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Current Opinion

Live and Let Die – Regulation of Villous Trophoblast Apoptosis in Normal and Abnormal Pregnancies

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ABSTRACT

Since 1995 the number of publications investigating apoptosis in villous trophoblast has increased exponentially. This scientific interest is in part due to observations that this specialised form of cell death is increased in pregnancy complications such as pre-eclampsia and intra-uterine growth restriction. In addition, apoptosis is described in normal villous trophoblast and elements of the apoptotic machinery are involved in the fusion between cytotrophoblast and the overlying multinucleate syncytiotrophoblast. The increase in descriptions of apoptotic cell death in villous trophoblast has been accompanied by investigations of regulators of apoptosis. It is anticipated that understanding the regulation of apoptosis in villous trophoblast may provide new insights into placental pathologies. This review describes current knowledge regarding the expression and function of these regulators in villous trophoblast, both in normal and complicated pregnancies.

1. Introduction

Since Levy and Nelson reviewed the regulation of apoptosis in trophoblast in 2000 [1], the number of investigations regarding the control of apoptosis in the placenta and specifically villous trophoblast has increased exponentially (Fig. 1). This growth in interest has stemmed from two main avenues of investigation. Firstly, apoptosis is increased in villous trophoblast in pregnancies complicated by gestational trophoblast disease [2,3], pre-eclampsia [4,5] and intra-uterine growth restriction (IUGR) [6,7], and secondly, apoptotic elements are associated with the fusion of cytotrophoblast and the overlying multinucleate syncytium [8]. As a consequence, regulators of apoptosis are now considered to have a major role in maintaining the integrity of villous trophoblast.

2. Cell turnover and programmed cell death

In mature tissue, undergoing proliferation, cells must die or be lost to maintain tissue homeostasis. Consequently, proliferation and programmed cell death are tightly regulated processes. The mammalian cell cycle is divided into distinct phases [9]. Quiescent (non-dividing) cells exist in the G_0 phase and enter the cell cycle at G_1. They pass through the S phase when DNA is replicated, progressing through the G_2 phase before entering mitosis (M-phase). Progression through each phase is regulated by the activity of cyclin/cyclin-dependent kinase (CDK) complexes. While levels of CDKs remain unchanged [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]. Several protein inhibitors of cyclin/CDK complexes have been described including p16, p21, p27 and p57.

Cell death is divided by histological observations into programmed cell death or necrosis. Programmed cell death is further divided into two forms, apoptosis and autophagy. Apoptosis was first described in 1972, when pathologists identified a pattern of cell death in which organelles became fragmented, condensed and packaged with cell membranes into dense apoptotic bodies for phagocytosis by neighbouring cells or macrophages [13]. This process was termed apoptosis from the Greek resembling the "curling up and dropping off" of leaves or flowers of a tree. Although the nuclear membrane remains intact, the nuclear lamina is broken, allowing nuclear DNA to be cleaved in a rapid non-sequence specific manner into 200 base pair fragments [14,15]. To assist in phagocytosis, the plasma membrane undergoes specific changes, most notably the externalisation of phosphatidylserine [16]. Following phagocytosis, the small membrane bound fragments are digested by lysosomal enzymes. Importantly, no material remains in the extracellular space, thereby avoiding an immune response [13]. Due to the nature of the processes involved, apoptosis is energy dependent.

Autophagy, "self-consumption", described more recently, has elements of both apoptosis and necrosis [17]. Necrosis, from the Greek "nekros" (dead body), varies from apoptosis in that it does not require cellular energy and results in the loss of cytoplasm and organelles to the extracellular matrix.

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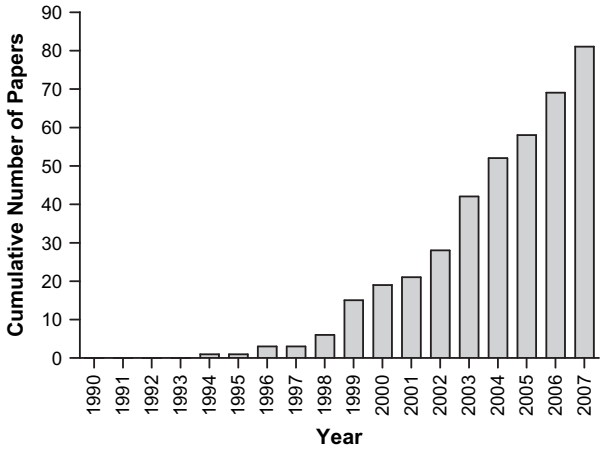

Fig. 1. Histogram indicating the expansion in the number of papers published on villous trophoblast apoptosis from 1990 to 2007. Data was obtained using Pubmed with search terms: villous trophoblast and apoptosis limited to human excluding review articles.

