Minireview article

PARALLEL MECHANISMS BETWEEN PLACENTAL AMYLOIDOSIS/PREECLAMPSIA AND NEURODEGENERATIVE DISEASES

Placental Prion like proteins in Preclampsia-a mini review

ABSTRACT

This short review summarizes recent studies on placenta-preeclampsia ~~(PE)~~ in the mother and/or intrauterine growth restriction ~~(IUGR)~~ in the child. The ideas raised here are framed within a paradigm that favors the opening of new research lines in these themes and are focused on the outlining of early investigation and/or an adequate treatment for mothers who develop the pathology. Thus, this review focuses on those studies that categorize PE in the group of pathologies defined as "conformational diseases", as a consequence of the misfolding of proteins due to endoplasmic reticulum ER stress. In this particular case, the ER stress that develops in the syncytiotrophoblast ~~(ST)~~ because of the oxidative stress caused in the placenta by the hypoxia that occurs as a consequence of the failure in the remodeling of endometrial arteries. This leads to an increased ~~ST~~ syncytiotrophoblast apoptosis with detachment of misfolded proteins into the maternal circulation, which in turn would be primarily responsible for the signs of ~~PE~~ preeclampsia in the mother: proteinuria, edema, and hypertension. The review also analyzes the ~~PE~~ preeclampsia-prions-placenta relationship, since the normal cell-surface protein PrPc is normally present in the plasma membrane of ~~ST~~ syncytiotrophoblast , but appears to be increased in cases of ~~PE~~ preeclampsia . However, although neurodegenerative disorders resulting from conformational changes in the prion protein from its normal cellular form, PrPc, to the infectious scrapie isoform, PrPSc are well known, limited information is available on Pr Pc and PrPSc in the ST, hence review on these proteins gains more attention in normal and pathological placenta.

Placenta and preeclampsia

The passage of nutrients from the maternal blood to the fetus is mediated by the placenta, so the normal fetal metabolism and growth require of an adequate exchange across this organ [1]. The trophoblast is the epithelium that covers the placental fetal villous tree and during development differentiates into two layers: the syncytiotrophoblast (ST) and the cytotrophoblast (CT). The former is externally located and contains many nuclei and a continuous cytoplasm, forming a syncytium. The latter consists of a monolayer of ovoid cells immediately underlying the ST. Both structures contribute to the formation of the villi and ultimately the placenta. Villous CT fuse in order to form the ST layer that contributes to the metabolic exchange of gas and nutrients, as well as to the process of waste elimination [2, 3]. Apoptosis of the trophoblast has been observed to naturally occur in placentas of normal human pregnancies but, as expected, placentas from women with preeclampsia (PE) or intrauterine growth retardation (IUGR) show enhanced apoptosis when compared with placentas from normal pregnancies [4].

PE is a systemic pregnancy syndrome that affects about 3-5% of all pregnancies [5]. This pathology is an important contributor to maternal and perinatal morbidity and mortality worldwide. Because there is no cure other than delivery, PE is the leading cause of iatrogenic preterm birth. Despite to be of unknown etiology, it is currently

accepted that this pathology originates in the placenta [6] due to the fact that the maternal symptoms (high blood pressure and proteinuria) disappear once the organ has been expelled after delivery [7, 8].

Oxidative stress

To date, PE has been related to the process of hypoxia due to ischemia/reperfusion experienced by the placenta as a consequence of extravillous trophoblast failure in the process of endometrial spiral arteries remodeling. The involvement of oxidative stress (OS) in the early placental hypoxia development has been previously proposed in the mechanism of the syndrome [1, 5, 8, 9]. Due to the fact that the human fetal-placental vasculature lacks autonomic innervation, it is reasonable to assume that autocrine and/or paracrine agents such as the NO radical may play an important role in the regulation of fetal-placental blood flows [9].

