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Title: Mitochondrial [dys]function; culprit in pre-eclampsia?

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Abstract

Mitochondria are extensively identified for their bioenergetic capacities; however, recently these metabolic hubs are increasingly being appreciated as critical regulators of numerous cellular signaling systems. Mitochondrial reactive oxygen species have evolved as a mode of cross-talk between mitochondrial function and physiological systems, to sustain equipoise and foster adaption to cellular stress. Redox signaling mediated by exaggerated mitochondrial-ROS has been incriminated in a plethora of disease pathologies. Excessive production of mitochondrial-ROS is intrinsically linked to mitochondrial dysfunction Furthermore; mitochondrial dysfunction is a key facilitator of oxidative stress, inflammation, apoptosis and metabolism. These are key pathogenic intermediaries of pre-eclampsia, hence we hypothesize that mitochondrial dysfunction is a pathogenic mediator of oxidative stress in the pathophysiology of pre-eclampsia. We hypothesize that mitochondrial-targeted antioxidants may restrain production of ROS-mediated deleterious redox signaling pathways. If our hypothesis proves correct, therapeutic strategies directly targeting mitochondrial superoxide scavenging should be actively pursued as they may alleviate maternal vascular dysfunction and dramatically improve maternal and fetal health worldwide.

Introduction:

Pre-eclampsia is a multisystemic disorder of pregnancy, which affects more than eight million pregnancies worldwide annually and is the leading cause of maternal death. Pre-eclampsia is clinically defined as hypertension and proteinuria with onset following the 20th week of pregnancy. Despite intensive investigation, the pathophysiology of pre-eclampsia remains largely unknown but it appears that decreased placental perfusion, resulting from deficient invasion of the maternal uterine wall underlines the current perception for the pathology of pre-eclampsia (1). During uncomplicated pregnancy maternal uterine spiral arteries are remodeled by invading fetal extravillous and endovascular trophoblasts (2).

In pre-eclampsia, there is substantial evidence of shallow trophoblast invasion of uterine vasculature, with only superficial decidual regions of the vascular wall undergoing transformation (3). Dysfunctional placentation in early pregnancy is thought to propagate an exaggerated hypoxic/ischemia placental environment. Placental ischemia is inherently linked to elevated production and secretion of placental-derived circulatory mediators, including anti-angiogenic factors, soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which induce widespread maternal endothelial dysfunction (1). Failure to remodel spiral arteries results in high-pressure blood-flow mediated placental damage and intermittent fluctuations in oxygen delivery, which expose the placenta to oxidative stress (4). Uncomplicated pregnancy is itself a state of oxidative stress as a result of augmented maternal metabolism and the subsequent metabolic activity of the placenta. However,

during pre-eclampsia the compensatory properties regulating the placental oxidative state are aggravated, leading to increased production of pathogenic factors and subsequent vascular dysfunction. During pre-eclampsia, oxidative stress manifests in both the placenta and maternal circulation (4), with evidence of reduced antioxidant defences (5), elevated free radical formation, placental lipid peroxides and isoprostanes (6).

Hypothesis

We hypothesize that dysregulation of mitochondrial function modulates oxidative damage, which is evident in the pathogenesis of pre-eclampsia. We propose that mitochondrial-targeted antioxidant therapeutics will alleviate mitochondrial dysfunction and the aberrant regulation of mitochondrial reactive oxygen species (mROS) and consequently ameliorate the pathologic clinical characteristics of pre-eclampsia.

Basis for the hypothesis

Mitochondria

Mitochondria are dynamic intracellular double membrane organelles, located within the cytoplasmic zone of eukaryotic cells. Mitochondria are empirically known for their core involvement in the energy transduction process resulting in adenosine triphosphate (ATP) production from metabolic fuels. The mitochondrion consist of two phospholipid bilayers which subdivide the organelle into four sectors including, the outer membrane, the inner membrane space, inner membrane and matrix (7). The machinery required for

efficient operation of oxidative phosphorylation is retained in the inner mitochondrial membrane and hence this is the site of mROS generation.

