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ORIGINAL RESEARCH

Pregnancy, a test case for immunology

Arjun Devanesan[1]

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Abstract
The traditional conception of immune function is that of a system which differentiates the organism's own tissues (the self) from any foreign invaders (nonself), preserving the former by rejecting the latter. In a mammalian pregnancy, however, the immunologically foreign foetus is accepted by the gestator's immune system. This presents a serious challenge to the self–nonself theory which has sometimes been called the immunological paradox of pregnancy. In this paper I shall defend the self–nonself theory against the critique posed by Thomas Pradeu. In addition I critically examine the alternative he proposes—the continuity theory. The main problem I will raise for any theory of immunology is that the phenomenon to be explained in pregnancy is the non-rejection of the foetus despite the triggering of the gestator's immune system. I will argue that contemporary modified versions of the self–nonself theory can rise to this challenge but that continuity theory cannot. As such, the immunology of pregnancy gives us a good reason to favour contemporary self–nonself theory over the continuity theory.

Keywords Pregnancy · Immunology · Continuity theory · Self–nonself · Pradeu

1 Introduction

The traditional conception of immune function is that of a system which differentiates the organism's own tissues (the self) from any foreign invaders (nonself), preserving the former by rejecting the later. In a mammalian pregnancy, however, the immunologically foreign foetus is accepted by the gestator's immune system. This presents a serious challenge to the self–nonself theory (sometimes called the immunological paradox of pregnancy). In his 2012 book "The Limits of the Self: Immunology and

✉ Arjun Devanesan
adevanesan@doctors.org.uk

[1] King's College London, London, UK

Biological Identity" Thomas Pradeu presents this and other problem cases in immunology to argue that the self–nonself theory should be abandoned in favour of his own theory, continuity theory.

In this paper I shall defend the self–nonself theory against Pradeu's continuity theory. I shall show that while the immunology of pregnancy is not paradoxical for continuity theory, there are a number of important immune behaviours in pregnancy which are inconsistent with it. I shall further explain how these findings are, however, consistent with contemporary versions of the self–nonself theory which also avoid the paradox.

In the first section of the paper I present some basic immunology background and Pradeu's (2012) critique of the self–nonself theory. He argues that the theory fails because of its claim that 'nonself' is a general criterion of immunogenicity—that is, a trigger for immune rejection. He correctly points to a number of cases where the immune system appears to rightly reject the self (in the case of normal tissue turnover) and accept the nonself (in the case of symbiotic bacteria and foetuses). Given these numerous counterexamples to the theory, Pradeu suggests that it be abandoned.

In the second section I then discuss Pradeu's (2012) continuity theory, which he proposes as a superior unifying account of immunology.[1] According to the continuity theory, the immune system does not operate on the basis of the distinction between the traditional conception of self and nonself and so there is no paradox of pregnancy to be solved. Continuity theory provides valuable insight into the functioning of the immune system and avoids an important paradox. This theory's claim to fame is that it proposes a general tigger for the immune system which accommodates pregnancy, normal tissue turnover and symbionts and which the self–nonself theory is unable to provide.

While Pradeu discusses tissue turnover and symbionts in detail, he deals only briefly with pregnancy. So, my third section presents a more detailed account of the immunology of pregnancy. In pregnancy the foetus displays a unique molecular signature which includes paternal antigens i.e. it is antigenically nonself. But instead of rejecting the foetus, the gestator's immune system seems to not only accept it but to actively facilitate its implantation and development. At first pass, this might seem to favour the continuity theory over the self–nonself theory, but my next two sections argue against this conclusion.

The fourth section shows how contemporary versions of the self–nonself theory can account for the behaviour of the uterine immune system during pregnancy, by appealing to the mechanisms by which local immune populations recognise and respond to foreign antigens. Local immune populations have special sensitivities for specific foreign antigens which enables the immune system to respond in tailored ways depending on which foreign antigen is presented and where. As to the reason why the antigens presented by the foetus provoke such an idiosyncratic response in the uterus, the natural response is to offer an evolutionary explanation for immune populations in certain anatomical locations developing special immune responses to particular foreign antigens (Parham & Moffett, 2013).

[1] Continuity theory is also outlined in Pradeu (2019) but I will be focusing on the original exposition.

Finally, in the fifth section I will argue that these findings present a substantial problem for the continuity theory. I argue that pregnancy is a counterexample to continuity theory because the immune system in the uterus is triggered by the foetus but tolerates it. One might avoid this counterexample by appealing to the special conditions in the uterus and the context sensitivity of the immune system but I will argue that this is ad hoc. I will show that continuity theory cannot provide a reason the uterine immune system behaves in such a unique way in response to foetal antigens and that the evolutionary approach offered above cannot be accommodated.

2 A short primer on immunology and some terminology

2.1 Terminology

There is no space here to set up the basic terminology of immunology but I will briefly review some important terms for the sake of clarity further on.[2]

Firstly, an antigen is simply a molecular pattern which triggers some response in an immune effector when the antigen binds to its receptor. The term should not presuppose that antigens always trigger destruction of the object on which they are found, or that they are always foreign. Here, foreign objects are those which do not exist as a result of cell division from the original single cell bottleneck i.e. zygote, of an organism. An immune effector is a cell with a receptor for some particular antigen and which, when triggered by the antigen binding to the receptor, responds in some particular way. There are a wide variety of potential responses to a immune trigger. These include rejection i.e. destruction of whatever carries the antigen, tolerance (inhibition of rejection), or tolerance with remodelling of the surrounding tissues.

