Available online at www.sciencedirect.com
SCIENCE DIRECT
Reviews in Gynaecological and Perinatal Practice 6 (2006) 80–86
Reviews in GYNAECOLOGICAL AND PERINATAL PRACTICE
www.elsevier.com/locate/rigapp

Placental cell turnover in health and disease

Alexander Heazell [a,*], Lynda Harris [b], Karen Forbes [b], Ian Crocker [a]

[a] *Maternal and Fetal Health Research Centre, St Mary's Hospital, Manchester M13 0JH, UK*
[b] *Division of Human Development, University of Manchester, St Mary's Hospital, Manchester M13 0JH, UK*

Received 22 September 2005; accepted 20 December 2005
Available online 19 January 2006

Abstract

Pre-eclampsia (PE) and intra-uterine growth restriction (IUGR) cause significant maternal and perinatal morbidity and mortality. Placental dysfunction is central to the development of both conditions. Although the pathophysiology of these conditions is unknown, there is common placental pathology with an increase in apoptotic cell death seen within the trophoblast. In addition, in pre-eclampsia, apoptotic fragments of syncytiotrophoblast have been detected in the maternal circulation. Both hypoxia and reactive oxygen species have been proposed as potential mediators of the insults to the placenta in pre-eclampsia and IUGR resulting in apoptosis. Cell proliferation and apoptosis are tightly regulated by oncoproteins. The increased apoptosis observed within trophoblast is associated with an alteration in oncoprotein expression within placental tissue. Further investigation of these oncoproteins capable of detecting or responding to cell damage may improve understanding of the pathophysiology of pre-eclampsia and IUGR.

Keywords: Pre-eclampsia; IUGR; Apoptosis; Oncoproteins

1. Introduction

Successful pregnancy is dependent on normal placental function, commencing from implantation of the embryo, until delivery of the infant. Pre-eclampsia (PE) and intra-uterine growth restriction (IUGR) affect 2–4% and 4–8% of pregnancies, respectively, and may co-exist [1,2]. In the most recent enquiries into perinatal mortality, 5% of stillbirths and 13% of maternal deaths in the UK were attributed to pre-eclampsia [3,4]. Both pre-eclampsia and IUGR are related to placental dysfunction, the onset of which occurs before the clinical symptoms and signs of disease. Although the exact cause of placental pathology in pre-eclampsia and IUGR is unknown, the primary defect is the insufficient remodelling of spiral arteries by trophoblast, reducing the blood supply to the placenta [5]. This is associated with a reduced trophoblast invasion. Secondary changes include an increase in apoptosis, a form of cell death, in placental tissue of pregnancies complicated by PE and IUGR [6–8]. Therefore, it is hypothesised that the control of cell proliferation, invasion and apoptosis within placental tissue may be involved in the development of IUGR and PE. This article discusses the development and maintenance of normal placental tissue and reviews the evidence for abnormal cell proliferation and apoptosis in placental pathology.

2. Cell proliferation

The mammalian cell cycle is divided into distinct phases, termed G_0, G_1, S, G_2 and M (Fig. 1) [9]. Quiescent (non-dividing) cells exist in the G_0 phase and enter the cell cycle at G_1. They then pass through the S phase where their nuclear DNA is replicated and progress through the G_2 phase before entering mitosis (M phase). The G_1 and G_2 phases exist to provide time for additional cell growth between cycles of DNA replication and cell division.

The cell cycle is strictly controlled and transition between each phase is regulated by the activity of cyclin/cyclin-dependent kinase (CDK) complexes, which are predominantly localised to the nucleus. While levels of CDKs remain

* Corresponding author. Tel.: +44 161 276 5460.
E-mail address: alex_heazell@talk21.com (A. Heazell).

1871-2320/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.rigapp.2005.12.003

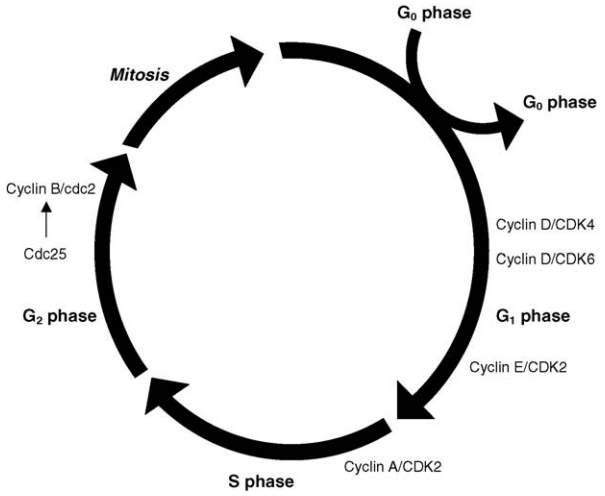

Fig. 1. The mammalian cell cycle quiescent cells are maintained in the G_0 phase of the cell cycle, and re-enter the cycle in the G_1 phase. DNA replication occurs in the S phase, and in the G_2 phase cells are prepared for mitosis, when they divide forming two daughter cells. Cell cycle progression is controlled by positive (cyclins and cyclin-dependent kinases (CDK)) and negative (CDK inhibitors) cell cycle regulatory proteins.