On the other hand, OS constitutes a unifying mechanism of injury involved in many types of disease. It occurs when there is an imbalance between the production of ROS and the ability of the biological system to readily detoxify these reactive oxidative species (ROS) or the tissues cannot easily repair the resulting damage [10]. In PE it has been shown that enhanced ROS generation leads to a decrease in the NO bioavailability [11]. Increased generation of superoxide anion by the placenta leads to increased peroxynitrite production, resulting in further oxidative stress and endothelial dysfunction in PE patients [8]. Additionally, it has been well established that NO disrupts the mitochondrial respiratory chain in a dose dependent manner, causing changes in the mitochondrial Ca^{2+} flux that induce ER Stress in pluripotent stem cells [12]. Taking all of these evidences into account, it is plausible to assume that OS developed in the placenta by the exaggerated generation of ROS would trigger ER stress in the organ, which in turn will increase the apoptosis of the ST.

Placental ER stress and Amyloidosis

In the last few years, a number of studies suggesting that PE could be triggered by disorders in the folding of proteins in the ER of the ST, which results in amyloid deposits in this organelle [13-16] have been published. In light of this evidence, the accumulation of misfolded protein in the ER lumen has been defined as 'ER Stress' [17-20].

In addition, ER stress has recently been identified as a major regulator of cell homeostasis through its involvement in post-translational protein modification and folding, as well as its capacity to activate the unfolded protein response (UPR) which aims to restore the homeostatic balance within the ER [21]. If this cannot be achieved, the cell apoptotic machinery becomes consequently activated. The initial intent of the UPR is to adapt the cell to the changing environment, and reestablish normal ER function. These adaptive mechanisms involve transcriptional programs that induce expression of genes that enhance the protein folding capacity of the ER, and promote ER-associated protein degradation to remove misfolded proteins [17]. Persistent protein misfolding initiates apoptotic cascades [21] that are known to play fundamental roles in the pathogenesis of multiple human diseases, including diabetes, atherosclerosis, PE and neurodegenerative diseases [14-16,22,23], all of which have been defined as "conformational diseases".

The ER stress due to misfolded proteins in the ST increases placental apoptosis in this epithelial layer [16, 18]. Moreover, due to the fact that the ST establishes direct contact with the maternal blood, the apoptotic process produces detachment of the syncytial infolding proteins, accumulated due to ER stress, to the maternal blood.

Consequently, these particles will be mainly responsible for the development of PE symptoms in the mother. Recently , we found that the Amyloid A (AA) was present in the ST of PE and IURG placentas, and that the degree of apoptosis of the CT regulates the amyloidosis destiny of the AA in the ST [16]. In brief, in PE cases the misfolded proteins are expelled to the maternal blood. On the contrary, in the IURG cases they are deposited on the basal lamina of the trophoblast, without being expelled from the placenta, but also altering the mother/fetus metabolic exchange, thus producing IUGR. Moreover, Hitomi et al., [24] suggested that activation of ER-resident caspase-12 indirectly activates cytoplasmic caspase-3 and might be important in ER stress-induced neuronal apoptosis as a consequence of the presence of misfolded proteins. This is in agreement with our ~~the~~ placental study ~~of Bosco et al.,~~ [16] which showed the presence of active caspase 3 in the CT of PE placentas with AA amyloidoses, but not in the CT of normal placentas.

It has also been reported that caspase-12-deficient mouse cortical neurons were defective in apoptosis induced by amyloid-beta protein, but not by trophic factor deprivation [25]. Thus, caspase-12 mediates an ER-specific apoptosis pathway and may contribute to amyloid-beta neurotoxicity. This idea is in concordance with Fu et al., [26] who found significantly higher caspase 12 activity in placentas of early or late severe PE. It is important to note that ER stress apoptosis can be induced by other various pathological conditions that alter the ER function. In the same line of evidence, Wang et al., [27] experimentally induced ER stress and apoptosis in placentas of pregnant rats exposed to lead, which was accompanied by an increase in the caspase-12 mRNA expression, and Xu et al., [28] found an increase in the early expression of ER stress markers, followed by increased activity of caspase 12 in placental trophoblast exposed *in vivo* and *in vitro* to T. gondii, followed by an increased apoptosis of the exposed trophoblasts. Similar results were found by Wang et al., [29] in neural stem cells exposed to this parasite. It should be emphasized that in the last three investigations no studies were carried out in order to evaluate the presence of misfolding proteins in the placentas, which would have allowed amyloidosis to be discarded. It is also important to note that in a case control study where pregnant women suspected of T. gondii infection were treated with spiramycin, a macrolide antibiotic administered before 18 weeks of pregnancy in order to reduce the rate of transmission of the parasite to the fetus, reported a reduced incidence of pregnancy-induced hypertension [30]. On the basis of these results, the association of T. gondii infection with hypertension disease during pregnancy needs to be further investigated.

