Immunobiology of the Trophoblast: 
Mechanisms by Which Placental Tissues 
Evade Maternal Recognition and Rejection 

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1 Introduction

The ability of women to gestate a fetus that is immunologically foreign has been the subject of intense study since the early 1950s. Indeed, an often-cited review of this problem was published in the 1960s by BILLINGHAM (1964), a colleague of Sir Peter Medawar. To this day the precise mechanisms supporting this phenomenon are still undefined, although several possibilities exist. The complexity of this problem is underpinned by the possibility that an immunobiological endeavor such as pregnancy probably does not, nor should not, rely on any one specific immune mechanism for success. It is well established that many pregnant women do not reject their embryos; what remains controversial, however, is to what extent an aberrant immune response to the pregnancy is responsible for those instances in which the fetus is lost. In fact, it is an assumption for us to discuss this problem as though it is

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essentially immunological, albeit this is our persuasion (FAULK et al. 1978; FAULK and McINTYRE 1981, 1983; TORRY et al. 1989).

For successful pregnancy to occur in the fully immunocompetent woman the fetus must be able to evade either maternal immune recognition (the afferent arm) or immune rejection (the efferent arm). Conceivably, both mechanisms may be operative at the maternofetal interface. The end result of these processes is the same; a genetically foreign embryo is allowed to implant and develop for the duration of the gestation period. The mechanisms by which the fetus derives this privilege may be quite distinct. These range from modulation of maternal immune responses (for example, blocking antibodies) to the uniqueness and largely uncharacterized nature of characteristic trophoblast antigens (for example, HLA-G).

Essential to pregnancy and pivotal to the understanding of immune events at the maternal-fetal interface is the trophoblast. Because the trophoblast is thought to line all areas of contact between the fetus and mother, the trophoblast rather than the fetus per se must avoid being targeted by the maternal immune system. The ability of the trophoblast to evade immunological detection and/or rejection is the focus of this review, with the caveat that biochemical knowledge of the various types of so-called trophoblast antigens remains far from complete.

2 Evasion of the Afferent Arm of the Immune System

2.1 Role of Classical HLA Gene Expression

Perhaps the single most important facility that trophoblast possesses to evade maternal immune detection is the ability to suppress expression of conventional, polymorphic HLA class I and II antigens (reviewed by HUNT and ORR 1992). It is the lack of expression of classical histocompatibility antigens HLA-A, B, C, DR, DQ, and DP that separates placentation from other solid organ allografts. In addition to the lack of constitutive expression of classical HLA antigens, the trophoblast is thought to be resistant to cytokine-induced upregulation of these antigens (HUNT et al. 1987). This trait appears to be unique to trophoblast, for other somatic mammalian cells can be induced to increase expression of classical class I antigens (DAVID-WATINE et al. 1990).

The molecular mechanisms regulating HLA gene expression in trophoblast have received a great deal of investigative attention. What follows is an overview of the regulatory mechanisms thought to influence HLA expression in trophoblast. Readers are encouraged to examine a recent review of this subject published by Le BOUTEILLER (1995).

At the molecular level, the lack of expression of classical HLA class I antigens in trophoblast may result from both transcriptional and post transcriptional regulatory processes. Transcription of classical class I antigens in human trophoblast appears to be down-regulated by both cis-acting and trans-acting mechanisms. One