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Immunology of normal pregnancy

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Summary Since Medawar's initial contemplations in 1953 on the mechanisms of immune evasion allowing for the survival of the allogeneic conceptus in an immunologically competent mother, physicians and immunologists alike have struggled to understand the immunological paradox of pregnancy. Ultimately, our attempts to define the immunology of normal pregnancy have broadened our appreciation of the myriad mechanisms at play that enable the promotion of implantation and maintenance of pregnancy. In this review, we summarise what is known regarding the immunology of normal pregnancy, with special emphasis on the relation to common disorders of pregnancy.

Introduction

Higher eukaryotes are capable of discriminating self from non-self and thus mount an allogeneic immune response to protect themselves against foreign organisms and defend against infection. In pregnant mammals, this response allows for both maternal and fetal immune competence while enabling fetal (allograft) survival. Thus, two unique immunological stories unfold during pregnancy. First, a fetus living in an isolated, sterile environment develops the essential framework of the immune system so that it can mount an adequate, albeit immature, immune response. Second, a combination of fetal and maternal immunological factors conspires at the maternal–fetal interface to allow, and perhaps encourage, growth of the semi-allogeneic conceptus. Indeed, emerging evidence suggests that the immunological recognition of pregnancy is important for the maintenance of gestation, as well as modulation of common disorders of pregnancy including pre-eclampsia.

To fully understand how these two stories evolve would be to completely understand immunology itself; as yet, only part of either story has been revealed. This chapter reviews the ontogeny of the fetal immune response and the immunological relationship between the mother and conceptus. A basic understanding of these issues is of more than academic interest, because many disorders of the fetus or mother are due to aberrant immunology of pregnancy. Most clinicians recognise the immunological pathophysiology of red blood cell and platelet alloimmunisation, neonatal systemic lupus erythematosus, idiopathic thrombocytopenic purpura, myasthenia gravis and heritable congenital immunodeficiencies. In addition, common obstetric conditions, such as spontaneous abortion, fetal death, pre-eclampsia, fetal growth retardation, placental insufficiency and preterm labour appear to be, at least in part, immunologically mediated. As to the latter, both spontaneous preterm birth as well as preterm, premature rupture of membranes (PPROM) has been, in part, ascribed to aberrancies in modulation of both the maternal and fetal inflammatory response.

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In this review, we will provide a brief overview of the immune system in order to provide a contextual basis for the consideration of the means by which the 'foreign objects of pregnancy' (placenta and fetus) avoid maternal rejection while simultaneously allowing for the development of the fetal immune response. We will then discuss the role of the innate immune response in reproductive biology. Finally, we will provide a review of a limited number of elements of neonatal immunity in order to provide a more global perspective of the role of immunology in pregnancy.

Overview of the immune system

The immune system has two defence systems: *innate* and *adaptive* (Figs. 1 and 2). Traditionally the two are viewed as discrete, with the *innate immune response being a non-specific reaction to foreign antigens*, while *adaptive immunity occurs in response to specific antigens*. Recent research suggests, however, that in order to meet both the organ and species-specific needs of protection, epithelial cells of the female reproductive tract have evolved in mammals to include functional aspects of both innate and adaptive immunity.

Adaptive immune response

B and T lymphocytes arise from a common bone marrow-derived precursor that becomes committed to the lymphocyte lineage. Early maturation of both lines is characterised by cell proliferation induced by cytokines, primarily interleukin (IL)-7, which leads to quantitative increases in immature lymphocytes. The subsequent generation of antibody diversity and the T-cell receptor (TCR) repertoire is generated during somatic recombination involving multiple germline gene segments. Following somatic recombination and expression of antigen receptor chains (as either membrane-bound Ig κ or TCR α, γ) diversity is further enhanced by combinatorial juxtaposition with respective associative chains (Ig λ or TCR β, δ).[1]

B-lymphocyte maturation and activation

The means by which mature, resting B cells are induced to proliferate and differentiate into immunoglobulin (Ig) secreting plasma cells is a complex, multi-stage process. Engagement of the B-cell antigen receptor alone results in initial activation and very limited B-cell growth. However, sustained growth and/or differentiation into plasma cells requires additional signals.[2–4] In mammals, B and T cells differentiate from a pool of multipotential, self-renewable, progenitors that are maintained throughout the life span of an individual.[5,6] During ontogeny, cells from the haematopoietic lineage are sequentially generated in the para-aortic splanchopleura of the embryo, the yolk sac, the fetal liver and, ultimately, the bone marrow. Between weeks 8 and 12 of human gestation, the fetal liver becomes colonised and organs of primary B lymphoid differentiation (fetal liver, spleen and bone marrow) begin to alter their microenvironment to provide for the commitment and generation of B lineage cells.[7]

B-cell differentiation occurs in two stages. The first leads to the production of a cell capable of responding to antigen, termed 'antigen-independent differentiation'. The second stage occurs after such a cell is exposed to antigen ('antigen-dependent differentiation'). The relative abundance of B-cell progenitors (pro-B cells whose immunoglobulin genes are in germline configuration) in embryonic liver and embryonic and adult bone marrow suggest that antigen-independent B-cell differentiation occurs primarily in the embryonic liver and bone-marrow. In contrast, the antigen-dependent phase may be viewed as taking place mainly in secondary lymphoid organs such as lymph nodes, spleen, Peyer's patches and tonsils.[8] During the

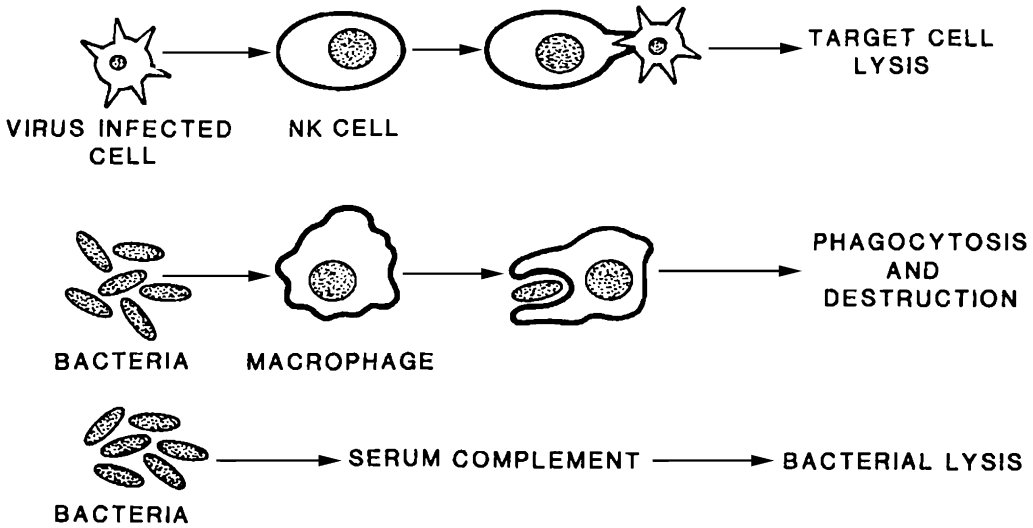

Figure 1 The innate immune response. Innate immunity implies intrinsic resistance not acquired through contact with an antigen and includes physical barriers as well as non-specific immunological factors that bar the entry of foreign material. The primary effector cells of the innate immune response are phagocytic cells (polymorphonuclear cells or neutrophils, phagocytic circulating monocytes, fixed macrophages of the reticuloendothelial system) and natural killer (NK) cells.