In another line of evidence, transthyretin (TTR) is a homotetrameric serum and cerebrospinal fluid protein. The TTR dissociation forms monomer misfolding, a variant of TTR that results in familial amyloid polyneuropathy, familial amyloid cardiomyopathy, or familial central nervous system amyloidosis [31]. TTR is also a carrier protein for thyroxin and retinol binding protein, which are secreted by trophoblast. McKinnon et al., [32] and Mortimer et al., [33] have reported that human placenta secretes TTR into the maternal and fetal circulations and that placental TTR secreted into the maternal placental circulation can be taken up by the trophoblasts and translocated to the fetal circulation, thus conforming a TTR shuttle system. This may have important implications for maternal-fetal transfer of thyroid hormones, retinol/retinol binding protein and xenobiotics, all of which bind to TTR. Additionally, Fruscalzo et al., [34] demonstrated that TTR is dysregulated in cases of IUGR and severe early onset PE, and Kalkunte, et al., [13] showed the presence of amyloid aggregates of TTR in PE placentas, as well as in the serum of these patients.

Taken together, all these evidences allow us to postulate that by effect of the OS the placenta develops ER stress in the ST and CT, which leads to the accumulation of misfolded proteins and, if the quantity greatly increases, this will finally activate the UPR with the consequent increase of ST apoptosis and therefore the release of the misfolded proteins into the maternal blood, which in turn will trigger the symptoms of PE in the mother.

Normal cellular prion protein form in placenta

The study of this prion protein was initiated due to its involvement in a number of related neurodegenerative disorders seen in various species (bovine spongiform encephalopathy in cattle, scrapie in sheep and Creutzfeldt–Jakob disease in humans). The name 'prion' (for Proteinaceous Infectious) was coined as the infectious agent of these diseases was found to be significantly constituted by proteins [35]. A protein with identical sequence was found to be expressed in significant quantities in the brains of non-diseased animals. Hence, a consensus was reached that the protein existed in two distinct forms: the normal cellular prion protein form (PrPc) and the diseased or scrapie form (PrPSc). However, recent evidence suggests that the scrapie form of the protein may be sufficient by itself for transmission of the disease [36]. Transmissible spongiform encephalopathies (TSE) or prion diseases are characterized by the deposition of PrPc in the structurally altered PrPsc form. While PrPc configuration is primarily α-helix and susceptible to proteolysis, PrPSc instead forms fibrillar aggregates containing a high percentage of β-sheet and is rather resistant to proteolytic digestion [37]. TSE condition is accompanied by physiological symptoms similar to those of aging which, in turn, have been shown to be affected by divalent metal ions [38,39]. Over the past three decades, the role of metal ions in TSE has attracted considerable attention particularly since 1970s, when $Cu2^{+}$ chelator-induced histopathological changes were documented to be similar to scrapie [40]. Metal ions have been implicated as potential pathogenic candidates owing to their properties of being free-radical generators and their association with metalloenzymes such as superoxide dismutases (SODs), redox enzymes important for cellular resistance to oxidative stress [41]. Pathological features of TSE resemble neuronal and brain tissue loss as is observed in the case of free radical-mediated oxidative damage [42].