Immune rejection is a term which is meant to refer to the occurrence of tissue destruction in response to an antigen-receptor interaction where this destruction is not part of a physiological process of remodelling. That is to say, it is the process whereby some tissue is removed from the local environment while leaving the surrounding tissues more or less intact.

Immune tolerance, on the other hand refers to the occurrence of tissue non-destruction in response to an antigen-receptor interaction.[3] It is worth noting that a number of responses fall under the term 'tolerance' because the immune system can respond in many ways other than 'rejection'. As we will see, at least two include tolerance where there is no response (or where rejection is inhibited), and tolerance where the response is remodelling.

Finally, it is worth distinguishing what are called the innate and acquired immune systems. The innate immune system is composed of cells and molecules which are able to fully respond to an antigen without prior exposure and this response is not

[2] I would recommend, Warrington et al., (2011), Marshall et al., (2018) or the first chapter of Pradeu's (2012) book, "The limits of the self: Immunology and biological individuality" for an excellent review.

[3] This is, admittedly, quite simplistic and there are various kinds of immune tolerance but this will be clarified later on. Immune tolerance is more than the absence of rejection as it is an actively regulated process. The tolerance of the foetus by the gestator is a particular and special kind, with important and unique regulatory mechanisms, as we will see.

significantly improved with successive exposures. As we shall see, the innate immune system is not purely destructive but also participates in remodelling. These cells display receptors to evolutionarily conserved antigenic patterns on bacterial cells and other pathogens. Examples of cells which are part of the innate system are Natural Killer (NK) cells, Macrophages and Dendritic cells.

The acquired immune system is so-called because it requires exposure to an antigen in order to fully develop mechanisms for destroying it. It is also the system classically associated with immune 'memory' and repeat exposure to an antigen strengthens the adaptive immune response.[4] As such, it is also called the adaptive immune system. In order to activate the adaptive immune system, an antigen must be displayed on a Major Histocompatibility Complex (MHC) molecule. These are molecules on the surfaces of cells with which other immune cells interact. MHC Class I molecules are expressed on all human cells and are also known as the Human Leukocyte Antigen (HLA) molecule. MHC molecules are inherited from both parents and each human (with the exception of monozygotic twins) displays a unique MHC molecule on its cells.

3 Pradeu's critique of the self–nonself theory

As Pradeu correctly points out in his book, the term 'self' in self–nonself theory has a number of different meanings (Pradeu, 2012). Two of these in particular give rise to the immune paradox of pregnancy. The 'self' can be defined as all those cells and tissues which bear the same MHC markers and are therefore descended from the same zygote. On this definition, the foetus is nonself and displays different MHC molecules from the gestator.

On another definition, the 'self' can be defined as that which does not trigger an immune response. According to classical self–nonself theory, the immune system is meant to accept only the self and reject the nonself, so anything accepted by the immune system must be the self (under normal circumstances). However, the foetus is tolerated by the immune system of the gestator and therefore 'self' according to this definition. Given that the foetus is both 'self' and 'nonself' according to the classical self–nonself theory (which accepts both of the above definitions of 'self'), the immunological tolerance of the foetus by the gestator is paradoxical.

In his third chapter, Pradeu then points to a number of other problem cases for the self–nonself theory. Firstly, "contrary to the assertions of the self–nonself theory, the immune system continuously reacts to endogenous antigens (i.e. to the 'self')" (Pradeu, 2012). One important case is the immune system's role in clearing up the organism's own dead cells. Certain immune cells called phagocytes engulf and dispose of dead cells which are 'self' insofar as they display self antigens, similar to how they react with and engulf foreign bacteria (nonself). Furthermore, while it is known that cancers evade immune rejection, the immune system's role includes cancer suppression. Most cases in which a cancerous cell spontaneously emerges as a result of mutation, the

[4] As Pradeu (2012) correctly points out, however, some kinds of repeated exposure induces tolerance rather than accentuating the adaptive immune response.

immune system recognises and destroys it despite it being, for all intents and purposes, 'self'. This is part of normal healthy tissue maintenance and it is well known that immune suppression increases the risk of developing cancer (see Gale & Opelz, 2012 for example). So the immune system does not normally always tolerate the self.

Pradeu then points to converse cases, where the immune system tolerates the non-self. Pregnancy is, of course, a classic example which we will explore further in this paper but Pradeu focuses on a number of different cases. One important example relates to bacteria in the human gut. These bacteria perform a number of critical roles in the gut such that it would not be able to properly function without them. Furthermore, the gut has a rich and highly active immune system which is constantly interacting with these foreign microorganisms and yet does not reject them. So the immune system does not always reject the nonself.

Given these findings, Pradeu suggest that the self–nonself theory is beyond rescue and suggests that it be abandoned. Instead he argues that we should adopt a new theory of immune function, one which he develops in his book.

4 Pradeu's continuity theory

Pradeu calls his radical alternative to the self–nonself theory the continuity theory. According to continuity theory, 'the triggering of an immune response is due to… a sudden appearance of antigenic patterns in the organism that differ strongly from those with which the immune system is continuously interacting' (Pradeu, 2012).

The most radical feature of this theory is that it rejects the distinction between native and foreign, according to the immune system. That is to say, it rejects the notion that the immune system makes a distinction between 'self' and 'nonself' on the grounds of genetics or histocompatibility. According to the continuity theorist, it would not matter to the immune system where new cells came from when they replace the old. What matters is that the process is gradual as is often the case in normal growth and tissue turnover.

