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Cytokine secretion in decidual mononuclear cells from term human pregnancy with or without labour: ELISPOT detection of IFN-γ, IL-4, IL-10, TGF-β and TNF-α

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Abstract

Cytokines are believed to be important in maintaining pregnancy and in the process of labour induction in humans. The aim of this study was to investigate the secretion of the cytokines interferon-γ (IFN-γ), interleukin-4 (IL-4), IL-10, transforming growth factor-β (TGF-β) and tumour necrosis factor-α (TNF-α) in decidual tissue with or without labour.

Decidual tissue was collected from 32 healthy women undergoing elective caesarean sections before the onset of labour ($n = 17$) or after normal vaginal delivery ($n = 15$). Mononuclear cells were analysed for cytokine secretion with ELISPOT. To validate the widely used method of tissue collected at caesarean sections and after vaginal deliveries as a representative of before and after labour, respectively, placenta biopsies were collected from 12 healthy women to study the expression of the prostaglandin pathway enzymes cyclooxygenase-2 (COX-2) and microsomal prostaglandin E_2 synthase (mPGES).

Decidual mononuclear cells from term human pregnancy spontaneously secrete IFN-γ, IL-4, IL-10, TGF-β and TNF-α. No difference was seen in cytokine secretion with or without labour, indicating that decidual leukocytes are not the main cell population responsible for plausible cytokine regulation in the process of termination of pregnancy. Placental tissues obtained after vaginal delivery showed a higher

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mRNA expression of the prostaglandin regulating molecules COX-2 and mPGES than tissues from caesarean sections before the onset of labour, validating that the model can be used as a representative of the state before and after labour.

Keywords: Parturition; Prostaglandins; COX-2; mPGES

1. Introduction

The immune system is tightly regulated during pregnancy in order to avoid rejection of the semi-allogenic foetus. In addition, the immune system also seems to contribute to the development of a normal pregnancy including induction of parturition. It is widely accepted that prostaglandins (PGs) play a crucial role in the onset of labour. Prostaglandins and their receptors are regulated by, for example, hormonal changes, mechanical pressure of the uterine wall and the secretion of cytokines (Hertelendy and Zakar, 2004; Keelan et al., 2003; Yellon et al., 2003). The secretion and effect of different cytokines and prostaglandins seem to vary between different tissues and fluids in the uterine environment (Alfaidy et al., 2003; Marvin et al., 2002; Mitchell et al., 2004; Osman et al., 2003; Young et al., 2002). To elucidate the role of different sets of molecules in the induction of labour in humans, samples taken from caesarean section were used to represent a state before labour, whereas samples from vaginal deliveries are used to represent the state after labour. Regulation of cytokines is important in both maintaining pregnancy and the process of labour induction. Pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, IL-8 and tumour necrosis factor-α (TNF-α) have been shown to increase in cervical tissues along with labour (Sennström et al., 2000; Winkler et al., 1998), although opposing results on TNF-α have been reported (Osman et al., 2003; Young et al., 2002). Interferon-γ (IFN-γ) represents cell-mediated type I immunity and has been shown to be detrimental to pregnancy in mice (reviewed in Raghupathy, 1997). Labour, in contrast, has been proposed to be a type I phenomenon (Wegmann et al., 1993). As for TNF-α, IFN-γ expression in labouring/non-labouring tissues show different patterns with regard to the methods and tissues used in different studies (Hanna et al., 2004; Veith and Rice, 1999). IL-10 is a potent cytokine that counteracts the effects of inflammatory and type I actions. We have previously demonstrated high spontaneous secretion of IL-10 in leukocytes as well as in enriched macrophages from decidua in early normal pregnancy, indicating a role in maintaining pregnancy in humans (Ekerfelt et al., 2002b; Lidström et al., 2003). IL-10 has also been shown to prevent LPS-induced preterm birth in a mouse model (Dudley et al., 1996b). A withdrawal of IL-10 would thus be a potential mechanism in the induction of labour, and a decrease in IL-10 production in placental and decidual tissues along with gestation and with labour has indeed been shown (Hanna et al., 2000; Simpson et al., 1998), although functional studies show opposite effects of IL-10 in different tissues (Mitchell et al., 2004). Other down-regulatory agents include the anti-inflammatory cytokine transforming growth factor-β (TGF-β) and the major type 2 immunity cytokine IL-4, which have both been detected in decidua, at mRNA and protein levels for TGF-β and at mRNA levels for IL-4 (Marvin et al., 2002; Wilczynski et al., 2002). However, their role at term pregnancy seems uncertain since no dif-