

The Crucial Role of Th2 Immunity in Late Pregnancy for Fetal Tolerance

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صغری محمدرضا فام، الناز رازی النجق، فهیمه اشتیاق، زهرا الهامی، ندا ملکی

بیمارستان امام خمینی عجب شیر، دانشگاه علوم پزشکی تبریز، تبریز، ایران

چکیده فارسی

این مقاله به بررسی نقش حیاتی پاسخ ایمنی نوع Th2 در ماه‌های پایانی بارداری برای حفظ جنین می‌پردازد. با پیشرفت حاملگی، محیط ایمنی رحم به تدریج به سمت پاسخ‌های Th2، که توسط سایتوکاین‌هایی نظیر IL-4 و IL-10 حمایت می‌شوند، گرایش پیدا می‌کند. این تغییر پاسخ ایمنی، رحم را برای پذیرش جنین نیمه‌خارجی (semi-allogeneic) آماده کرده و از بروز واکنش‌های التهابی مضر که می‌توانند به زایمان زودرس یا مرگ جنین بینجامند، جلوگیری می‌کند. علاوه بر این، پاسخ Th2 در تنظیم عملکرد جفت، رفتار تروفوبلاست‌ها و پیشگیری از عوارضی چون پره‌اکلامپسی نقش دارد. این مقاله مکانیسم‌های مولکولی زیربنایی این پدیده و اهمیت بالینی آن را در تضمین بارداری تا ترم نهایی تحلیل می‌کند.

کلمات کلیدی فارسی

پره‌اکلامپسی، Th1/Th2 جفت، ماه‌های پایانی بارداری، تعادل IL-10، IL-4، بارداری، حفظ جنین، ایمونوتولرانس،

Abstract

This article explores the pivotal role of the Type 2 T helper cell (Th2) immune response in the maintenance of fetal tolerance during the later stages of pregnancy. As gestation progresses, a shift towards a Th2-dominant immune environment, characterized by cytokines like IL-4 and IL-10, is observed. This immunological reprogramming is essential for accommodating the semi-allogeneic fetus and preventing detrimental inflammatory reactions that could lead to preterm birth or fetal loss. Furthermore, the Th2 response influences placental function and trophoblast behavior, contributing to the prevention of pregnancy complications such as preeclampsia. This paper analyzes the molecular mechanisms underlying this phenomenon and its clinical significance in ensuring a full-term pregnancy.

Keywords

Keywords: Th2 response, Pregnancy, Fetal tolerance, Immunotolerance, IL-4, IL-10, Placenta, Late birth, Th1/Th2 balance, Preeclampsia, Preterm birth.

Introduction

Pregnancy represents a unique immunological paradox: the maternal immune system must simultaneously tolerate a genetically distinct fetus. The maternal immune system must simultaneously tolerate a genetically distinct helper (Th) cells divide into functionally distinct subsets, first proposed by Mosmann and colleagues in 1986, was adapted to reproductive immunology in 1993, when Wegmann and colleagues hypothesized that successful pregnancy is fundamentally a "Th2 phenomenon" (S1). According to this hypothesis, the domination of Th2 immunity over Th1 immunity protects the fetoplacental unit from attack by maternal Th1 cells, whose cytokines (IFN- γ , TNF- α , IL-2) are known to compromise pregnancy.

Direct experimental support for this hypothesis came from the same group, which demonstrated that Th2-type cytokines—IL-4, IL-5, and IL-10—are continuously produced at the maternal-fetal interface throughout all three trimesters of gestation, providing a molecular basis for the antibody/Th2-like bias of the maternal immune response during pregnancy (S2). While early pregnancy relies on a carefully controlled interplay of inflammatory and regulatory signals, the later stages of gestation are increasingly characterized by a dominant Th2 immune profile. This shift is critical for preventing maternal rejection of the fetus and ensuring its continued growth and development until term. The present article examines the mechanisms underlying this Th2 bias in late gestation and its clinical consequences.