On the other hand, PrPc, a copper-binding glycophosphatidylinositol-anchored protein whose function is to protect the cells against oxidative stress and to prevent the apoptosis it is expressed in the plasma membrane of neural and not neural tissues [43-46]. A number of roles in neuroprotection, cellular homeostasis, response to oxidative stress, cell proliferation and differentiation, synaptic function and signal transduction have been proposed for PrPc [43,46]. Additionally, it has been shown that the abnormal isoform of PrPSc is able to induce further PrPc → PrPSc transition, accumulating in infected brains and forming amyloid plaques involved in prion diseases such as TSE, a disease with neuronal death and gliosis, producing extensive and sponge-like tissue vacuolization [37,38,47]. Additionally, Hetz et al., [48] demonstrate that prion diseases characterized by accumulation of the misfolded protease-resistant form of the prion (PrPSc) produce neuronal death by apoptosis that also correlated with caspase 12 activation in neural mouse cells treated with PrPSc. Furthermore, it has also been reported that the hypoxia-inducible factor-1 alpha (HIF-1α), which appears to be a master regulator of the cellular response to hypoxia [49], regulates PrPc expression in order to protect against neuron cell damage [50]. In correlation with this, a variety of studies have shown that women with PE are characterized by persistently elevated placental HIF-1α levels that promote enhanced transcription of genes encoding the

soluble antiangiogenic protein fms-like tyrosine kinase-1 (sFlt-1), the soluble antiagiogenic factor endoglin (sEngs) and endothelin-1 (ET-1), a powerful vasoconstrictor known to contribute to this pregnancy pathology [51-55]. Moreover, Donadio et al., [56] and Alfaidy et al., [57] reported that PrPc is highly expressed in the human placenta, especially in CT and ST, and Hwang et al., [58] found that the immunohistochemical expression of PrPc was increased in CT and ST of PE placentas versus those from the controls. Additionally, Brown et al., [59] and Brown and Besinger [60] demonstrated in mouse neurons that PrPc may directly or indirectly regulate the activity of Cu/Zn superoxide dismutase (Cu/Zn SOD). In this context, our group found a decreased activity of Cu/Zn SOD in PE placentas versus normal placentas with an increased of F2-isoprostanes, a lipid peroxidation indicator [61]. Furtheremore, Klamt et al., [47] found a decreased activity of SOD in liver, heart, hippocampus and cerebellus in PrPc knockout and wild-type mice and an oxidative damage in proteins and lipids. In addition, Anantharam et al., [46] found that PrPc plays a proapoptotic role during ER stress.

On the bases of the above arguments, we consider of the essential interest to carry out new research aimed at investigating the possible presence of PrPsc in ST and CT in cases of severe PE and eclampsia. This, due to the fact that poorly folded proteins form amyloid precipitates, and because in PE, our group found a decrease in the activity of the antioxidant enzyme SOD [61] which is regulated by PrPc [60]. It is noteworthy that in the cases of pregnant mothers who develop eclampsia, the maximum expression of PE, the maternal endothelial damage can lead to severe intracranial (intracerebral and subarachnoid) hemorrhage and cerebral venous thrombosis, preceded by visual hallucinations and the final appearance of convulsions and coma [62].

We would like to hypothetically propose that the presence of PrPSc in the ST and CT of the placenta of these mothers could be related to the increase of apoptosis in these cells and also with the significant maternal endothelial damage observed, since the release of PrPSc into the maternal blood would allow these misfolded proteins reach the blood-brain barrier. Therefore, it would be essential to perform brain biopsies of women who have died from eclampsia for the determination of amyloidosis and/or PrPSc [63]. Finally, it is important to note that in sheep placentas exposed naturally to PrPSc, the presence of PrPSc in the trophoblast has been shown by immunohistochemistry and/or ELISA essays [64].

CONCLUSIONS

This review concludes that the latest studies show evidence of a relationship between the presence of placental amyloidosis and PE. The amyloidosis condition may be either due to an increased ER stress in the trophoblast, or to an increase in the caspase 12 activity in the ER of these cells and an increase in caspase 3 activity in the CT, whose cells define the fate of the misfolding proteins in the ST.

This review also emphasize the presence of the normal prion PrPc in the plasma membrane of the CT and ST, whose presence has been noticed to increase in cases of PE. However, it is important to analyze what type of response will occur if *in vitro* BeWo cells are subjected to exposure of the prion isoform PrPSc.

PROJECTIONS

Future studies are required in order to elucidate the functional role of increased amyloidosis and PrPc in the placenta of PE pregnancy, and to establish whether the

determinations of amyloids [14] or PrPc [59] in urine or serum of this women could be used to prevent or predict this pregnancy pathology.

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