epigenetically)[84–87] repress expression and induction of polymorphic class I and class II MHC molecules, these cells can serve as neither a source of HLA antigens nor a target of maternal anti-HLA responses in normal pregnancy. MHC repression in trophoblast cells is widely believed to be critical for immunological evasion. Surprisingly, two studies contradict this idea: in mice, targeted expression of paternal MHC in the placenta failed to affect fetal viability, despite inciting maternal alloreactivity.[88,89]

While syncytiotrophoblast in the human placenta lacks MHC, extravillous trophoblast cells express certain MHC molecules that modulate activity of maternal immune cells for the benefit of fetal survival. Expression, regulation, and function of the unique trophoblast MHC has been extensively reviewed,[90–92] and can be summarized as follows:

- Extravillous trophoblast cells express non-polymorphic class Ib molecules, HLA-E, -F, and -G, and the polymorphic class Ia molecule, HLA-C.
- Each of the trophoblast-specific HLA molecules serve as ligands for receptors on uterine NK cells, and can inhibit their cytotoxic function.
- Trophoblast HLAs and their alternatively spliced isoforms may also inhibit T-cell proliferation and maturation of dendritic cells.[93,94]
- Trophoblast HLAs also stimulate uterine NK cell growth factors that promote spiral artery remodeling, which is critical for maternal vascular support of the growing placenta and fetus.[95]
- Imbalanced expression and genetic polymorphisms of class I and class II MHC expression by trophoblast cells, and their receptors by uterine leukocytes, have been implicated in pregnancy complications in women.[96–102]

4.3 | Minor histocompatibility antigens

A third hurdle to successful transplantation involves differences in minor histocompatibility (H) antigens between donor and recipient. Minor H antigens, which mediate chronic graft rejection, are peptides derived from normal self proteins that arise because of non-synonymous genetic polymorphisms between individuals. If these polymorphisms result in peptides that can be presented by host class

I and/or class II MHC molecules, cytotoxic and helper T cells can respond—particularly if PAMPS or DAMP danger signals are present.

In hematopoietic stem cell transplantation, recipients undergo conditioning radiation and/or chemotherapy, which deplete host hematopoietic cells. This reduces incidence of graft rejection and creates a niche for the donor cells. However, donor lymphocytes can still recognize host minor H antigens, which poses a significant risk for graft-versus-host disease. Although immune reactions to minor antigens are weaker and slower than alloresponses against MHC, they often necessitate long-term immunosuppression in recipients.

The "male" antigens encoded on the Y chromosome are classic examples of minor H antigens, and cause rejection of male to female grafts in an otherwise matched transplantation scenario. However, most minor antigens are autosomally encoded: there are more than 100 known minor antigens, and likely hundreds or even thousands yet undiscovered[103]—far too many to match in the clinic.

Minor H antigens are expressed ubiquitously, including in the placenta.[104] Unlike MHC, minor antigens are abundantly expressed in the human placenta, including in the syncytiotrophoblast and extravillous trophoblast. Studies in mice revealed that both class I- and class II-restricted minor H antigens expressed by the fetus, including male antigens, can escape the into the maternal circulation and prime maternal T cells.[105,106] This occurs through cross-presentation of antigens that escape into the maternal circulation by maternal antigen presenting cells,[107] in much the same way donor antigens are cross-presented by host antigen presenting cells in transplantation. These studies have been corroborated in women; such as maternal anti-MHC-specific T cells, minor H antigen-specific T cells can persist as memory cells in vivo for years following pregnancy.[108–111]

4.4 | How do fetal antigens access the maternal immune system?

The hemochorial arrangement of the human (and model rodent) placenta facilitates antigen access to the maternal immune system, particularly when maternal blood flow to the placenta is established. Antigens gain access to maternal antigen presenting cells in lymphoid organs as they are released from the placenta into the maternal circulation. There are at least three mechanisms by which fetal antigens access the maternal lymphoid system: by direct expression and release from trophoblast, through release via extracellular vesicles, and via fetal microchimerism. A fourth possibility exists and warrants further exploration: through genetic alteration of maternal cells to express fetally-derived genes.

The syncytiotrophoblast, which is inundated with maternal blood for two-thirds of pregnancy, provides an exceptionally large surface area[112] from which fetal antigens are expressed and can escape directly into maternal circulation. This cell layer also releases large quantities of extracellular vesicles that carry minor antigens together with known modulators of maternal immune cells such as PDL1, FasL, and TRAIL.[104,113–117] These modulators, whether associated with trophoblast cells or the extracellular vesicles they release, likely modulate maternal immunoreactivity toward the fetus, and theoretically have the potential to reach any vascularized organ in the mother.

