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REVIEW ARTICLE

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Cytokines in the perinatal period – Part I

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ABSTRACT
Successful pregnancy requires a state of immune homeostasis. Maternal tolerance of the genetically distinct fetoplacental unit is in part mediated by maternal and fetal pro- and anti-inflammatory cytokines; these cytokines have also been implicated in different pregnancy-related pathologic states. This two-part series seeks to provide anesthesiologists with an overview on selected perinatal cytokines in an effort to identify opportunities for research and improvements in clinical care. In part one, we review basic and pregnancy-related elements of the immune system, with an emphasis on the role of cytokines. From this foundation, we offer a perspective of a unique phenomenon witnessed within obstetric anesthesia – maternal temperature elevation associated with labor epidural analgesia.

Introduction

In the half century since Sir Peter Brian Medawar and Sir Frank Macfarlane Burnet received the Nobel Prize for their work on acquired immunological tolerance,[1] an improved understanding of maternal tolerance to the genetically distinct fetoplacental unit has developed. Medawar's proposed maternal immune *suppressed* state[2] has evolved to an immune *modulated* state;[3] instead of a silenced system that allows greater susceptibility to infectious diseases, the maternal immune system retains an adaptive, robust response with distinct and overlapping mechanisms.[4] These mechanisms involve regulatory T cell (Treg) recruitment,[5,6] major histoco mpatibility complex down-regulation,[7] dendritic cell entrapment,[8] complement modulation,[9,10] chemokine silencing,[11] indolamine 2,3-dioxygenase-expressing myeloid suppressor cell production,[12] progesterone secretion,[13] and interleukin-10 (IL-10) expression.[14] Although an in-depth discussion of each mechanism is beyond the scope of this review, a partial analysis of their integration is helpful in understanding their roles.

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Cytokines: hormones of the hematopoietic system

Cytokines are a complex, pleiotropic group of soluble, cell-signaling proteins that affect the biologic behaviors of hematopoietic cells and processes, such as inflammation, septic shock and wound healing.[15] Cytokines include chemokines (direct immune cells via chemotaxis to sites of inflammation), interferons (mediate cellular responses predominately to viral infections), interleukins (promote cell proliferation, maturation, migration, differentiation, and activation) or colony-stimulating factors (stimulate proliferation and differentiation of other target cells) (Fig. 1). The term interleukin (IL) was coined in an attempt to standardize the nomenclature of molecules secreted by leukocytes. However, because a diverse number of hematopoietic and non-hematopoietic cells can produce the same interleukin, a number of redundant classification systems have been created, including a recent, novel one that uses enhanced crystallography techniques to identify distinguishing structural features.[16]

Although similar to hormones in their ability to act at systemic and local levels, cytokines are somewhat unique in the large numbers of 'target cells' responsive to their influence. Moreover, instead of production being restricted to a single organ, cytokines are

