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Short communication

Alternative theories: Pregnancy and immune tolerance

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ABSTRACT

For some time, reproductive immunologists have worked to understand the balance between maternal tolerance of the fetus, maternal health, and fetal protection which leads to successful pregnancy in mammalian species. We have always understood the potential importance of multiple factors, including nutrition, genetics, anatomy, hormonal regulation, environmental insult and many others. Yet, we still struggle to combine our knowledge of these factors and immunology to finally understand complex diseases of pregnancy, such as preeclampsia. Data, and potentially other factors (e.g. politics, economics), support the work to fit pregnancy into classical immune theory driven by the concept of self-non-self-discrimination. However, based on data, many classical theorists call pregnancy "a special case." This review is a first-pass suggestion to attempt to view three models of immune system activation and tolerance as potential alternatives to classical self-non-self-discrimination and to propose a theoretical framework to view them in the context of pregnancy.

1. Introduction

1.1. Why do this?

Though we are committed and focused on understanding the mechanisms underlying preeclampsia and other complex diseases of pregnancy, from time to time it is important to take the opportunity to expand thinking and reexamine the models which drive our hypotheses and experimental designs. Rather than fall into the political mode dividing ideas into camps and distinct paradigms, it is useful to take a more holistic, or systems, or comparative approach. 'Truth' is more likely to be attained from an assimilation of diverse viewpoints. The basic paradigm which drives reproductive immunology is bound by classical models of self-non-self-discrimination. Hypotheses, experiments, and interpretation of data continues to proceed in reference to this paradigm and efforts are easily divided as being supportive or provocative. However, there exist more than one alternative to this basic paradigm, and there is potential to view each in the context of the basic question of maternal tolerance of the fetus, even though the main proponents of these theories may not have specifically addressed pregnancy. What follows is a discussion of these 'alternatives'. Each section talks about the basic model, and what supporters of the model have said about its relationship to maternal tolerance or what I have garnered from the model about what it might say about maternal tolerance. Finally I talk about what working with the model might lead to in the future.

2. Self-non-self-discrimination

2.1. Self-non-self-discrimination, but what is self?

Classic immune theory posits that the immune system responds by activation and proliferation by recognition of antigen that is non-self. The critical problem with this theory, brought forward by many of the authors of the theories presented below (Janeway, 1992; Matzinger, 1994, 2001; Smith and Popmihajlov, 2008), begins with the idea of what is self, and what is non-self. Far back in evolutionary time, with simple, self-contained maybe single-cell organisms that experienced little in the way of novel proteins throughout the life, it might have been relatively simple to ascertain the difference. A caveat even to this is the issue of food. But I think that as soon as complex modes of communication with perhaps secreted proteins became possible the problem arose. Moreover, the engulfment of other organisms with different sets of proteins (such as the precursors to mitochondria) or other mechanisms of parasitism, symbiosis or other "biological cohabitation", made the problem more complicated. Further development of biologically complex organisms made the problem even more frustrating. What does one do, theoretically with novel proteins generated developmentally? Although applied to all aspects of immunity, there are many points where theories of self-non-self-discrimination run into "trouble" and rely on exceedingly complex, convoluted and potentially not internally consistent explanations. One possible example might be T cell development in the thymus. By this theory "self" at one point dictates continuation on the developmental path, while at another,

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"self" dictates death. Both time (point of development) and place (proximity and immediate source of signals) (Hengartner et al., 1988; Bonomo and Matzinger, 1993; Mostardinha and de Abreu, 2012) have to be superimposed on "self-non-self" that gets T cells through their developmental program and out into the periphery. Many years and much hard work has brought more details to the model, but this has only expanded the idea that alone, self-non-self-discrimination cannot explain the entire process. Determination of how much of the process is explained is difficult and confounded by point of view.

For many years, a physiologically special case has been used to make hypotheses about the immune system and derive data to support self-non-self-discrimination theory. Transplanted organs, obviously "non-self" to varying degrees as generated by clinical constraints, express their own complement of immunologically relevant proteins (e.g. MHC) and critically active immune cells (e.g. dendritic cells) which communicate "non-self" to the host. Many transplanted tissues are rejected by the host immune system, and observations related to these rejections are said to support and provide the mechanisms underlying the theory. The host that does not reject the transplanted organ is said to be tolerant, and the entire field is driven by comparison of what occurs in this instance as opposed to "normal" conditions under which the organ is rejected.