Although in vivo information remains sparse on how placental vesicles modulate the maternal immune system, they do access maternal lung macrophages, which can serve as antigen presenting cells.[118] Surprisingly, vesicles seem to access lymphoid organs only rarely.[118,119] Since fetal antigens are presented to and detected by T cells within lymphoid organs, it is possible that free, rather than vesicle-associated, antigens are important in priming maternal T cells.[120]

Fetal cells also actively traffic into and lodge within the mother during pregnancy, and persist there for many years—even decades.[121] Even as early as the first trimester, microchimeric fetal cells can transfer into maternal blood across all of pregnancy. Fetal microchimerism is often cited to provide fetal antigen that elicits maternal T cell and antibody responses.[111,122,123] It seems likely that this is true, particularly in the case of alerting maternal immune cells to paternally-inherited fetal MHC,[124] which the trophoblast lacks.

Another possible source of fetal antigen arises from extracellular vesicles that carry fetal genetic material. Lotvall et al.[125] showed that exosomes can transfer and express mRNA from donor cells to targets via exosomes. Further, studies using model proteins and reporters demonstrated that vesicles could transfer mRNA between oligodendrocytes and neurons[126]; between immune cells and Purkinje neurons[127]; between tumor and host cells;[128,129] and between individual tumor cells.[129] In these studies, exosomes from Cre-expressing cells carry Cre mRNA into reporter target cells, which then translated the message into functional protein. As a result, Cre recombinase induced reporter gene expression. Placental extracellular vesicles from Cre-expressing fetuses similarly induced genetic recombination in dendritic cells in vitro, revealing horizontal genetic transfer and expression of functional fetal protein in target cells.[118] Thus, placental vesicles could mediate exchange of functional genetic material between the mother and fetus, causing expression of fetal proteins in maternal cells.

5 | "FORMER MATERNAL SELF": TISSUE-SPECIFIC FETAL-PLACENTAL ANTIGENS

5.1 | A paradigm shift in our understanding of immune tolerance

The prevailing view of immune tolerance in pregnancy has been that peripheral mechanisms dominate, wherein mature T cells encounter paternal and paternally-inherited fetal antigens in lymphoid tissues and the reproductive tract as they are introduced or expressed.[130] Virtually all focus has been on paternally-inherited fetal antigens—those to which the mother is exposed for the first time—including MHC, minor antigens, and blood group antigens. However, a key principle in immunology is that tolerance to tissue-specific antigens is indispensable: without self-tolerance, lymphocytes attack

self-tissues, shutting down organ function as a result of devastating autoimmune disease.

Prior to the early 2000's, immunological dogma stated that tolerance to tissue-specific antigens is established by peripheral tolerance mechanisms. Many immunologists believed that central tolerance, which occurs during T-cell development in the thymus and requires antigen expression therein, directs tolerance only to ubiquitous self-antigens. This opinion presumed that tissue-specific antigens were unlikely to be expressed in the thymus.

Around the turn of the century, several discoveries changed this perception dramatically. First, early studies of targeted genes and proteins, and later global RNA expression strategies, revealed that medullary thymic epithelial cells, which were already known to mediate negative selection of self-reactive T cells, promiscuously express thousands of antigens otherwise expressed in only a few other tissues.[131–133] Second, genetic mapping studies revealed that mutations in the *AIRE* gene (*a*uto*i*mmune *re*gulator) are solely responsible for causing autoimmune polyglandular syndrome type 1 (APS-1) in humans, a disease in which patients suffer hypoparathyroidism, adrenal insufficiency, and/or chronic mucocutaneous candidiasis.[134,135] Third, targeted deletion of *AIRE* in mice mimicked APS-1, and showed that as a transcription factor, AIRE regulates expression of tissue-specific antigens in medullary thymic epithelial cells (mTEC).[136] In fact, genes expressed in medullary thymic epithelial cells represent nearly every organ system in the body.[132,133]

AIRE induces expression of tissue-specific genes in mTEC by targeting transcriptionally repressed genes.[137,138] These cells then process and present them directly to developing T cells; alternatively, local dendritic cells may phagocytose mTEC-expressed antigens and cross-present them to the T cells.[139] These mechanisms promote deletion of autoreactive T cells[140,141] and production of antigen-specific regulatory T cells.[142–144] Altogether, the discovery of promiscuous gene expression by mTEC, AIRE, and the mechanisms by which they induces T-cell tolerance resulted in a paradigm shift in our understanding of how the immune system tolerates self.