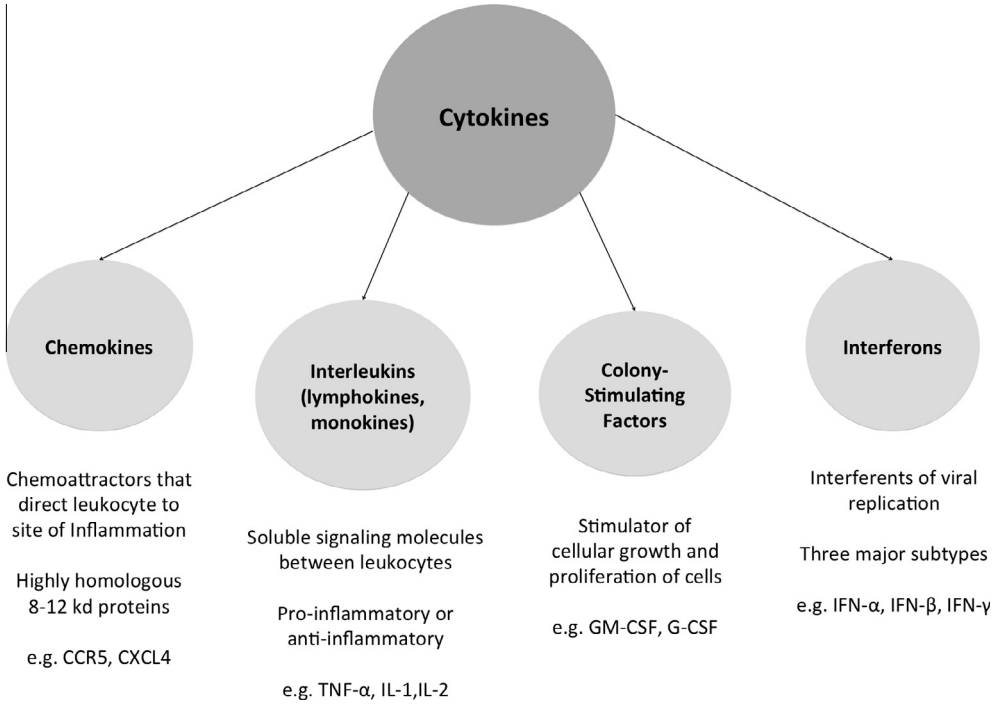

Fig. 1 An umbrella term that refers to a small soluble protein made by one cell to act upon another, cytokines have both classic and modern designations, making their nomenclature complex. For example, some cytokines have multiple names, such as the chemotactic cytokine CXCL8, which is also known as IL-8.

synthesized by a variety of hematopoietic cells, including erythroid progenitors, megakaryocytes, myeloid cells (e.g. macrophages, dendritic cells, neutrophils, mast cells), and lymphoid cells (e.g. T cells, B cells, natural killer (NK) cells).[17] Different immune cells can secrete the same cytokine and clusters of immune cells can establish intricate microenvironments that are functionally pro- or anti-inflammatory, based on the specific cytokines present.

Cell mediators of the maternal–fetal interface

In early pregnancy, as well as during the secretory phase of the menstrual cycle, the endometrium undergoes cell differentiation to facilitate implantation of the conceptus. Differentiated endometrial stromal tissue, called the decidua, represents the maternal–fetal interface where immune homeostasis and tolerance occur. The decidua is comprised of a number of maternally-derived cell types, whose specific roles are still under investigation (Fig. 2); these cells, and their relative proportions, include: decidual natural killer (dNK) cells (70%), macrophages (20%), T cells (10–20%), and rare dendritic cells, B cells and NKT cells.[18]

The dNK cells, derived from uterine NK cells, first appear in the endometrium during the secretory phase of the menstrual cycle.[18] Their primary role is to promote trophoblast invasion and vascular remodeling to maximize placental perfusion, a process likely regulated by cytokine and chemokine expression.[19] Mice deficient in NK cells demonstrate abnormally thick decidual arterioles with narrowed lumens. In the more complex spiral arteriole remodeling process present in humans, altered function of dNK cells impairs the transformation from high resistance, low-flow to low resistance, high-flow arteries; this likely has relevance to the pathogenesis of preeclampsia and fetal intrauterine growth restriction. In addition, altered dNK cell activities are associated with spontaneous pregnancy loss, and as such, have been targeted in an attempt to treat infertility and miscarriage.

In the peripheral blood, macrophages function to present antigens, remove microbes through phagocytosis, and minimize the impact of inflammatory mediators.[20] Believed to possess similar roles in the presence of placental and decidual infections, decidual macrophages may also be involved in parturition, given their selective accumulation in preterm and term patients undergoing labor when compared to those undergoing elective cesarean delivery without labor.[21] Decidual macrophages defy categorization into conventional M1 (pro-inflammatory) and M2 (anti-inflammatory) classifications given their secretion of both types of cytokines. For example, during the first trimester, decidual macrophages produce IL-10, a potent anti-inflammatory cytokine; however, with lipopolysaccharide stimula-