Mitochondria are unique organelles as they possess their own DNA (mtDNA) within the cell, distinct from the nucleus. Mitochondrial DNA is located in the mitochondrial matrix and encodes 13 polypeptides required for oxidative phosphorylation, while the remaining proteins required for efficient mitochondrial function are nuclear-encrypted and shuttled into the mitochondria (7). Mitochondria are metabolic hubs that repeatedly adjust their number, size, structure and dynamics in response to both intracellular and extracellular stimuli respectively. These metabolic units consume 90% of the O_2 content in eukaryotic cells for oxidative phosphorylation and subsequent ATP synthesis (8). Consequently, the mitochondrion retains the highest volume of antioxidants in eukaryotic cells (9).

Mitochondrial Function: Oxidative Phosphorylation

Historically, the primordial function of mitochondria is the synthesis of ATP by oxidative phosphorylation via the transfer of electrons through a series of multi-subunit complexes (10). Complexes I, II, III and IV configure the electron transport chain (ETC) on the inner mitochondrial membrane. Tricarboxylic acid cycle (TCA) products NADH and succinate, donate electrons to Complex I (NADH:ubiquinone oxidoreductase) and Complex II (Succinate: ubiquinone oxidoreductase) respectively. These electrons are passed to ubiquinone and subsequently transported to Complex III (ubiquinol:cytochrome C oxidoreductase) (10). Electrons then shuttle to cytochrome C and flow to

Complex IV (cytochrome C oxidase), where they finally reduce oxygen to water. The energy released at Complex I, III and IV is utilized to pump protons to the inner membrane space. This proton motive force generates a gradient and the mitochondrial membrane potential (MMP). Complex V (ATP synthase) links proton flow down this gradient to formulate ATP which fuels widespread metabolic processes (11).

Reactive Oxygen Species (ROS)

Reactive oxygen species are derived from the one electron reduction of oxygen and are relatively short-lived in the cell. There are numerous potential sources of ROS within the cell, including NADPH oxidases, xanthine oxidase and cytochrome p450 intracellular enzymes (12), however our hypotheses will focus on mitochondrial-generated ROS. Mitochondria are the major cellular producers of ROS. Mitochondrial ROS were initially described as by-products of oxidative phosphorylation, however, exciting new evidence has established mROS as important physiological regulators of intracellular signaling pathways, including differentiation, immune cell activation and autophagy (13). Electrons “leak” while being transferred between complexes in the ETC, in particular at Complex I and III respectively. The one electron reduction of oxygen by the respiratory chain generates superoxide, in isolation this ROS isn’t very potent, however it can react with nitric oxide leading to the production of the mercurial reactive nitrogen species peroxynitrite (14).

In physiological conditions, most superoxide is effectively transformed to hydrogen peroxide (H_2O_2) by superoxide dismutase 2 (SOD2) in the

mitochondrial matrix and by SOD1 in the intermembrane space. H_2O_2 is the main redox signal as unlike superoxide it can easily shuttle through the mitochondrial membrane into the cytoplasm of the cell (15). H_2O_2 can merge with ferrous ions leading to the creation of the highly reactive hydroxyl radical which causes widespread deleterious oxidative damage, often seen in numerous pathologies (12). Given their potency, the signaling capacity of mROS is tightly regulated by numerous systems within mitochondria. Primarily, H_2O_2 is fully reduced to water by various antioxidant enzymes including peroxiredoxins, glutathione peroxidases and catalases. Peroxiredoxins are highly abundant in mitochondria and are hypothesized to be the most significant scavenger of nanomolar levels of H_2O_2 (13). Glutathione peroxidases are less abundant and operating with reduced glutathione as a cofactor are proposed to scavenge ROS at higher intracellular concentrations. Catalase has an inferior affinity for H_2O_2 and is limited to peroxisomes (16).