5.2 | Is there a role for AIRE in maternal tolerance to fetal antigens?

More than 60% of women suffering from APS-1 are affected by primary infertility or fetal loss.[145] Further, representation and regulation by AIRE in thymic medullary epithelial cells includes fetus and placenta-specific antigens (Petroff, Grzesiak & Ahn, unpublished).[131–133,146] The ovary and placenta are likely primary targets of autoimmunity in women with APS-1, as evidenced by the presence of anti-gonadal and anti-placental antibodies.[147–149] Studies using AIRE-deficient mice have also revealed profound female infertility or subfertility. These mice undergo age-dependent autoimmune-mediated depletion of ovarian follicular reserves[136,147,150] Prior to follicular loss, young females exhibit peri-implantation loss, characterized by small implantation sites that disappear by mid-gestation.[151] Mice in which AIRE was eliminated just prior to pregnancy also experienced subfertility; this study further suggested that extrathymic AIRE-expressing cells mediates tolerance to fetal antigens.[152] Finally, embryonic grafts transplanted into AIRE-deficient mice become surrounded by lymphocytes, suggesting that these mice fail to tolerate embryonic tissue and/or placental tissue (Warren and Petroff, unpublished).

Thus, the discovery of AIRE and its regulation of tissue-specific antigens reminds us that fetal antigenicity may not be dictated solely by paternal origin, but that we must also consider maternal tolerance to fetus- and placenta-specific antigens independent of their parental origin. Paradoxically, these are antigens that were, at one time, expressed by the mother herself, in her own fetal/neonatal life. In a landmark study that confirmed a long-suspected notion, AIRE-mediated tolerance was shown to be established during neonatal life.[153] This raises the intriguing possibility that females establish tolerance to fetal-placental antigens that will reveal themselves again later in life, when pregnancy occurs and her own fetus begins to express them.

5.3 | Other evidence supporting maternal-fetal central tolerance.

Despite increasing evidence of regulation of fetal antigens by AIRE, we know little about mechanisms of central tolerance in pregnancy. Additional conspicuous links between pregnancy and the thymus exist. Some evidence suggests that regulatory T cells, which that are critical for maternal-fetal tolerance,[45,154–157] originate from the thymus and replicate in the periphery.[158] Under the influence of progesterone, the thymus involutes dramatically in pregnancy. In mice, more than 70% of thymic mass and 95% of cellularity disappears by the second half of pregnancy, rebounding only after lactation.[146,159] This may occur in all mammals, including women, which undergo altered thymic output during pregnancy.[160–163] The nuclear progesterone receptor is dramatically upregulated in cortical thymic epithelial cells and mediates thymic involution, likely by signaling changes in thymocyte trafficking and lymphopoiesis.[146,164,165] Further, prevention of thymic involution by cell-specific deletion of progesterone receptor may compromise allogeneic pregnancy,[146,165] suggesting a possible role in tolerance to paternally inherited antigens.

6 | FUTURE DIRECTIONS

A number of clinical syndromes, such as preterm birth and preeclampsia, involve high levels of inflammation and immune dysregulation. As indicated, blood group incompatibility, particularly of *RHD*, causes true “fetal allograft rejection”. However, less certainty is placed on whether other obstetrical syndromes are mediated by

antigen incompatibility; it is clear that co-evolution of the reproductive and immune systems required that fetuses avoid the expression of highly antigenic proteins.

A classical approach to determining the necessity of a given factor for a pathophysiological process is ablation/replacement, and this approach has been used extensively in reproductive immunology. One firm requirement for allogeneic pregnancy appears to be regulatory T (T_{reg})cells, which has been shown by a number of studies independently. Moreover, successive pregnancies cause antigen-specific T_{reg} cells to expand more rapidly and to a greater degree than in first pregnancies, suggesting that these cells, such as conventional T cells, possess memory[166] T cells also expand during pregnancy in women, and reduced expansion is associated with adverse pregnancy outcome.

While a number of studies have confirmed that T_{reg} cells are critical for pregnancy, little is known about their mechanism of action; important questions remain about which effector cells are controlled by pregnancy-induced T_{reg}, and whether antigen-specificity and/or cell–cell contact is required for their function during pregnancy. Indeed, there is a need for identifying the source of T_{reg}; it is possible that those specific for paternally-inherited fetal antigens differentiate peripherally, and those specific for "former-self" fetal antigens originate in the thymus. Further, the target specificity of conventional and regulatory T cells that react in pregnancy remains an important unanswered question.[167]

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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