According to Pradeu (2012), in which he proposed continuity theory, 'the continuity theory's central claim is that the triggering of an immune response is due to any strong discontinuity in the expression of antigenic patterns that the organism interacts with, which is to say the sudden appearance in the organism of antigenic patterns strongly different from those with which the immune system continuously (i.e., regularly) interacts'. This notion of 'discontinuity' is further specified in quantitative terms.

Firstly, the quantity of antigens presented to immune cells determines whether they will be provoked. 'In most cases very small quantities of antigen will not provoke an immune response; if it does, this is very quickly interrupted' (ibid, 2012). Secondly, the rate of change is important. If an antigen appears gradually it will not provoke a response to surrounding immune cells. 'Just as the quantities of antigen play a role in triggering an immune response, so too does the speed at which the antigen appears' (ibid, 2012). Thirdly there is the aspect of the molecular morphology of antigens which Pradeu calls the 'degree of molecular difference'. If a new and distinct antigen appears on the scene, this will trigger an immune response only if the degree of molecular difference is sufficient. Fourthly, an antigen may be presented for prolonged

periods and so induce immune tolerance i.e. 'If an antigen is continuously present for a relatively long period of time in the organism and regularly interacts with its immune receptors, it can lead to tolerance instead of an immune response' (ibid, 2012).

Finally, Pradeu (2012) states that 'antigenic continuities are local; that is, the place in the organism where reactions between immune receptors and ligands are produced is an important element in determining if there will be an immune response of rejection.' This is in line with other authors on the topic who demonstrate the context sensitivity of immune responses. So, for example, Pradeu (2012) points out that certain bacteria in your gut may not trigger an immune response but if they make their way into your blood stream or into your lungs, they will trigger a response and be eliminated.

Continuity theory seems to dispel some of the mystery surrounding maternal tolerance of the foetus. After all, the fact that the foetus is antigenically foreign is not a problem here. Pradeu does not especially make the argument that continuity theory solves the immunological paradox of pregnancy but by dispensing with the notions of self and nonself, on which the paradox is based, it certainly seems to dissolve it. Furthermore, Pradeu explains the tolerance of the foetus by the gestator in terms of "induction of continuity": "Immune cells interact with these… [foetal] antigens, which are initially in small quantities and encountered progressively" (Pradeu, 2012).

Similarly, the reason provided for the tolerance of bacterial symbionts in the gut is because they are presented gradually after birth. As he argues, "exogenous entities, such as bacteria, which are introduced in small quantities into the organism and with which the immune system interact repeatedly and progressively, are tolerated. This is typically the case with the bacterial colonisation of the host that occurs in the intestine immediately after birth" (Pradeu, 2012).

Importantly, Pradeu claims that his theory unifies under a single organising principle, all immune phenomena seen in all living things. He claims, for example, that "the main arguments in favour of [his] theory: it is a highly inclusive, unifying theory, meaning that it gathers under a unique explanation many different immune mechanisms, occurring in a number of different species". There are a number of ways in which scientific theories unify phenomena, and in this case Pradeu suggests that his theory unifies immune phenomena by explaining them all with a simple criterion for the triggering of the immune system involving continuity and discontinuity.

As such, it appears that the immunology of pregnancy should lead us to favour continuity theory over its rival, self–nonself theory. However, in the following sections I will argue against this conclusion. First, in the next section I will provide a detailed account of the immunology of pregnancy in which I show that the immune system is triggered by the foetus but instead of rejecting it, dramatically remodels the uterine lining in order to facilitate its implantation and growth. I then show that contemporary self nonself theories can accommodate these findings but that continuity theory cannot.

5 A molecular account of immune interactions in pregnancy

The conventional wisdom of the classical self–nonself theory predicts that the mother will reject the foetus. Transplants from one body to another are usually rejected by the recipient, so "how does the pregnant mother contrive to nourish within itself, for

many weeks or months, a foetus that is an antigenically foreign body?" (Medawar, 1953). This led many authors to view the relationship between the mother and foetus as essentially anatgonistic.

This kind of thinking is partly corroborated by the fact that the interface between the placenta and the maternal uterine decidua[5] is rich with immune cells[6] and the presence of inflammation was thought to be synonymous with some kind of process of tissue rejection. It was thought that the maternal immune system is in constant conflict with the paternal antigens present on foetal cells and the success of pregnancy depends on the foetus employing mechanisms to evade the maternal immune response. The fact that the foetus is not habitually rejected has been attributed to a number of possible mechanisms including total systemic immunosuppression of the mother or local immunosuppression at the placental-decidual interface (Howes, 2007a).

Spontaneous miscarriage or pre-term labour were then naturally thought to occur when the foetus fails to suppress or evade the maternal immune response. This has led to a number of immune therapies for recurrent miscarriage which have almost universally failed (Moffett, 2021). The idea that immunosuppression should improve the chances of successful pregnancy is derived from the idea that immune suppression improves the chances of a foreign transplant surviving in a new host. This idea, when applied in pregnancy, has been proven wrong in several recent studies (Mor et al., 2017). Hanna et al (2006) also demonstrated that decidual NK cells are needed for foetal trophoblast cells to invade the decidua, and that rather than being suppressed by the trophoblast,[7] decidual NK cells facilitate trophoblast invasion and recruit blood vessels (angiogenesis) to aid in formation of the placenta. Similarly, dendritic cells are needed for decidual development and formation of the kind of endometrial vascular network needed to sustain the developing foetus (Tagliani & Erlebacher, 2011).