Regulation of mROS is not only controlled by antioxidant scavengers, but also by factors mediating mROS production including increased mitochondrial membrane potential, reduced oxygen levels, calcium concentration and inefficient mitophagy. Mitochondria and mROS are critical redox signaling nodes. Redox signaling ensues when a biological system changes its response to a shift in the level of a specific ROS or a swing in the redox state of a responsive group (15). mROS promote redox signaling by causing a reversible post-translation modification, affecting the activity of the protein. H_2O_2 covalently modifies thiol groups of specific cysteine residues located

within redox-sensitive target proteins. If the modification occurs at an active site, the impact on the protein is loss of function, however thiol oxidation can also regulate the activity of target proteins in numerous other ways including, altering binding affinity, modifying activity of a transporter (12). Alternative redox signals can cause irreversible alkylation of thiols as is evident in the activation of certain transcription factors (15).

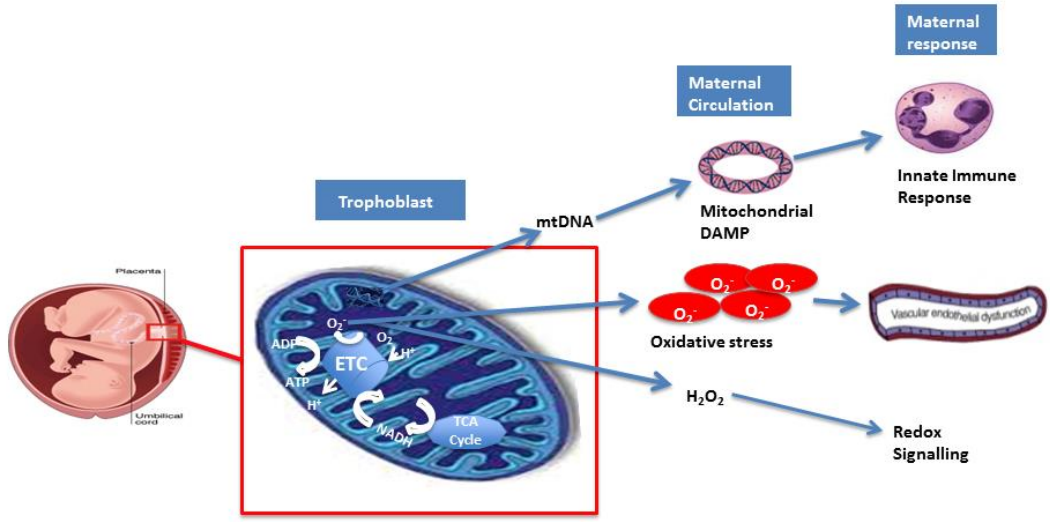


Figure 1. Mitochondria are critical metabolic signalling organelles in pre-eclampsia
The placenta is a highly metabolic organ. The central role of mitochondria is the synthesis of ATP by oxidative phosphorylation. Electrons donated from carbohydrates oxidized by the tricarboxylic acid (TCA) cycle including NADH pass through the electron transport chain (ETC) and ultimately reduce O_2 to form H_2O. As electrons are transported a proton (H^+) gradient develops across the inner mitochondrial membrane facilitating the conversion of ADP to ATP by Complex V of the ETC. Superoxide (O_2^-) is generated by the ETC and is converted to hydrogen peroxide (H_2O_2), which can easily diffuse through mitochondrial membranes and mediate redox signalling. Mitochondrial dysfunction leads to exaggerated O_2^- generation (oxidative stress) with subsequent maternal endothelial dysfunction. Mitochondrial DNA (mtDNA) is localised to the mitochondrial matrix, mtDNA can act as a damage-associated molecular patterns (DAMPs) and activate the maternal innate immune system.