unchanged throughout the cell cycle [10], cyclins have a short half-life and undergo a cycle of synthesis and degradation during each round of replication [11]. Damaged cells halt cell cycle progression by either inhibiting the activity of the cyclin/CDK complexes or reducing the production of cyclins [12].

3. Cell death and apoptosis

In a mature tissue undergoing proliferation, cells must also be lost to maintain a constant cell number. Cell death is divided by histological observations into apoptosis or necrosis. During necrosis, which always results from a pathological process, the cell lyses and cytoplasm and organelles are lost into the extracellular matrix, where they may induce an immune response. In contrast, apoptosis is a controlled, energy dependent process, in which cell components including DNA are broken down and cell organelles fragment. These organelles condense and are packaged within the cell membrane, producing characteristic dense apoptotic bodies. The plasma membrane containing these condensed organelles is inverted, leaving phosphatidylserine residues, normally found on the internal aspect of the plasma membrane exposed on the surface [13]. This facilitates phagocytosis of the apoptotic bodies by surrounding cells and subsequent digestion by lysosomal enzymes. This packaging and removal of cell components prevents the induction of an immune response.

Apoptosis has been described in various physiological and pathological conditions. Apoptosis may occur as ''programmed'' cell death, for example at a particular stage of embryonic development, a cell may undergo apoptosis to create lumina within tubular structures, or digits from limb buds [14,15]. Perhaps the most important role of apoptosis is to enable normal cells to respond to damaging stimuli, especially those which alter DNA, including radiation, hypoxia and reactive oxygen species, thereby removing damaged cells from the organism and preventing neoplasia.

The similar appearances of apoptotic cells between species and individual tissues of an organism suggests a well preserved control mechanism. Apoptosis may result from a pathway which is initiated from within the cell as a response to damage (intrinsic), or from a signal originating outside the cell (extrinsic). These pathways are not distinct and cross-activation occurs during propagation of the apoptotic signal. Both pathways culminate in the activation of aspartate specific cysteine proteases, known as caspases. The aspartate amino acid residue is an uncommon site for proteases, allowing caspases to digest specific intracellular proteins or activate enzymes essential in apoptosis. For example, pro-caspase molecules contain an aspartate residue within their pro-domains, allowing their activation by other caspases upstream in the cascade. The caspases are classified according to their function within this cascade, into upstream initiator caspases (2, 8, 9 and 10) and downstream effector caspases (3, 6 and 7). The effector caspases also act on initiator caspases via a positive feedback loop to potentiate the apoptotic signal.

In response to cellular damage, particularly damage to DNA, the intrinsic pathway of apoptosis is activated (Fig. 2). Although this involves many signalling pathways, a common mechanism involves p53, a transcription factor which is upregulated and activated. The activation of p53 promotes binding to the promoter regions of pro-apoptotic genes including Bax (a mitochondrial pore protein) and p21 (a cell cycle inhibitor) which promotes their transcription [16,17]. Pro-apoptotic mitochondrial pore proteins such as Bax increase mitochondrial membrane permeability, leading to the release of cytochrome *c*. This allows the formation of the ''apoptosome'' within the cytoplasm, a complex consisting of cytochrome *c*, apoptotic protease-activating factor-1 (APAF-1) and pro-caspase 9 [18]. Pro-caspase 9 is cleaved and activated within this complex, and the resulting active form of caspase 9 goes on to activate caspases 3, 6 and 7 [18]. It is these caspases that initiate digestion of intracellular proteins and DNA during apoptosis.

The extrinsic pathway of apoptosis utilizes receptors which bind either pro-survival or pro-apoptotic ligands (Fig. 2). An example of these, the tumour necrosis factor (TNF) receptor family, has been studied in depth. Binding of TNF with TNF receptor 1 stimulates association of the TNF receptor-associated death domain with the TNF receptor [19,20]. The resulting complex combines with pro-caspase 8, cleaving it to generate active caspase 8, which can then cleave effector caspases [21].