Moira Howes (2007a) called the antagonistic relationship hypothesised by traditional immunology the foreign foetus model: "Underlying the foreign fetus model is that idea that maternal–fetal relations are essentially antagonistic and so must be managed through barriers, evasion, and suppression". A typical example of this kind of model is expressed by David Haig (1993) where he argues that natural selection should lead to a conflict between the foetus and the mother given that they have conflicting interests and fitness. According to this view, the foetus strives to drain more nutrients from the mother in order to maximise its chances of surviving, evolving a more efficient and invasive placenta, and the mother strives to prevent this using barriers and other forms of suppression.

This kind of thinking is immediately met with the immunological puzzle that pregnancy is less likely to be viable when partners have similar MHCs compared to when their MHCs are very different. Offspring inherit their MHC from both parents such that they end up with a combination of alleles and so display a unique set of MHCs.

[5] The decidua is the layer of the uterus which forms under the influence of progesterone during pregnancy and is shed during childbirth, hence the meaning of 'decidua' is 'falling off'. It forms the part of the uterus which is in contact with the placenta.

[6] 70% of cells in the uterine decidua are Natural Killer Cells (NK), with macrophages, Dendritic cells and T-Cells comprising the rest.

[7] The trophoblast is the outer part of the early foetus (blastocyst) which interacts with the uterine wall and forms a large part of the placenta.

Partners with similar MHCs should produce a foetus with an MHC morphology more similar to the gestator's i.e. the foetus will more closely immunologically resemble the gestator, and is therefore less likely to trigger the gestator's immune system. Yet this is detrimental to foetal implantation (Beydoun & Saftlas, 2005; Chaouat, 1993; Creus et al., 1998; Vomstein et al., 2021).[8]

The current thinking is that pregnancy actually has three immune phases (Mor et al., 2017). The first phase, in which implantation occurs, is characterised by a robust inflammatory response leading to breakdown and remodelling of the uterine layer of the uterus at the site of implantation in order to facilitate invasion of the trophoblast. This inflammatory milieu promotes the growth of new blood vessels at the site which will go on to form the maternal blood supply for the developing placenta. However, it is worth stressing that this inflammatory response in which the immune system destroys maternal tissue does not destroy the antigenically foreign foetus.

So, the emerging evidence suggests that the activation of the maternal immune system is *necessary* for foetal implantation and it is more likely to accept a foetus which is more antigenically different. This suggests that while it may be the case that 'nonself' antigens are not always triggers for immune *rejection*, and in fact the opposite is true in the case of pregnancy, recognition of the foetus as 'nonself'[9] is important for the triggering of the uterine immune system which in turn is important for a successful pregnancy. This indicates that the immune distinction between 'self' and 'nonself' based on histocompatibility antigens is an important explanation for the initial immune response which facilitates foetal implantation. It also shows that the phenomenon to be explained here is not simply the tolerance of the foetus but the tolerance of the foetus *despite triggering the gestator's immune system*.

The second phase is anti-inflammatory and occurs during the period of foetal growth and maturation. In this phase, a number of immune regulatory mechanisms are employed to reduce inflammation and promote active tolerance of the foetus. This stage of pregnancy shows us that 'immune tolerance' is not simply the absence of immune rejection. The interaction between the gestator's immune system and the foetus is radically different to that which occurs when its immune system interacts with tissues of the uterus during the normal menstrual cycle (Berbic & Fraser, 2013),[10] and include the effects of a number of specialised regulatory cells such as regulatory T Cells (TReg).

A large inflammatory response is needed to initiate the third stage which is labour and birth. In the case where an inflammatory response occurs secondary to an infection

[8] The data on the association between MHC (or HLA) sharing between partners and the risk of recurrent foetal loss is not consistent. However, in a metanalysis there appeared to be an modestly increased risk associated with HLA-A and HLA -DR sharing (Odds ratios 1.44 and 1.33). These studies only look at the association between HLA sharing and foetal loss but there are also associations with diseases of pregnancy like pre-eclampsia (see below) which further suggests that HLA sharing is detrimental to implantation overall, though it does not necessarily cause foetal loss.

[9] This is insofar as 'self' is defined as that which bears the same MHC molecule.

[10] I have not included the technical details of this difference but they are neatly summarised in Mor et al., (2017) for those interested.

in the second trimester of pregnancy, preterm labour and foetal loss may occur. A pro-inflammatory response is crucial for labour, however, and a number of these pathways have been shown to initiate and sustain labour until delivery (Mor et al., 2017).

All these mechanisms occur on the decidual side of the decidual-placental interface. Until recently, little attention was paid to foetal immune mechanisms. This was probably because the foetus was thought not to have a mature or functioning immune system until very late in its development. However, recent research has shown functioning immunity in even the earliest stages of foetal development (McGovern et al., 2017; Reyes & Golos, 2018). So it is becoming clear that the foetus has an immune system from very early on and that this immune system interacts with and, to some extent, regulates the maternal immune system at the site of placental attachment.

It is a well known fact that foetuses express paternal antigens which are recognised by maternal T-Cells and yet this does not trigger the maternal immune system's destructive capacities. This is the source of the so-called immunological paradox of pregnancy explained earlier i.e. "during pregnancy a semiallogeneic fetus survives despite the presence of maternal T cells specific for paternally inherited histocompatibility antigens" (Tafuri et al., 1995). Given what is known about the role of HLA molecules, some recent experimental evidence has focused on the role of trophoblast and placental HLA molecules in inducing maternal tolerance of the foetus.