Mitochondrial Dysfunction

Mitochondrial dysfunction plays a critical role in numerous human pathologies predominantly due to the prominent function of dynamic mitochondria in cellular metabolism. There are a number of different protagonists that participate in perturbing the status of mitochondria in eukaryotes, these include decreased ATP production, loss of mitochondrial transmembrane potential with subsequent increase in mROS production, calcium

dysregulation and mtDNA damage (11). Excessive oxidative damage, resulting from mitochondrial disruption is evident in the pathophysiology of various disease states including atherosclerosis and diabetes. Mitochondrial DNA is extremely susceptible to oxidative damage given its close proximity to ETC in the mitochondrial matrix and its paucity of protective histones and chromatin (17). The consequence of mtDNA damage has garnered significant attention in the immunology field recently when it was established that mtDNA act as a damage-associated molecular patterns (DAMPs) and activate the innate immune system in certain pathologies (18).

Distorted mitochondrial dynamics has additionally been mooted as potential instigators of mitochondrial dysfunction. Mitochondria exist as tubular network in cells, they constantly endure fission and fusion events to preserve and regulate their structure and integrity. Mitochondrial fusion involves extending and tethering of neighboring mitochondria to form the filamentous network, while fission describes the division of mitochondria. Mitochondrial homeostasis is vital to maintain efficiency, hence exaggerated dysregulation of either of these two mechanisms leads to mitochondrial dysfunction and subsequent elevation in mROS (7).

The health of mitochondria is in part mediated by their biogenesis, the inducible transcriptional co-activator peroxisome proliferator activated receptor γ co-activator 1-α (PGC-1α) is a well characterized pleiotropic orchestrator of mitochondrial biogenesis, homeostasis and mediates a ROS defense. Abnormal PGC-1α signaling can lead to diminished mitochondrial

biogenesis and contribute to dysregulated metabolic outcomes (19). Healthy functioning mitochondria enforce certain quality control mechanisms to eradicate damaged mitochondria. Mitophagy is a subtype of macroautophagy where damaged mitochondria are sequestered in autophagosomes and removed and the constituents recycled for new biosynthesis (13). Disturbance of this homeostatic mechanism can result in increased occupation of damaged mitochondria and detrimental oxidative damage.

Evaluation of the hypothesis

Evidence of mitochondrial dysfunction in pre-eclampsia

There is substantial circumstantial evidence to link mitochondrial dysfunction with pre-eclampsia, including oxidative stress, inflammation and apoptosis (20); these stressors are widely acknowledged to regulate the pathophysiology of this devastating disorder (Figure 1). Furthermore mitochondrial dysregulation and the resultant elevation in mROS have been shown in *in vivo* murine studies to mediate development of hypertension (21), the dominant clinical characteristic for pre-eclampsia. There is a substantial mitochondrial content in the placenta, in part to mediate the elevated metabolic activities during pregnancy. It has been shown that mitochondrial dysfunction is a pathogenic mediator of oxidative stress in pre-eclampsia, with increased mitochondrial lipid peroxidation and enhanced susceptibility to oxidation evident in mitochondria of pre-eclamptic placentas (22).

Further evidence of a pathogenic link between distortion of mitochondrial function and development of pre-eclampsia was recently described where the activity of the placental mitochondrial electron transport chain was greatly exaggerated in pre-term pre-eclampsia patients compared to normotensive controls and this activity correlated with elevated soluble levels of anti-angiogenic factors (23). Furthermore a recent murine study established a significant link between placental STOX1 expression (pre-eclampsia susceptibility gene) and dysregulated mitochondrial dynamics with a consequent increase in mROS production (24).

