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Decidual cytokines and pregnancy complications: focus on spontaneous miscarriage

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ABSTRACT

The establishment of pregnancy requires the co-ordinated implantation of the embryo into the receptive decidua, placentation, trophoblast invasion of the maternal decidua and myometrium in addition to remodelling of the uterine spiral arteries. Failure of any of these steps can lead to a range of pregnancy complications, including miscarriage, pre-eclampsia, fetal growth restriction, placenta accreta and pre-term birth. Cytokines are small multifunctional proteins often derived from leucocytes and have primarily been described through their immunomodulatory actions. The maternal–fetal interface is considered to be immunosuppressed to allow development of the semi-allogeneic placental fetal unit. However, cytokine profiles of the decidua and different decidual cell types suggest that the *in vivo* situation might be more complex. Data suggest that decidual-derived cytokines not only play roles in immunosuppression, but also in other aspects of the establishment of pregnancy, including the regulation of trophoblast invasion and spiral artery remodelling. This review focuses on the potential role of decidua-derived cytokines in the aetiology of unexplained spontaneous miscarriage.

1. Introduction

Several pathological conditions of pregnancy, including pre-eclampsia (PE), fetal growth restriction (FGR) and miscarriage, are associated with deficient invasion of extravillous trophoblast (EVT) cells into the decidua and myometrium in addition to incomplete remodelling of the uterine spiral arteries. EVT invasion and remodelling of the uterine spiral arteries are highly complex processes that require the dynamic interplay of many different biological signals from different cellular sources, including the decidua. Of particular note are the decidual cytokines and how their dysregulation may play a role in the aetiology of pregnancy complications. This review discusses the pathophysiology of spontaneous miscarriage, key processes in the establishment of pregnancy that may be causative of this pregnancy complication, in addition to decidual cytokines shown to be dysregulated in miscarriage, their cellular sources, known functions and how they may contribute to the pathogenesis of miscarriage.

2. Cytokines

Cytokines are small (5–20 kDa) signalling proteins produced by a wide range of cells. They show diverse functions, including regulation of cellular invasion and both humoral

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and cell-based immune responses. These cell-based and humoral immune responses are mediated by different sets of cytokines that can be grouped according to their main function for example; pro- and anti-inflammatory, or associated with different T helper (Th) subsets referred to as Th1, Th2, Th17 and regulatory (Treg) cells. Major pro-inflammatory cytokines include TNF, IL-1β, IL-6 and CXCL8/IL-8, while anti-inflammatory cytokines include IL-10 and TGF-β. Signature cytokines of Th-associated responses are: interferon (IFN)-γ (Th1); IL-4, IL-5, IL-9 and IL-13 (Th2); IL-17A and IL-17E (Th17); IL-10 and TGF-β (Treg). Several other cytokines also exist that do not precisely fit into the groups described, such as interferons, chemokines, and growth factors. The area is complex because of a redundancy in cytokines with antagonistic, synergistic, similar and sometimes identical effects; for instance, there are at least 37 interleukins and approximately 50 chemokines. In this review we focus on a limited number of established and well-known cytokines in reproductive biology, but also include recent advances that confirm or challenge our understanding of this complex area of biology.