The extravillous trophoblast (EVT) cells of the placenta extrude into the maternal blood supply and are therefore constantly interacting with the maternal immune system, not just the immune cells concentrated in the decidua but in the peripheral blood as well. Most cells in the body express a combination of the MHC markers HLA-A, HLA-B and HLA-C but EVT cells only express HLA-C and HLA-G (Xu et al., 2020). These molecules interact with decidual NK cells via their killer cell immunoglobulin like receptors (KIRs) and the degree and success of placentation is crucially mediated by a highly specific interaction between HLA-C molecules on EVTs and KIRs on decidual NK cells.[11]

Howes (2007a) is right to point out that the notion of the foetus as a 'foreign invader' is not supported by the experimental literature. While the foetus is clearly nonself insofar as it has distinct histocompatibility antigens from the gestator, and the more nonself the better it seems, it is also clearly not just tolerated but actively accepted by the gestator's immune system. We can see from examining immunity in pregnancy that the uterine immune cells distinguish between their own members, the cells of the uterus and those of the foetus on the basis of histocompatibility complexes i.e. they distinguish self from nonself. They are galvanised into action by the recognition of nonself foetal antigens but rather than rejecting the foetus, they then proceed to facilitate its implantation, growth and development. While this is clearly inconsistent with classical self–nonself theory, it is also inconsistent with continuity theory which states that the immune system is triggered by discontinuities and will reject the trigger. In the following sections I will examine the extent to which these theories are able to account for these findings and therefore accommodate the immunology of pregnancy.

[11] For example, a gestator homozygous for the KIR A haplotype, with a foetus that inherited paternal HLA-C2 is likely to have insufficient placental invasion and develop diseases of pregnancy like pre-eclampsia (Hilby et al., 2004).

6 Contemporary self–nonself theories in response to the paradox of pregnancy

It is now widely acknowledged that, until recently, a number of misconceptions about the function of the maternal immune system in pregnancy was driven by a theory of immunity derived from transplant medicine (Moffet, 2021; Mor et al., 2017). In this section I will outline the salient aspects of the theory and consider the problems that mammalian pregnancy poses for it. I will then distinguish aspects of the theory which are consistent with mammalian pregnancy and explanatorily useful, from those which are not. Ultimately, I will conclude that there are versions of the self–nonself theory that are consistent with the physiology of pregnancy and so we should not dismiss the self–nonself distinction.

While there are a number of different versions of the self–nonself theory in contemporary immunology literature (see Cohen, 1992 and Janeway, 1989 for example), the idea of an immune system was first developed as an explanation for how a human organism defends itself against infection and immunology first became a scientific discipline in the process of developing vaccines against infectious diseases. As such, the immune system has been thought of as a physiological system whose function is to defend the host from microbial invasion (Tauber, 2017).

The question then arises as to how the immune system identifies these organisms and distinguishes them from the tissues of the host. The notion that the function of the immune system is to differentiate 'self' from 'nonself' is usually associated with the work of Frank Burnet (1969). The basic idea is that the immune system is only triggered if it encounters substances which are foreign to the organism itself like bacteria or viruses and the immune system responds by destroying whatever activated it.

Another major piece of the self–nonself theory earned Dausset, Benacerraf and Snell the Nobel Prize in 1980. This was the discovery of an important molecular signature that the immune system recognises and which is uniquely expressed on *only* those cells which are descendants of the same single-cell bottleneck (a zygote). They therefore indicate shared ancestry and were an ideal candidate for a molecular signature of the 'self' (Dausset, 1981). In line with the self–nonself framework, these were called the major histocompatibility complex (MHC) or Human Leukocyte Antigens (HLA) in humans. These antigens form a complex which is unique to each organism, so much so that Dausset called them the organism's identity card.

If and when the immune system comes into contact with MHC molecules or other antigens which are nonself, self–nonself theory predicts that it will attack and destroy whatever is presenting them. While it has long been recognised that certain microbes, albeit nonself in nature, are not invariably rejected (like symbiotic microorganisms in the gut), transplants which display foreign histocompatibility antigens are never accepted by the immune system of the recipient. As such, the idea that markers of 'nonself' *always* trigger immune rejection comes mainly from experiments in transplant medicine where transplants which display foreign histocompatibility antigens are always rejected.

However, this leads to an obvious puzzle in pregnancy. As far as the behaviour of immune system is concerned, it seems like the foetus is being treated as part of the

maternal 'self' even though it expresses 'nonself' antigens. Now we could think that the immune system is making a mistake or the foetus is evading the maternal immune system like a parasite, but that is clearly absurd. The mother's immune system must accept the foetus under normal circumstances in order for reproduction to successfully occur. So at face value, we ought to accept that the immune system is doing the right thing and the foetus is in fact part of the maternal 'self' i.e. normal pregnancy is not pathological. This generates the traditional immunological paradox of pregnancy, the foetus is both 'self' and 'nonself' depending on how these are articulated i.e. it is nonself as defined by histocompatibility but self as defined by immune tolerance.

Contemporary self–nonself theories that emerge from consideration of these kinds of problem cases appear to have a core idea that the immune system distinguishes self from nonself in order to avoid autoimmune disease (pathological rejection of the self), protect the host from microbial invasion, but allows nonself in some special cases. For example, Janeway (1989) argues that "The most critical property of the immune system is its ability to discriminate self from nonself." However, he also argued that the immune system has the means to distinguish different types of 'nonself' and react according to whether they are infectious nonself or noninfectious nonself based on additional triggers.

