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Review article

Embryotoxic cytokines—Potential roles in embryo loss and fetal programming

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ABSTRACT

Cytokines in the reproductive tract environment at conception mediate a dialogue between the embryo and maternal tissues to profoundly influence embryo development and implantation success. Through effects on gene expression and the cell stress response, cytokines elicit an epigenetic impact with consequences for placental development and fetal growth, which in turn affect metabolic phenotype and long-term health of offspring. There is substantial evidence demonstrating that pro-survival cytokines, such as GM-CSF, CSF1, LIF, HB-EGF and IGFII, support embryos to develop optimally. Less attention has been paid to cytokines that adversely impact embryo development, including the pro-inflammatory cytokines TNF, TRAIL and IFNG. These agents elicit cell stress, impair cell survival and retard blastocyst development, and at sufficiently high concentrations, can cause embryo demise. Experiments in mice suggest these so-called 'embryotoxic' cytokines can harm embryos through pro-apoptotic and adverse programming effects, as well as indirectly suppressing uterine receptivity through the maternal immune response. Embryotrophic factors may mitigate against and protect from these adverse effects. Thus, the balance between embryotrophic and embryotoxic cytokines can impart effects on embryo development and implantation, and has the potential to contribute to endometrial 'biosensor' function to mediate embryo selection. Embryotoxic cytokines can be elevated in plasma and reproductive tract tissues in inflammatory conditions including infection, diabetes, obesity, PCOS and endometriosis. Studies are therefore warranted to investigate whether excessive embryotoxic cytokines contribute to infertility and recurrent implantation failure in women, and compromised reproductive performance in livestock animals.

1. Introduction

After conception, the embryo traverses the oviduct before reaching the uterus to complete blastocyst development and implantation. In this free-floating phase the embryo is highly responsive to external signals that, through epigenetic mechanisms, contribute to setting the trajectory of the embryo's future developmental program. There is an evolutionary benefit of this sensitive stage – the embryo can sense and respond to local signals, in order to achieve a phenotype suited to the external environment. Embryo plasticity is thought to have evolved to provide the best chances of offspring survival and reproductive success to the organism – but there is a cost when the resulting phenotype constrains capacity to withstand health and environmental challenges after birth (Waterland and Jirtle, 2004).

An emerging view is that the female reproductive tract is not passive but plays an active role in the process driving plasticity prior to and during implantation (Robertson, 2010), and indeed can be a powerful force in selectively supporting or eliminating embryos (Teklenburg et al., 2010; Macklon and Brosens, 2014). This view is supported by data from several mammalian species indicating that uterine receptivity rather than ovulation and conception is rate-limiting in reproductive success (Foote and Carney, 1988). In women, it is estimated that around 30% of naturally conceived fertilised oocytes do not successfully implant (Norwitz et al., 2001), and implantation failure is even higher in assisted reproductive treatment cycles (Boomsma et al., 2009).

The complex, dynamic milieu of bioactive agents mediating maternal tract–embryo communication includes an array of cytokines and growth factors. These agents have paracrine cell–cell signalling actions that directly affect embryo viability and developmental potential (Hardy and Spanos, 2002; O'Neill, 2008; Richter, 2008), as well as regulating uterine receptivity (Dimitriadis et al., 2005). Cytokines permeate the zona pellucida and ligate specific cell surface receptors to activate intracellular signalling pathways, which in turn modulate gene expression and impact cellular functions including metabolism, secretory function, differentiation and the cell stress response. The maternal cytokine milieu is emerging as an important determinant of embryo

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survival and implantation competence, and can shape post-implantation development in both positive and negative ways (O'Neill, 2008; Robertson et al., 2015).

The balance of cytokines is responsive to systemic and local regulation by a wide range of maternal parameters and environmental exposures (Robertson et al., 2015), and provides a likely mechanism by which the consequences of these conditions are exerted on embryo development and implantation. Several health conditions and disease states have potential to alter reproductive tract cytokines, either by direct effects on the physiological function of the reproductive tissues, or by systemic elevation of circulating pro-inflammatory agents. Although preimplantation embryo development is well known to be susceptible to maternal health status, there has been poor understanding of the upstream signals that affect embryo survival, development and epigenetic modification. Some metabolic, chemical or physical insults might directly impact the cell stress response, apoptotic machinery and the epigenome, but this would require agents to access and act locally in the reproductive tract. It seems more biologically plausible that the effects of maternal conditions are communicated by local interlocutory mediators to influence embryonic survival and programming, as well as uterine receptivity.

There is a substantial literature on pro-survival embryotrophic factors secreted from female tissues and produced endogenously within the embryo (Dimitriadis et al., 2005; Thouas et al., 2015). In this review, we focus on their counterpart embryotoxic cytokines that exert adverse effects on preimplantation embryo development. These are pro-inflammatory cytokines that, in excessive concentrations, can harm embryo survival and development and/or induce altered developmental programming. Given the ethical and practical challenges of studying human tissues, we refer mainly to data from animal species, while drawing on human studies when possible. Collectively, the assembled evidence indicates that elevated pro-inflammatory cytokines contacting the developing embryo can contribute to the inhibitory effects on fertility of some common health conditions, and also exert effects on developmental programming to mediate intergenerational transfer of metabolic disease susceptibility.