3. Apoptotic pathways

The similar appearance of apoptotic cells between species and tissues of an organism suggests a highly preserved control mechanism. Apoptosis may result from a pathway which is initiated from within the cell (intrinsic) or one which originates from an external signal (extrinsic). These are not distinct pathways and cross-activation occurs [18]. Both pathways culminate in the activation of aspartate-specific cysteine proteases, known as caspases, which digest intracellular proteins thereby mediating apoptotic cell death (Fig. 2). The caspases are a family of 14 proteolytic enzymes [19]. Caspases-2, -3, -6, -7, -8, -9 and -10 are associated with apoptosis, and these can be sub-divided into initiator (2, 8, 9, 10) and effector caspases (3, 6, 7), dependent on their place and function in the caspase cascade [19] (Fig. 2). Caspases have a cysteine residue within their active site and cleave proteins after aspartate amino acid residues, an uncommon substrate for proteolytic enzymes, allowing caspases to be highly specific [19]. Pro-caspases contain aspartate residues allowing cleavage and activation by caspases upstream in the enzymatic cascade. The flow of caspase

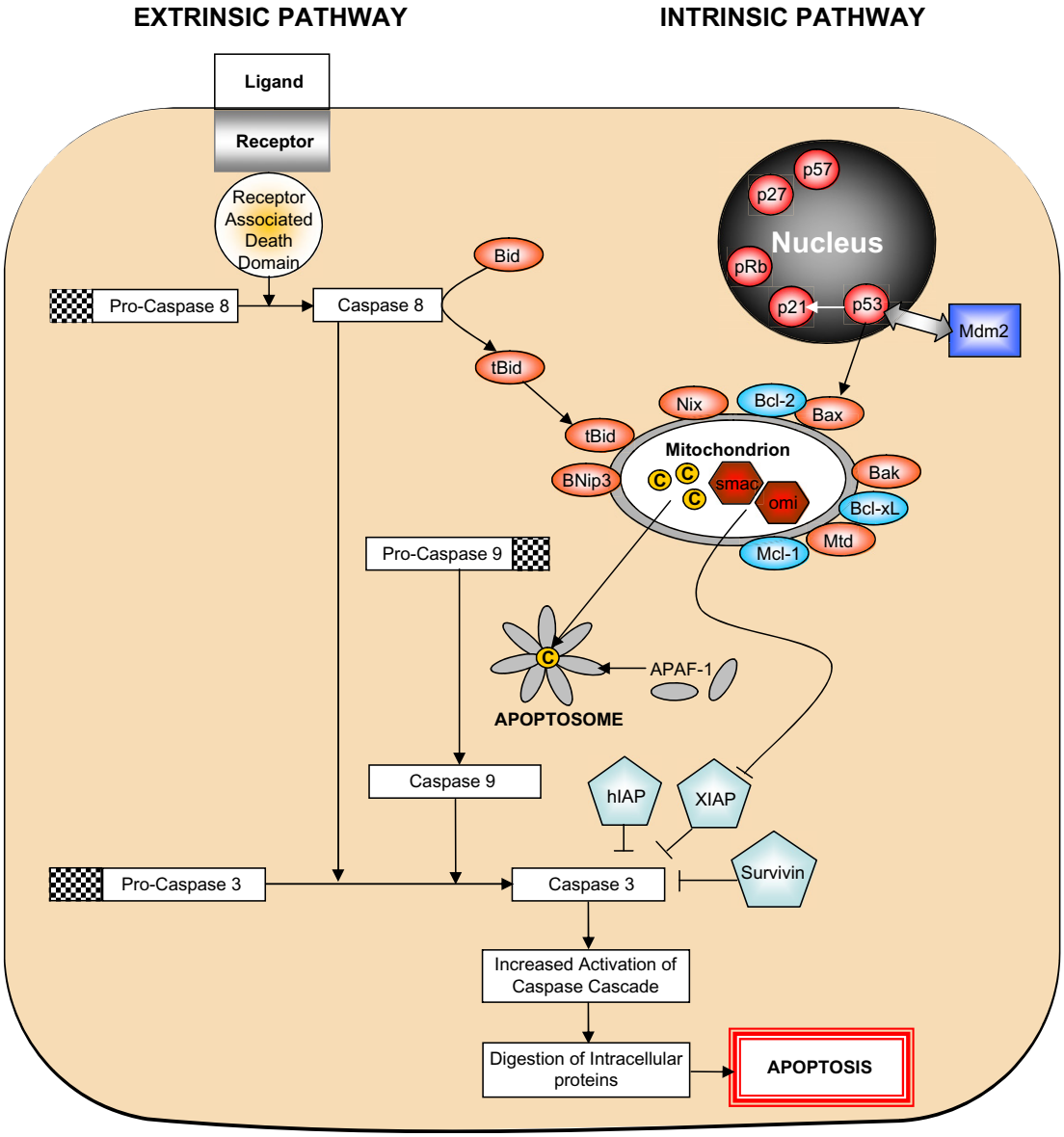

Fig. 2. Schematic representation of extrinsic and intrinsic apoptotic pathways. Pro-apoptotic proteins are shown in red and anti-apoptotic proteins in blue. Proteins which predominantly act at the nucleus are shown in small circles, Bcl-2 family proteins are shown in ovals and IAPs in pentagons. Cytochrome *c* is depicted by yellow circles.