One contemporary version of the self–nonself theory, responding to these experimental findings, has been called the pattern-recognition receptor (PRR) theory after the idea that the immune system recognises and responds to specific antigenic molecular patterns called pathogen associated molecular patterns (PAMPs) on bacteria and other infectious agents or damage associated molecular patterns (DAMPs) on damaged native tissue (Murphy et al., 2022; Li & Wu, 2021; Matzinger, 2007). What this theory does not presuppose is that there is a universal trigger for immune activation or rejection. Immune responses are, according to PRR theory, specific to particular antigen-receptor interactions.

Here, MHC molecules present one of many molecular patterns that the immune system recognises and responds to. In the case of the organism's own MHC pattern, its immune system recognises it but does not respond with rejection. In the case of foreign transplants, nonself MHC molecules are triggers for immune rejection. Given that the foetus presents foreign MHC molecules, it has been thought that the appropriate model to apply in this case is the transplant model which predicts the immunological rejection of the foetus (Moffett, 2021). This is clearly incongruous with the physiology of pregnancy.

However, if we examine a PRR theory like Janeway's, we might be led to a view of the immune system as a means by which the host regulates its interaction with its environment (see Tauber, 2017 for such a view). This is, of course, consistent with the idea of the immune system as a system which defends against infection. Microbes are rejected if they are harmful e.g. salmonella species, or are rejected if they are in a place in which they will cause harm e.g. the bloodstream. However, they may also be accepted if they are beneficial or conducive to the survival or flourishing of the host e.g. lactobacillus species in the gut.[12]

[12] One might wonder how the immune system acquired this capacity to discriminate harmful from benign or helpful bacteria and the simplest explanation is an evolutionary one. Associations with certain microbial

The recognition that immune responses are not just triggered by detection of 'nonself' but also by the detection of harm led Fuchs and Matzinger to develop the 'danger theory' of immunology (Matzinger, 1994). According to this theory, the function of the immune system is still to protect the host organism from harm and the immune system is sensitive to signals of 'danger' rather than signals which indicates a degree of 'foreignness'. It will therefore be activated against 'dangerous' self in the case of injury, and accept 'benign' nonself in the response to symbiotic bacteria.

Dreifus (1998) illustrates the theory nicely: "Imagine a community in which the police accept anyone they met during elementary school and kill any new migrant (sic). That's the Self/Nonself model. In the Danger Model, tourists and immigrants are accepted, until they start breaking windows. Only then do the police move to eliminate them. In fact, it doesn't matter if the window breaker is a foreigner or a member of the community. That kind of behaviour is considered unacceptable, and the destructive individual is removed.[13]" While Matzinger rejects the self–nonself theory in its classical form (Matzinger, 2007), there is nothing in danger theory which is inconsistent with the claim that the immune system *distinguishes* self from nonself. It simply claims that the immune system also distinguishes harmful from benign nonself and similarly, harmful (e.g. cancers) from benign self. This would be what Moira Howes (2007b) calls a three-signal theory.[14]

Immunologists have attempted to explain the immunology of pregnancy in various ways and pregnancy shows us that markers of 'nonself' are not always triggers for immune rejection. However, while nonself is not always a trigger for immune rejection, the immunology of pregnancy shows us that the immune system *does* distinguish self from nonself, insofar as 'self' is defined according to a certain MHC molecular pattern. It is just that the immune system is not always triggered in order to reject, sometimes it is triggered in order to accept, and the behaviour of the immune system depends on context.

Remember, I argued above that the paradox of pregnancy comes from accepting two meanings of 'self': that which bears the same MHC molecule and that which is tolerated by the immune system. Modern self–nonself theories accept the former but reject the later, thereby avoiding the paradox. The lesson to be learned from pregnancy is not that the self–nonself theory is incorrect per se but that the immune system may

Footnote 12 continued
species over evolutionary time has led to mechanisms which actively facilitate colonisation with some microbes but not others. These microbes facilitate a number of critical physiological processes in the human gut including the production of essential vitamins. In this way, it is thought that associations with certain microbes may have relaxed selective pressures on the host to obtain foods with these vitamins and facilitated dietary transitions, which enabled colonisation of new environments (Moeller & Sanders, 2020). The immune system, being the main way in which human hosts regulate their interaction with microbes, is thus thought to have evolved its receptor morphologies partly in response to the evolutionary and selection pressures (Mushegian & Medzhitov, 2001).

[13] This quote is a nice, succinct, illustration for danger theory. The analogy could, however, be seen as insensitive in the present day given its imagery of violence towards immigrants.

[14] The danger model seems to add a new immune signal "danger" to the previously standard two-signal self–nonself model. While Matzinger rejects the classical self–nonself model, the extent to which danger theory adds to rather than replaces the self–nonself model is an unsettled matter. See Howes (2007b) for more details.

accept 'nonself' in the ultimate service of the 'self' i.e. immune system sometimes accepts the nonself when it is benign or conducive to the flourishing of the self.[15]

The paradox only arises if we also accept that the immune system only accepts the self (which we have seen is, in fact, false). Instead, if we view the function of the immune system as preserving the self, and facilitating its flourishing, we should be happy to accept that this sometimes involves the immune system accepting nonself.

As I argued above, the reason the foetus is not rejected despite triggering the gestator's immune system has to do with the anatomical context i.e. the phenotype of immune cells in the uterus is such that they respond to foetal antigens by remodelling the uterine lining and facilitating implantation. This would not occur anywhere else in the body. While this is consistent with the PRR theory, we still need to know how the uterine immune cells develop their context sensitivity or how this sensitivity leads to their particular behaviour during pregnancy. This is the problem of understanding the special function of the immune system in the uterus i.e. the anatomical context.

