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Imitating a stress response: A new hypothesis about the innate immune system's role in pregnancy

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ABSTRACT

Recent research challenges long-held hypotheses about mechanisms through which pregnancy induces maternal immune suppression or tolerance of the embryo/fetus. It is now understood that normal pregnancy engages the immune system and that the immune milieu changes with advancing gestation. We suggest that pregnancy mimics the innate immune system's response to stress, causing a sterile inflammatory response that is necessary for successful reproduction. The relationship between external stressors and immunomodulation in pregnancy has been acknowledged, but the specific mechanisms are still being explicated.

Implantation and the first trimester are times of immune activation and intensive inflammation in the uterine environment. A period of immune quiescence during the second trimester allows for the growth and development of the maturing fetus. Labor is also an inflammatory event. The length of gestation and timing of parturition can be influenced by environmental stressors. These stressors affect pregnancy through neuroendocrine interaction with the immune system, specifically through the hypothalamic–pituitary–adrenal (HPA) axis and the hypothalamic–pituitary–ovarian axis. Trophoblastic cells that constitute the maternal–fetal interface appear to harness the maternal immune system to promote and maximize the reproductive success of the mother and fetus. Pregnancy is a time of upregulated innate immune responses and decreased adaptive, cell-mediated responses. The inflammatory processes of pregnancy resemble an immune response to *brief naturalistic stressors*: there is a shift from T helper (Th) 1 to T helper (Th) 2 dominant adaptive immunity with a concomitant shift in cytokine production, decreased proliferation of T cells, and decreased cytotoxicity of natural killer (NK) cells.

Inclusion of both murine and human studies, allows an exploration of insights into how trophoblasts influence the activity of the maternal innate immune system during gestation.

Introduction

What keeps the maternal immune system from rejecting the foreign fetus? For decades, the secret to this immune paradox has remained elusive. Current understanding suggests that rather than suppressing normal immune processes thought to protect the fetal allograft from maternal rejection, reproduction utilizes innate inflammatory immune mechanisms to succeed [1–3]. This paper will review the long-established traditional hypotheses related to the immune response in pregnancy, and recent literature that supports a new interpretation of these processes. Newer hypotheses presented here support an active role for the innate immune system in successful reproduction.

Traditionally the immune system has been thought of as the defense system for the human body. Innate immunity is the most ancient arm of our immune system; only jawed vertebrates are equipped with adaptive immunity [4]. Generally it is the perception of an external threat, or a physical stressor, that initiates the innate processes of an inflammatory cascade. Yet during the course of the menstrual cycle and normal pregnancy much of what transpires involves sterile inflammatory processes, not in response to danger signals, but rather carefully choreographed to promote reproductive success. What once was perceived as a suppressed system now appears to be physiologically activated innate immunity.

Recent research has established that innate immune processes are critical to all stages of pregnancy maintenance and success [2,5–8]. Innate immune cells prepare for and respond to the process of reproduction in much the same way that it responds to acute or naturalistic stressors. Endocrine and immune alliances

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evolve as hormones prepare the body for pregnancy, and then as the placenta matures it develops the ability to centrally regulate endocrine and immune processes. The responses of these systems in pregnancy appear to be multilayered and complex events in which various coalitions form and dissolve throughout pregnancy, culminating in parturition. The central role of the placenta is the key to understanding why the sterile inflammatory responses of the immune system do not target and attack the semi-allogeneic tissue of the fetus for removal.

Medawar and Wegmann's hypotheses examined

Sixty years ago, Peter Medawar, who developed the theory of acquired immunological tolerance, proposed the following hypotheses to account for the protected status of the fetus from maternal immune attack during pregnancy: (a) the mother's immune system becomes inactive during pregnancy; (b) the antigens on the fetus are not sufficiently developed to be recognized by the immune system; or (c) the separation between the two is somehow physiologically secure, walled off by the placenta [9]. Although there still appears to be merit to some pieces of these three hypotheses, this review will demonstrate that they have all essentially been disproven.

In the 1980's, Thomas Wegmann [10,11] proposed that it was the particular type of response from T helper lymphocytes that protected pregnancies from immune attack. The longstanding assumption of the inhibited Th1/dominant Th2 shift in pregnancy is now, like Medawar's hypotheses, undergoing major challenges.

Wegmann's hypothesis: some T helper cells dominate others in pregnancy

The majority of T helper cells are classified as either Th1 or Th2, based upon the type of cytokines they produce and the type of immune activity they promote. Th1 cells typically secrete pro-inflammatory cytokines, such as IL-2 and, interferon gamma (IFN-γ), Th2 cells secrete anti-inflammatory cytokines, such as IL-4, IL-5, IL-10, and IL-13 [1]. Generally Th1 cytokines activate innate immune responses and cell-mediated immunity, including phagocyte driven activity against infections, and cellular cytotoxicity, while Th2 cytokines suppress macrophage activity and cell-mediated responses while promoting humoral immune reactions and controlling mast cell-induced immune functions [12].