A study by Qiu et al. used mitochondrial DNA (mtDNA) as a biomarker of systemic mitochondrial dysfunction and recorded an increase in copy number in sera from pre-eclampsia patients (25), this was in accordance with evidence of increased placental mtDNA levels in pre-eclampsia (26). Further placental mtDNA studies have found a significant correlation between mtDNA copy number and markers of distorted mitochondrial biogenesis and cellular senescence (27, 28). Quantitative analysis of the mitochondrial placental proteome in pre-eclampsia reported increased abundance of proteins involved in apoptosis, oxidative stress, ROS generation, in addition to lower abundance of proteins regulating fatty acid oxidation (29). These results are consistent with other groups who described a reduced capacity for fatty acid oxidation in pre-eclampsia placentas (30) and human umbilical vein endothelial cells (HUVEC) (31) implying that diminished energy production is intrinsically linked to dysregulation of the feto-placental unit. We have recently

detected increased levels of plasma-induced mitochondrial-specific superoxide production in HUVEC's incubated with plasma from women with pre-eclampsia compared with matched controls and non-pregnant controls (32). Additionally, we have shown strong evidence of perturbation of mitochondrial function in the metabolite profile of plasma samples taken at 15±1 week's gestation from patients who developed pre-eclampsia (33).

Consequences of the hypothesis

A role for Mitochondrial Therapeutics in Pre-eclampsia?

Mitochondria are the major source of ROS but correspondingly these organelles are also prime targets of cellular ROS. Mitochondrial membrane, proteins and mtDNA are acutely susceptible to oxidative damage hence mitochondria are prime candidates for therapeutic strategies regardless of whether the damage to the actual organelle isn't the primary pathological insult. Despite extensive research, current antioxidant interventions are not clinically effective in resisting ROS-mediated pathological pathways. In excess of 800 peer-reviewed publications over the past 25 years have supported the hypothesis that oxidative damage is involved in the pathophysiology of pre-eclampsia yet there is a striking disconnect between data implicating oxidative processes and the failed vitamins C and E trials for preventing pre-eclampsia (34). One very plausible explanation is that these antioxidant nutrient regimens have missed the intracellular location, namely the mitochondria; hence they have failed to alleviate the pathological oxidative damage.

An essential component in the design and use of mitochondrial-targeted antioxidant therapies is that they should act on a particular ROS, as previous antioxidants have tended to have a broad specificity in the ROS they detoxify and their intracellular location. Recent work established that pre-treatment with selenomethionine amplified the placental actvity of specific antioxidants gluthathione peroxidase and thioredoxin reductase upon exposure to oxidative stressors (35).

The membrane potential of mitochondria *in vivo* is negative inside and much greater than in other organelles, which allows lipophilic cations such as triphenylphosponium (TPP) to selectively accumulate within mitochondria (36). Antioxidants conjugated to TPP therefore can be targeted to mitochondria at a dramatically higher concentration, increasing potency and allowing less of the compound to be used, thereby reducing extramitochondrial metabolism. Recent evidence has identified a prominent role for mROS in modulating hypertension (21)**.** Using two *in vivo* murine models of hypertension (AngII-induced and DOCA salt), this group eloquently demonstrated that mitochondria-targeted antioxidant therapies (Mito-Tempo) alleviated endothelial dysfunction, reduced vascular mitochondrial superoxide and subsequent hypertension (21). Interestingly, in both *in vivo* models of hypertension, Mito-Tempo achieved these beneficial effects at a dose 1000-fold lower than its non-targeted parent compound.

CONCLUSION

There is substantial evidence indicating a potential pathogenic role for dysregulation of mitochondrial function in mediating the clinical characteristics of pre-eclampsia. Redox signaling instigated by mROS is now widely implicated in a diverse range of biologically important systems. Direct evidence of this has transpired in the recent years with insight that mitochondria establish and sustain immune cell phenotypes. To date, targeting mitochondria have been largely overlooked as a potential therapeutic strategy for pre-eclampsia. We suggest that mitochondrial pharmacology is feasible, because therapeutics that target a limited number of mutual deleterious pathways have the potential to treat patients with pre-eclampsia.

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Declarations of Interest

None.

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