One approach to this challenge is to examine the evolution of immune cell receptors. A number of studies looking at the evolution of MHC molecules and lymphocyte (like NK cell) receptors in simian primates helps explain their particular phenotypes and diversity across species. These studies also partly explain the special phenotypes of certain immune populations within species and how these phenotypes might explain specific immune behaviours and immune mediated diseases. For example, the interaction between gestator decidual NK receptors (KIRs) and foetal HLA-C is crucial to successful placental implantation. So, while immune receptors in general demonstrate remarkable plasticity, NK receptors in humans are thought to have co-evolved with MHC receptors and as a result, are well preserved across primates (Parham & Moffett, 2013).

In fact, there is mounting evidence that NK receptor haplotypes have evolved under selective pressures from reproduction. Certain combinations of receptors in the gestator's NK cells and HLAs in foetuses are associated with a less invasive placenta. In those cases, maternal blood pressure is raised by chemicals released by the placenta in response to insufficient blood supply. This results in a condition called pre-eclampsia which, if it progresses, can be fatal in gestators (and therefore foetuses as well) (Hiby et al., 2004). It can also cause low birth weight which decreases the fitness of the offspring. As such, you would expect this combination to be less frequent in populations than more favourable ones, and that is what is found. We see worldwide inverse correlations between specific HLA and NK receptors haplotype frequencies (Parham & Moffett, 2013). While there is no scope here for full exposition of the evidence for the co-evolution of specific immune receptors and their associated antigens it is clear that this approach can potentially explain the unique response of a gestator's immune system to the arrival of a foetus (see also Nahmias et al., 2011).

[15] This is how the self–nonself distinction is conceived of and used in contemporary immunology (see Janeway's Immunobiology 2022, for example).

7 A problem for continuity theory

As I have shown here, the immunological stages of pregnancy are a finely orchestrated series of events made possible by the unique phenotype of immune cells found in the uterus. While this is paradoxical for classical self–nonself theory, contemporary versions can not only avoid the paradox but begin to explain how the unique phenotype of the uterine immune system evolved, what its function is and how it executes this function.

However, these findings pose a major challenge for continuity theory. Firstly, we know that tolerance of the blastocyst by the uterine immune system is not simply the absence of immune activation. As we have seen, the first stage of pregnancy is pro-inflammatory and the immune system is *triggered* by the blastocyst. According to Pradeu's third principle of continuity theory, the higher the degree of molecular difference the greater the discontinuity and the more likely there will be immune response of rejection. However, in pregnancy, the higher the degree of molecular difference, the more likely the blastocyst will be accepted.

Pradeu argues that the blastocyst is not rejected by the immune cells in the uterus because it presents itself gradually, and so is in fact continuous i.e. "The fetus begins its development in particular tolerogenic conditions… Immune cells interact with these semi-allogenic [foetal] antigens, which are initially in small quantities and encountered progressively" (Pradeu, 2012). Tolerance of the foetus by the gestator is then hypothesised to be "due to an induction of continuity" (ibid, 2012).

However, even accepting that the foetus presents as a continuity, the phenomenon to be explained is not the acceptance of the foetus as such but the acceptance of the foetus despite *triggering* the immune system, which a continuity would not do. So if we think that the foetus presents as a continuity, the triggering of the immune system would be a counterexample to Pradeu's theory.

Alternatively, it might be possible to consider the foetus as presenting a discontinuity because of the presentation of novel MHC markers, but this does not trigger *rejection* because of the special conditions of the uterus which promote tolerance. But, Pradeu does not give us any particular reason for these conditions which, in this case, represent the local context. Unless continuity theory can explain why those particular conditions are 'tolerogenic', explaining away the tolerance of the foetus despite triggering the gestator's immune system as a result of local conditions is ad hoc. So if continuity theory claims that the blastocyst presents a discontinuity in the form of a novel MHC pattern, then pregnancy still presents a counterexample to continuity theory because here a discontinuity does not trigger rejection.

As we have seen, the tolerance of the foetus by the gestator is not simply the absence of rejection but the initiation of a dramatic immune mediated process of remodelling. What is to explain this response if the blastocyst presents gradually and continuously and therefore does not present itself as a trigger for the uterine immune cells? If one thinks that the foetus presents as a continuity, we have the problem of explaining the triggering of the immune system and the dramatic remodelling process that ensues. If one thinks that the foetus presents as a discontinuity, then we have the problem of explaining why the foetus is tolerated. Simply explaining away these problems as a result of context sensitivity or local conditions is ad hoc. That is to say, claiming

that whether a local immune population responds to a discontinuity will depend on the context renders the whole notion that discontinuities are a sufficient criterion for immunogenicity hollow. It is like claiming that continuities do not trigger the immune system, except when they do.

In order for continuity theory to accept the context sensitivity of the immune system without this simply being ad hoc, one must have a way of providing a reason that special phenotypes of different immune populations respond to discontinuities in the ways that they do. So, Pradeu acknowledges context sensitivity and attempts to explain it in terms of the dynamics of continuity and discontinuity. Here, the idea is that particular immune cells will respond according to the history of their local environment. What is novel and discontinuous in one location will depend on what has occurred there in the past. So what is novel for one immune cell may not be novel for another.