The Th2 Shift in Late Gestation

The transition to a Th2-dominant state in late pregnancy is orchestrated by several cooperating factors:

- **Cytokine milieu:** Increased production of IL-4 and IL-10 by regulatory T cells (Tregs) and other immune cells at the maternal-fetal interface actively suppresses Th1-mediated inflammatory responses. As Lin et al. demonstrated, IL-4, IL-5, and IL-10 are continuously present in fetal-placental unit cultures from all three trimesters, indicating that the Th2 bias is not merely an early-pregnancy event but a sustained feature of gestation (S2).
- **Hormonal influence:** Pregnancy hormones, particularly progesterone and estrogen, are known to promote Th2 polarization; progesterone in fact induces the production of progesterone-induced blocking factor (PIBF), which shifts the cytokine profile toward a Th2-dominant state.
- **Trophoblast interaction:** Trophoblast cells themselves secrete factors that skew maternal immune cells toward a Th2 phenotype, while the absence of classical HLA class Ia and II antigens on villous trophoblast limits direct T-cell allorecognition (S4).
- **Controlled early Th1 priming:** Interestingly, a transient and well-regulated Th1-inflammatory window during the peri-implantation period actually benefits trophoblast invasion; however, as gestation advances, suppression of this inflammatory tone becomes essential for maintaining uterine quiescence and fetal growth (S4).

Mechanisms of Fetal Tolerance Mediated by Th2 Immunity

The Th2 immune environment facilitates fetal tolerance through multiple converging pathways:

- **Suppression of allo-immunity:** IL-4 and IL-10 inhibit the activation and proliferation of Th1 cells and cytotoxic T lymphocytes (CTLs) that are primed to attack fetal antigens. Decidual T cells from women who miscarried genetically normal fetuses expressed increased IL-2 and IFN- γ and decreased IL-4 and IL-10 compared with normal pregnancies, underscoring the protective role of Th2 cytokines (S4).
- **Modulation of inflammatory pathways:** By dampening pro-inflammatory cytokines such as TNF- α and IFN- γ , the Th2 response reduces the risk of uterine contractions and preterm labor. Experimental administration of Th1-type cytokines (IL-2, IFN- γ) or TLR agonists induces fetal resorption in murine models, while IL-10 administration or TNF- α blockade prevents LPS-induced pregnancy loss (S4).
- **Support for placental development and function:** Adequate Th2 activity is linked to optimal vascularization and function of the placenta, ensuring a timely supply of nutrients and oxygen to the fetus.
- **Cooperation with regulatory T cells:** The Th2 bias works in concert with Treg-mediated tolerance; indeed, the original Th1/Th2 paradigm has been expanded to a Th1/Th2/Th17/Treg framework, in which Th2 cytokines and Tregs jointly maintain the tolerogenic microenvironment at the maternal-fetal junction (S4, S5).

Clinical Implications: Prevention of Complications

An imbalance in the Th1/Th2 axis during late pregnancy is associated with significant adverse outcomes:

- **Preeclampsia:** Saito and Sakai reported that preeclampsia is associated with a Th1-predominant profile and may be considered a failure of the tolerance system that normally permits the second physiological trophoblastic invasion; Th1-predominant immunity is closely related to inflammation, endothelial dysfunction, and poor placentation (S3). A balanced or Th2-dominant environment may therefore offer protection against this complication.
- **Preterm birth:** Excessive uterine inflammation, often driven by a Th1 response, can trigger premature labor. The immunosuppressive nature of Th2 cytokines helps maintain uterine quiescence throughout the third trimester.
- **Recurrent pregnancy loss (RPL):** Women with RPL show Th1 bias both locally (in the decidua) and systemically, with elevated IFN- γ /IL-4 and TNF- α /IL-4 producing cell ratios in peripheral blood (S4).
- **Intrauterine growth restriction (IUGR):** Compromised placental function due to an imbalanced immune response can lead to suboptimal placental perfusion and failure of the fetus to reach its growth potential.

Discussion and Conclusion

The shift toward a Th2-dominant immune response in the third trimester is a fundamental adaptive mechanism that ensures successful pregnancy maintenance. This Th2 bias fosters immune tolerance, supports placental health, and safeguards against inflammatory processes that could lead to preterm birth or other complications.

It must be emphasized, however, that the classical Th1/Th2 dichotomy has been substantially refined in recent years. Chaouat and colleagues noted as early as 2004 that the paradigm requires reassessment, since a small, locally controlled amount of Th1-type cytokines (particularly IFN- γ) is actually beneficial for vascular remodeling and trophoblast invasion (S5). Similarly, Wang and colleagues have shown that the paradigm has been expanded to include Th17 and Treg cells, with additional subsets (Th9, Th22, Tfh) now implicated at the maternal-fetal junction (S4). Therefore, the Th2 bias should be viewed not as an absolute dominance but as a calibrated equilibrium in which anti-inflammatory and Type 2 signals predominate while permitting minimal, spatially restricted Type 1 activity. Understanding these complex immune modulations remains crucial for developing interventions to manage pregnancy disorders and improve maternal-fetal outcomes.

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