2. Cytokines in the oviduct and uterus

Several cytokines are expressed in distinct spatial and temporal patterns over the course of the ovarian cycle. Synthesis is regulated primarily by ovarian steroid hormones, acting in concert with local endogenous factors, signals from the conceptus, the reproductive tract microbiome and constituents of the male partner's seminal fluid. Systemic factors such as nutritional status and micronutrient availability, neuroendocrine signals, circulating and local hormones, growth factors and microRNAs, and genetic polymorphisms in cytokine and cytokine receptor genes also influence the cytokine balance (Fig. 1).

The epithelial cells forming the luminal surface of the oviduct and endometrium, and the endometrial glands are a major source of maternal cytokines released into the luminal fluid. Amongst the best studied are colony stimulating factor-1 (CSF1, also known as M-CSF), granulocyte-macrophage CSF (GM-CSF, also known as CSF2), leukaemia inhibitory factor (LIF) and transforming growth factor β (TGFB) (Dimitriadis et al., 2005; Thouas et al., 2015). Epithelial cells also secret chemokines and vascular endothelial growth factors (VEGFs), that can influence embryos as well as regulating leukocyte infiltration and vascular remodelling (Hannan et al., 2011).

Epithelial cell cytokine synthesis is not constitutive, but is regulated over the reproductive cycle. In women, estrogen-regulated cytokines including CSF1, GM-CSF and tumor necrosis factor (TNF) increase over the proliferative phase and peri-ovulatory phase. Expression shifts during the luteal phase when increasing progesterone dampens pro-inflammatory cytokines, driving a shift towards anti-inflammatory cytokines such as CSF1, LIF and TGFB once implantation commences (Dimitriadis et al., 2005; Thouas et al., 2015). The embryo secretes

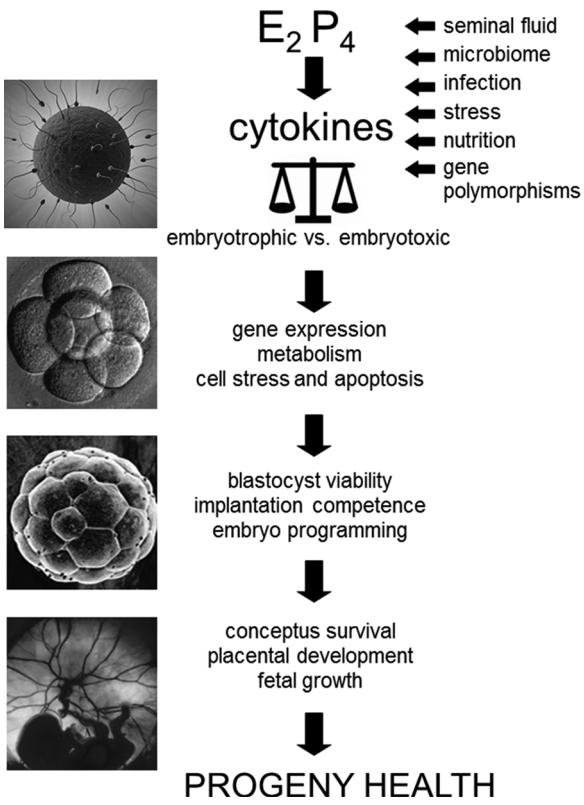

Fig. 1. Cytokine expression in the female reproductive tract is regulated by ovarian steroid hormones and a variety of intrinsic and extrinsic factors. The cytokine environment in the periconception period comprises both embryotrophic (pro-survival) and embryotoxic (pro-apoptotic) factors. Together these factors influence gene expression, metabolism, cell stress and apoptosis in the pre-implantation embryo to initiate downstream events impacting implantation, placental development and fetal growth, and ultimately the phenotype and health of progeny (updated from Robertson et al., 2015).

factors such as interleukin–1 B (IL1B) and human chorionic gonadotrophin (hCG) can regulate embryotrophic factor release from uterine epithelial cells, and this bidirectional communication synchronises embryo development with maternal tract receptivity (Thouas et al., 2015).

In many regards, the cytokine and immune cell response to embryo implantation reflects a controlled inflammatory response, akin to that seen in tissue injury and wound healing (Mor et al., 2017). Luteal phase progesterone is critical in the switch from a pro-inflammatory environment at conception, to a regulated and contained inflammation at implantation. This ensures the phenotype and balance of inflammatory mediators is consistent with continued development. When embryo implantation fails, or in a non-conception cycle, progesterone decline upon luteolysis causes a surge in pro-inflammatory cytokines such as TNF, IL6 and IL1 before menstruation commences (Salamonsen et al., 2002). A similar increase in TNF and IL8 expression is seen in Fallopian tubes after luteal phase administration of the progesterone antagonist RU486 (Li et al., 2004).

Comparable patterns are seen in the mouse but in this species there is additional regulation afforded by male seminal fluid contact. Effects of seminal fluid on cytokine release are well described in rodents and other species where seminal fluid accesses the uterine cavity to induce a surge in GM-CSF, IL6 and an array of chemokines from estrogen-primed uterine and oviductal epithelial cells after mating (Robertson, 2005; Bromfield et al., 2014). In women, seminal factors including TGFB and prostaglandin E2 (PGE_2) stimulate cervical epithelial cells to induce expression of IL8, GM-CSF, IL6 and various chemokines to in turn activate the immune adaptation required for pregnancy (Sharkey et al., 2012). Whether seminal fluid factors can impact cytokines in the