However, certain antigens such as foetal MHC molecules may be novel everywhere and yet only meet with a tolerant immune response in the uterus. So, context sensitivity does not generally seem to arise as a result of previous exposure to antigens in a particular anatomical location. Instead, there seems to be at least some degree of genetic predetermination of immune phenotypes and their special behaviours. The foetal immune system, rather than being immature (as was thought by early self–nonself theorists) is a complex and adapted system which undergoes important site specific modifications prior to encountering foreign antigens.

There are phenotypically different cells in different anatomical locations from birth, if not before (Henneke et al., 2021) and these phenotypical differences cannot be entirely explained by responses to their surroundings during foetal development. As previously discussed, decidual NK cells are phenotypically distinct from peripheral blood NK cells and these phenotypical differences are necessary for proper foetal implantation and the formation of the environment needed for foetal growth and development. However, these cells are intrinsically capable of responding to foetal antigens in a unique way long before they encounter them. So the development of their unique phenotype cannot be caused by the presentation of these as-yet unencountered antigens.

The uterus of a newborn female mammal has never seen the antigens which it ought to tolerate and indeed it will not see them until it reaches sexual maturity. Yet, the uterus of any female mammal has a well differentiated immune population, and by puberty is capable of accepting a certain kind of foreign antigen i.e. a foetus. This is not simply a question of the uterus exhibiting a generic 'receptivity' or 'tolerogenic environment' for novel antigens because the uterus must also be able to react to and reject bacteria and viruses before, during and after pregnancy. Induction of tolerance in continuity theory requires gradual (as opposed to abrupt) exposure to an antigen, but the 'tolerogenic environment' in the uterus is the result of the specific phenotypes of uterine immune cells which are present prior to the arrival of the foetus. As such, this environment cannot have developed as a result of the gradual presentation of foetal antigens alone. There seems to be a genetically predetermined element.

The simplest explanation of the decidual NK cell phenotype and its associated behaviours towards nonself MHC molecules is that it has evolved special receptors which respond to foetal antigens in order to coordinate the process of placental implantation. Advocates of continuity theory could, of course, accept this explanation but

then they would have to accept that the reason for this the immune response of decidual NK cells to foetal antigens is not foetal antigenic *novelty* but a genetically predetermined recognition of a particular molecular pattern by a family of immune receptors (KIRs). That is to say, they would have to accept that PRR theory explains decidual NK cell behaviour rather than continuity theory.

In fact, it is not possible for continuity theory to accommodate any evolutionary explanation of immune responses if its central principle is that the response of the immune system to a trigger will depend only on whether that trigger presents as a continuity or discontinuity. As Pradeu clearly states, "the [continuity] theory claims that an immune response is due to a molecular difference in the targets of immune receptors, rather than the exogenous ("foreign") nature of this difference. This molecular difference must be understood with regard to the construction of the organism *throughout its lifespan*" (Pradeu, 2012, emphasis added). There is, in this theory, no room for evolutionary determination of immune responses because this occurs over many lifespans. If the specific phenotype of an immune cell is genetically determined as a result of evolution, and the behaviour of this particular immune cell depends on this phenotype, then its response to an antigen is determined prior to its exposure to that antigen.

As such, a theory based on continuity or discontinuity alone does not have the conceptual resources to provide reasons for the specialisation of local immune populations or its functional consequences, especially if we have good evidence that they are genetically predetermined. Pradeu claims that ""what triggers an immune response is molecular difference" constitutes a simple, experimentally adequate, and unifying explanation for immune phenomena." However, the fact that context sensitivity of the immune system influences, and in some cases determines, immune responses points to the inadequacy of 'molecular difference' as a reason for some immune behaviours. In particular, the evidence from the behaviour of decidual NK cells points to molecular pattern recognition rather than simple recognition of molecular difference as the trigger for the special immune phenomena in pregnancy.

So, continuity theory is unable to account for an important case where the context sensitivity of the immune system is genetically predetermined because of the way mammals evolved to gestate their foetuses with placentas. Given that in pregnancy we see the association between an immune trigger, an inflammatory process and tolerance of the trigger and that continuity theory is unable to provide any explanation for this, pregnancy seems to be an anomaly for which continuity theory can, at best, only provide an ad hoc solution.

8 Conclusion

In this paper, I started by presenting the immunology of pregnancy as a problem for the classical self–nonself theory of immune function. Thomas Pradeu uses this and other problem cases to argue that the self–nonself theory should be replaced by his continuity theory where discontinuities are a general criterion for triggering the immune system.

However, I argue that the reason that the antigenically foreign foetus is tolerated in the uterus is because the uterus has a special population of immune cells whose

function it is to facilitate the implantation and growth of a foetus. I show that these cells do not just tolerate the foetus but tolerate it despite being triggered by it. In pregnancy, the immune system is triggered in order to develop an appropriate niche for the implantation and development of a foetus.

I then present a contemporary version of the self–nonself theory for which pregnancy may not be paradoxical and can accommodate these findings by appealing to mechanisms by which specific immune receptors react and respond to different antigens (PRR theory). Also, I have argued that PRR theory can also provide an evolutionary account of the development of particular immune receptors and the behaviours that they trigger which explains the immune phenomena we see in pregnancy.

Continuity theory cannot accept this evolutionary account because it entails that there are genetically predetermined immune responses and this runs counter to continuity theory's central principle. As such, pregnancy present a counterexample to continuity theory because we have a case where the triggering of the immune system leads to an inflammatory response but not rejection of the trigger, and no explanation for this anomaly. Moreover, continuity theory cannot appeal to the context sensitivity of the immune system as an explanation except in an ad hoc way. As such, the immunology of pregnancy provides a good reason to favour contemporary self–nonself theory over continuity theory.

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