In the early era after the discovery of the Th1/Th2 dichotomy, Wegmann et al. (1993) proposed that during pregnancy a Th2 response prevails, whereas a Th1 response is detrimental to pregnancy. From a general perspective and when considering systemic changes, this view is supported by observations such as the improvement of Th1-associated autoimmune disease multiple sclerosis (Confavreux et al., 1998) and rheumatoid arthritis (Ostensen and Villiger, 2007) during pregnancy. However, this view is likely too simplistic as Th1 cytokines have also been shown to be essential for the maintenance of pregnancy, *e.g.* IFN-γ is essential for successful pregnancy as it is pivotal in spiral artery remodelling and successful pregnancy outcome (Ashkar et al., 2000; Croy et al., 2003; Robson et al., 2012). Furthermore, a study using a Th2 knockout (IL-4, IL-5, IL-9 and IL-13 ko) mouse showed a normal reproductive outcome (Fallon et al., 2002), although different systems may be involved in the maintenance of mouse and human pregnancies. Additional cytokines, *e.g.* IL-15 and IL-18, which are not classed as Th1- or Th2-type cytokines, have been observed at the maternal–fetal interface (Chaouat et al., 2002; Murphy et al., 2009), and the broadening of the Th subset families to include Th17 and Treg has indeed challenged the paradigm and added to its complexity. Although IL-17 has been mostly associated with hyper-inflammation in autoimmunity, it was recently suggested that stromal cell-derived IL-17 might be present in the first trimester and might play a positive role in sustaining human pregnancy by recruiting Th17 cells, and by promoting trophoblast invasion and inhibiting trophoblast apoptosis (Wu et al., 2014). Conversely, Th17 cells have been reported to be rare and outnumbered by an enrichment of Treg cells (Mjösberg et al., 2010).

The human endometrium produces a wide variety of cytokines throughout the proliferative and secretory phase of the menstrual cycle (Tabibzadeh, 1991). These cytokines are believed to play a significant role in the modulation of the uterine environment, preparing the uterus for implantation of the developing conceptus and formation of a functional placenta during the establishment of pregnancy.

Prevention of maternal rejection of the fetus requires a regulated environment, which occurs primarily at the maternal–fetal interface and the uterine tissues. Classically, naive $CD4^+$ T-cells are the major producers of cytokines divided into the subsets of Th1, Th2, Th17 and Treg. However, at the maternal–fetal interface a plethora of Th-associated cytokines are also produced by trophoblast cells, stromal cells, epithelial cells, maternal T lymphocytes, macrophages, natural killer (NK) cells and other maternal leucocytes (Vince and Johnson, 2000), suggesting that the maintenance and development of the fetal–placental unit is dependent on these cytokines. The presence of cytokines at the maternal–fetal interface may influence the environment by regulating processes such as implantation, placental development, cytotrophoblast proliferation, angiogenesis, EVT cell invasion, spiral artery remodelling, cellular growth and apoptosis, in addition to induction of fetal tolerance (Piccinni et al., 2000; Drake et al., 2001; Dimitriadis et al., 2005; Lash et al., 2006; Murphy et al., 2009). However, this is a complex area of research because of the pleiotropy and redundancy of the cytokine network.

3. Miscarriage

Miscarriage is the commonest gynaecological emergency (70,000–90,000 per year in England and Wales) (Everett, 1997) and has huge financial and personal implications. The vast majority of miscarriages occur in healthy women during the first trimester of pregnancy. Between 11% and 20% of all clinically recognised pregnancies are lost before the 20th week of gestation. Most miscarriages are sporadic, that is they are non-recurring although a sub-set of women do suffer from recurrent miscarriage, defined as three or more consecutive miscarriages. It is likely that the aetiology of sporadic and recurrent miscarriage differs and therefore this article focuses on sporadic or spontaneous miscarriage.

Approximately 50% of miscarriages are associated with chromosomal abnormalities (aneuploidy) (Jauniaux and Hustin, 1992). However, the cause in the remaining 50% is unknown and the mechanisms involved in sporadic first-trimester miscarriages are poorly understood (Hustin et al., 1996), and it is these idiopathic cases that we concentrate on in this review.

Approximately 70% of early miscarriages have been associated with premature and continuous intervillous blood flow, evidence arising from flow patterns using grey-scale Doppler. This is linked to oxidative stress in villous trophoblast, an effect of a thin and disrupted trophoblast shell (Jauniaux et al., 1994, 2000). There is also evidence suggesting that deficient trophoblast invasion might be linked with first-trimester miscarriage; using a morphological method, Hustin et al. (1990) demonstrated reduced trophoblast invasion in early aneuploid miscarriages. It was this observation that led to the suggestion that trophoblast invasion and spiral artery remodelling might be primarily reduced in miscarriage, although reports are inconsistent. Ball et al. (2006a) assessed trophoblast subpopulations