However, "normal" is sometimes the successful and complicated interaction between novel, developmentally or physiologically regulated proteins and the host. A critical example is the fetal-placental unit. Cells from mother and baby intimately interact in ways that in several respects are very different than the interactions between a transplanted organ and a host. However, there are still several levels of interaction. First, there is direct interaction between fetal trophoblast and the population of cells present in the maternal decidua. Second, there is direct interaction between trophoblast and maternal vessels such that trophoblast occupies the position of maternal endothelial cell. Third, as the name hemochorial suggests, for some pregnancies, there is direct interaction between trophoblast and maternal peripheral blood. Fourth, there is evidence that fetal cells and cellular constituents are found in both maternal blood and maternal tissues, including lymphoid tissues–sometimes for long periods. Conversely, the same is true for maternal cells and the fetus. Not only are there several layers or extents of these interactions, but the exact physical nature of these interactions changes over time. These interactions occur with immunological consequences and, for example, fetal cells can regulate maternal immune cells (Olding and Oldstone, 1976).

To view pregnancy in terms of self-non-self-discrimination theory requires first that pregnancy is inherently not "normal" and further requires multiple mechanisms to account for these several layers of interaction and the changes that occur in these interactions over time. The list of these mechanisms is really beyond the scope of this commentary. It is interesting to note that over time a familiar pattern occurs episodically. A technological advance or increase in our ability to probe the complexities of biology allows for a potential mechanism of immune suppression, limitation, or derailment to be discovered (or rediscovered). Self-non-self-discrimination provides the theoretical basis to suggest that this mechanism is assayed as a potential mechanism of maternal tolerance. Manipulation of the mechanism leads to an outcome that can be interpreted as adverse. Removal of the mechanism entirely in animal models however does not result in the inability to reproduce or, evidence against the model is found in other animals or humans. The interpretation is that maternal tolerance to non-self is so critical that it requires overlapping and complementary mechanisms which may have evolved to be different in viviparous species. Additional mechanisms are assayed and manipulated together with this mechanism, and the results are similar: reproduction occurs. But significant diseases of pregnancy also occur without complete understanding. Science moves again when another potential immune suppressive mechanism to explain maternal tolerance is found. At issue here, is not the idea of "overlapping and complementary mechanisms", per se. The issue is that this thinking limits looking for other mechanisms than those theoretically supported by self-non-self-discrimination. What we seek is missing because there is something missing in the way we think. It seems that at minimum due diligence suggests a periodic look at other models. Do such models exist, or can they really be viewed as alternatives? Can any existing data be reasonably placed in these models?

3. "Evolutionary non-self" model (Janeway, 1992)

3.1. The basics of the model

Although not really intended to be an alternative to classical models, and not focused on pregnancy it might be useful to speculate, given current data, what evolutionary non-self and related models might say about maternal tolerance of the fetus. In this offshoot of classical immune models, the focus is on activation of the innate immune response as the critical mechanism for overall immune activation.

By this model, T cell receptor recognition of self-peptides in the context of MHC underlines the basis for development in the thymus and survival and initial activation in the periphery. However, activation is reliant on a costimulatory signal and this signal constitutes the point at which self is discriminated from non self. Three strategies for immune recognition are envisioned (Medzhitov and Janeway, 2002). The first is recognition of "microbial non-self" which occurs through binding of innate immune cell receptors expressed by dendritic cells or macrophages to pathogen associated molecular patterns (PAMPS) on infecting agents. The second is recognition of "missing self", that is recognition of molecules that are evolutionarily expressed on cells of the body or immune cells, but not bacteria, for example. The third is recognition of "altered self" which is said to occur when there is expression of new cellular markers or abnormalities in cellular markers in the wake of viral or other pathological infection.

"Tolerance" in this model could be viewed as an indirect process that occurs because microbial non-self is segregated from cells that could recognize it. Such segregation could occur via inhibitory signals expressed on the tissue of interest, by increased expression of unique "self" antigens and by pathogen-associated mechanisms to decrease expression of "altered self" after infection. Later versions of this model also rely on the activity of "suppressor cells" to limit the function of autoreactive T cells (Medzhitov, 2009).

3.2. Maternal tolerance

We could guess, according to this model, that the presence of fetal antigens at the maternal-fetal interface does not necessarily activate the immune system. However, when infection occurs, the pattern receptor mediated immune system occurs in order to protect the mother. This thinking supports interpretation obtained through experimental models of infection or inflammation-induced preterm birth (Elovitz et al., 2003; Bizargity et al., 2009). The fact that parasitic infection within the placenta leads to dire consequences (Kabyemela et al., 2013) also fits within this model.

There are observations related to maternal tolerance that could be in line with the model's focus on innate immune privilege. For example, the expression on the human zona pelucida of Sialyl-Lewis^x motifs which bind immune-suppressive ligands such as sieglec-9, expression of the immune modulating glycoprotein Glycodelin-A (reviewed in (Clark and Schust, 2013)) and expression of the mucinous glycoprotein MUC 16 (also known as CA 125) by the endometrium (Clark and Schust, 2013) are thought to suppress local activity of immune cells to protect the implanting embryo. For another example, the placenta expresses a number of small lectin molecules, the galectins, which are thought to be immune modulatory. The role of other unusual glycoproteins and their role in immune modulation in the reproductive track are being examined.