Wegmann proposed that a shift toward a Th2-dominant anti-inflammatory atmosphere allows pregnancy to progress, unbothered by potential attack from immune cells that would normally reject a foreign presence. This postulate encouraged a generation of research into the mechanisms involved in suppression of the cell-mediated immune responses conducted by T cells at the placental interface [13–15].

As research based upon Wegmann's proposal evolved, there appeared to be communication between Th1 and Th2 cells, particularly during pregnancy: they seemed to work in alliance [16]. Furthermore, it appears that these Th1 and Th2 cytokine secretion patterns are produced by several immune cell types and not solely by the T-lymphocytes. In pregnancy it is the uterine natural killer (uNK) cells, innate immune actors, that seem to be the primary cytokine secretors at the level of the trophoblast [2,17]. Decidual macrophages also secrete both types of cytokines [18]. Thus these patterns of cytokine secretion are now being referred to as type 1 and type 2 because of the multiple types of immune cells that are capable of producing these two patterns of immune response [19]. Moreover, the long-standing Th1/Th2 dichotomy now appears too simplistic. It has become clear that T cell activity is highly controlled during pregnancy, and that there is regulatory activity occurring within the NK cell population as well [19,20].

A new hypothesis: innate immunity and the stress response

The innate immune system is a rapid response mechanism. It is continuously operational, mainly involved with alerting other parts of the body to the presence of microorganisms and their products, and many other types of danger signals. Traditionally the innate immune response was thought to function primarily against hazardous foreign microbes encountered by the body, and to be "non-specific". However, the discovery of pattern recognition receptors such as toll-like receptors (TLRs) now expands this paradigm [21,22].

We hypothesize that many aspects of endocrine and immune response in normal pregnancy mimic the physiology of the stress response. Maier [23] has suggested that the body responds to stressors in much the same way that it responds to immune activation by a foreign pathogen. Indeed, activation of the innate immune system can occur in response to a range of danger molecules, including RNA, surfactant protein A, fibrinogen, fibronectin, autoimmune complexes, heat shock proteins, and other breakdown products from dying cells, which all lead to sterile rather than infection based inflammation [24]. This may be an adaptive response that protects the host from danger, modifying the effects of potential injury and infection through neurologic, endocrine, and immune signaling and action. This makes sense: alerting the body to the potential for invasion (when a threat is perceived) can help accomplish host survival, the primary objective of the immune system.

A related and usually secondary goal of the immune system, species propagation, is dominant during conception and pregnancy. During reproduction, innate immune processes primarily serve this second purpose. The belief that pregnancy was a profoundly immunosuppressed state caused confusion among proponents, as it suggested that pregnant women had a weakened immune system that could theoretically increase the risk of infection.

Both stress and inflammation in pregnancy are traditionally thought of as adverse events that lead to poor outcomes (e.g. [25,26]). Recent work on the role of inflammation in early gestation and parturition challenges this paradigm, as does the theory of allostasis, which suggests that the human body is designed to continually respond to challenges in the environment, by altering set points for multiple physiological reactions, facilitating adaptation [27–29]. The process of reproduction, like an acute or naturalistic stressor, presents an immune challenge to the host. These processes co-opt the host's systems, changing the behavior, both in terms of macro systems such as eating and sleeping habits, and also on a cellular and microcellular level, to increase the chance that the host will successfully reproduce. Thus, the immune system's goal in pregnancy is to help the pregnancy progress, while protecting the fetus and mother from external stressors, including pathogens.

We suggest that implantation causes a reaction similar to an acute, time-limited stressor, and an established pregnancy is comparable to a short-term naturalistic stressor. Both types of stressors potentiate innate immune responses, but suppress specific immunity [30]. There is an intensification of innate immunity, as demonstrated by an increased secretion of proinflammatory cytokines, which promote both NK cells and macrophage activation [31]. As in exposure to a naturalistic stressor, there is down regulation of Th1-type immunity during normal pregnancy [32–37] After successful placentation, which also requires a pro-inflammatory environment, the HPA axis is activated releasing cortisol to downregulate the production of excessive amounts of pro-inflammatory cytokines in an effort to restrain the immune response before it can cause severe physiological harm [30,38]. Certainly the fatigue and nausea so commonly associated with early pregnancy are "sickness behaviors": outward manifestations of this proinflammatory cytokine response [23]. Yet even this sickness behavior