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Short communication

Endoplasmic reticulum stress is induced in the human placenta during labour

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ABSTRACT

Placental endoplasmic reticulum (ER) stress has been postulated in the pathophysiology of pre-eclampsia (PE) and intrauterine growth restriction (IUGR), but its activation remains elusive. Oxidative stress induced by ischaemia/hypoxia-reoxygenation activates ER stress *in vitro*. Here, we explored whether exposure to labour represents an *in vivo* model for the study of acute placental ER stress. ER stress markers, GRP78, P-eIF2α and XBP-1, were significantly higher in laboured placentas than in Caesarean-delivered controls localised mainly in the syncytiotrophoblast. The similarities to changes observed in PE/IUGR placentas suggest exposure to labour can be used to investigate induction of ER stress in pathological placentas.

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1. Introduction

Insufficient remodelling of spiral arteries is thought to underlie several pregnancy complications, such as pre-eclampsia (PE), intrauterine growth restriction (IUGR) and preterm labour [1–3]. Secondary to this maldevelopment, placental malperfusion may result in a repetitive hypoxia-reperfusion type of injury resulting in oxidative stress, which can compromise normal function of cellular components including mitochondria and the endoplasmic reticulum (ER) [4,5].

The ER is the organelle responsible for the synthesis and post-translational modification of secretory and membrane proteins, prior to delivery to the Golgi apparatus for final targeting. The ER has its own intricate network of signalling proteins that continually senses and communicates ER status to the cell. When ER homeostasis is perturbed, these proteins coordinate the Unfolded Protein Response (UPR), a signalling cascade that aims to restore ER homeostasis and relieve the stress or induce apoptosis if this process fails [6].

Three highly conserved signalling pathways are activated in the UPR, including PRKR-like endoplasmic reticulum kinase (PERK) which in turn phosphorylates eukaryotic initiation factor 2 subunit α (eIF2α) and inhibits non-essential protein synthesis; activating transcription factor 6 (ATF6) which up-regulates ER chaperones (GRP78 and GRP94) to increase folding capacity; and inositol requiring protein 1 (IRE1) which in turn activates X-box binding protein 1 (XBP-1) and TRAF2 for up-regulating phospholipid biosynthesis, promoting mis-folded protein degradation and provoking inflammatory response [6,7]. These three signalling pathways are usually activated in a sequential manner dependent on the severity of ER stress stimulation [8,9].

We recently showed that ER stress might contribute to the pathophysiology of early-onset PE and IUGR, but not late-onset PE [10]. Our laboratory has previously demonstrated that exposure of placentas to labour can provide a useful *in vivo* model for studying cellular changes induced by oxidative stress seen in the pre-eclamptic placenta. In this study we further tested whether ER stress can also be induced by the labouring process in placentas from healthy pregnancies and the potential use a *in vivo* model to study placental cellular changes to ER stress in the absence of maternal factors.

2. Methods

A total of 16 placental samples were used for the study, including 8 caesarean section controls and 8 labour placentas. All placentas were delivered at term by standard vaginal delivery or by elective non-labouring caesarean section (CS) from normotensive healthy singleton pregnancies. Both groups had no history of cigarette smoking, diabetes, autoimmune diseases, thrombophilic conditions or complicated pregnancies.

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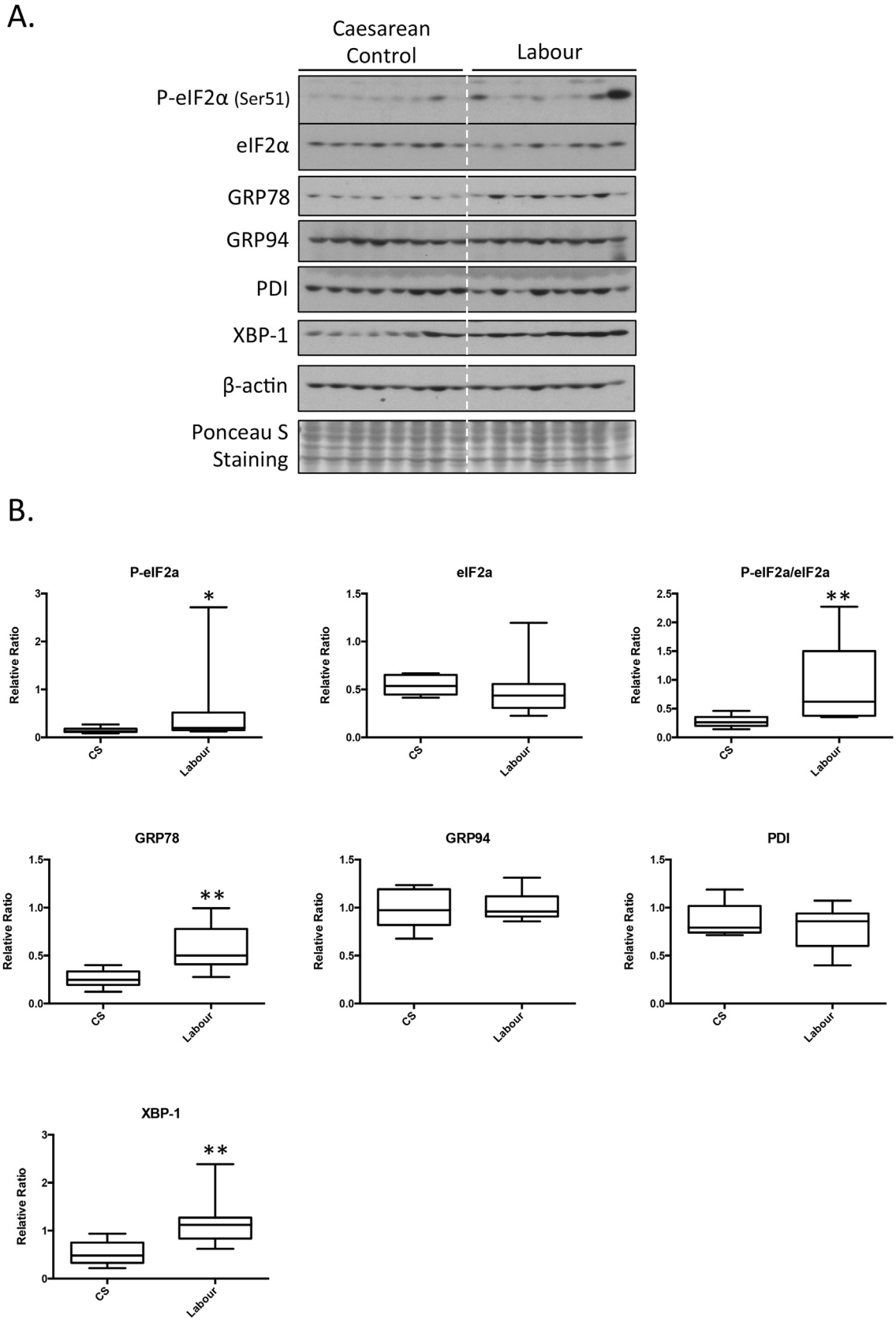

Fig. 1. Increase of ER stress markers in the vaginal delivery labour placentas compared to caesarean section placentas. A) Equal amount of proteins were subjected for Western blotting analysis with antibodies specific against a number of ER stress markers. β-actin was used for the loading control. B) Densitometry of bands expressed relative to normal controls (100%). Phosphorylation status is presented as the ratio between phosphorylated and total protein, both normalized to β-actin. Data are mean ± SD for eight placentas per group. "*" and "**" indicate $p < 0.05$ and $p < 0.01$ respectively.

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