OXIDATIVE STRESS IN FETAL PROGRAMMING OF CARDIOMETABOLIC SYNDROME

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ABSTRACT

Cardiometabolic syndrome (CMS) is now a disease entity recognized by the World Health Organization. Emerging evidence from both human epidemiological and animal studies indicates that adult CMS may have its origins in early life and can be programmed by intrauterine and early postnatal environments; a phenomenon known as fetal programming of adult disease. This mini-review discusses [1]how exposures to various insults from the mother during gestation and/or lactation programs the fetus that prompts the development of CMS during adulthood; [2] what are the currently known underlying mechanisms, with emphasis on the role of tissue oxidative stress; and [3] whether CMS in the offspring can be reprogrammed via targeting maternal tissue oxidative stress. Translational perspective of the research field is also discussed.

Keywords: fetal programming, oxidative stress, cardiometabolic syndrome, reprogramming therapy, antioxidants.

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Introduction

Cardiometabolic syndrome (CMS) is now a disease entity recognized by the World Health Organization [1]. It represents a cluster of metabolic abnormalities characterized by insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension and central adiposity, all of which are risk factors for cardiovascular disease (CVD). The global prevalence of CMS has grown considerably over the past decade, and is estimated to reach around 40% of the world's adult populations by 2025 [2]. Moreover, emerging evidence suggests that in addition to its known causal factors such as obesity, alcohol, and unhealthy lifestyle, CMS may have its origin in fetal life [3]. This raises the concern that intergenerational transmission of this disorder may impact the offspring during adulthood. This mini-review discusses [1] how exposures to various insults from the mother during gestation and/or lactation programs the fetus that prompts the development of CMS during adulthood; [2] what are the currently known underlying mechanisms, with emphasis on the role of tissue oxidative stress; and [3] whether CMS in the offspring can be reprogrammed via targeting maternal tissue oxidative stress.

Fetal Programming of Cardiometabolic Syndrome

Mounting evidence from both human epidemiological and animal studies indicates that adult CMS may have its origins in early life and can be programmed by intrauterine and early postnatal environments; a phenomenon known as fetal programming of adult disease [4]. This phenomenon was later expended to "developmental origin of health and disease" (DOHaD) based on the seminal work published in the late 80s and early 90s by David Barker and his colleagues, which demonstrated that fetus who cannot acquire sufficient nutrients to grow normally during infancy is at higher risks for CVD in adult life [4,5]. According to the DOHaD hypothesis, exposure to maternal stimuli at critical periods of development "programs" a series of changes in fetal structures and functions that are retained in later life and increase the risks for adult CMS [reviewed in 3,6,7]. An array of factors has so far been identified to prime fetal programming. These factors range from unhealthy maternal habits such as smoking, alcohol consumption, malnutrition (both under- and over-nutrition) or physical inactivity to disease conditions that include hypertension, diabetes, obesity, infection, depression, anxiety, and complications such as preeclampsia, gestational diabetes mellitus, fetal hypoxia, medications, preterm delivery and environmental pollutants [reviewed in 6-9]. The placenta serves as the interface between the adverse intrauterine environment and the fetus. All these stimuli can compromise the functions of the placenta, perturb enzymatic placental barrier and reduce nutrient supply and oxygen access to fetus [reviewed in 8,10], leading to detrimental consequences in fetal development and long-term effects in adult health.

It is not surprised that the underlying etiology of fetal programming of adult CMS (FPCS) is multi-factorial and involves complex mechanisms in both mother and fetus. Although it is beyond the scope of this mini-review to expound on these mechanisms in detail [see 8,10-12 for review], a survey of literature on FPCS reveals that the mechanisms can be grouped into at least six categories. These include mechanisms that affect [1] cellular and molecular responses to stress, such as epigenetic (e.g., DNA methylation, histone modifications and non-coding RNAs) regulation of DNA transcription [13], expression of transcription factors [14], endoplasmic reticulum response [15], redox and immune responses [10]; [2] mitochondrial biology [16], including mitochondrial biogenesis and bioenergetics, as well as dynamics [13], [3] organogenesis [17], such as reduced nephron size and mass in the kidney, β cells mass in the pancreas, and defected myogenesis in skeletal muscles; [4] functional

pathways and systems [17, 18], including nitric oxide pathway, nutrient sensing cascade, hypothalamic-pituitary-adrenal axis, renin-angiotensin-aldosterone system (RAAS), and autonomic nervous or immune systems; [5] gut microbiota [19], including alterations in bacterial ontology, changes in bacterial richness and diversity, and dysbiosis; [6] a combination of more than one of the above categories. It is noteworthy that one key element that is engaged in all the aforementioned mechanisms is tissue oxidative stress, which will be elaborated in the following sections.

Tissue Oxidative Stress in FPCS

Tissue redox homeostasis is maintained through processes that balance the production and degradation of reactive oxygen species (ROS). Physiological levels of ROS are crucial to mother and fetus by virtue of their roles in cell signaling and gene transcription that are indispensable for fetal development. However, under suboptimal intrauterine conditions, the redox homeostasis is perturbed, and levels of ROS increased as a result of imbalance between productions over degradation of the oxidants, leading to oxidative stress damage that compromises fetal development. Maternal undernutrition [19] or diabetes [20], prenatal glucocorticoid administration [21], preeclampsia [21], air pollutant [22] or exposure to high-fructose diet [23], and/or high-fat diet [24] during pregnancy and lactation are a few conditions that prime tissue oxidative stress in FPCS. Some of these maternal insults (e.g., prenatal glucocorticoid and high fructose diet) upregulate the expressions of enzymes for the production of ROS [20,23], some (e.g., maternal diabetes and high fat diet) downregulate the expressions of antioxidants [20,24], and some (e.g., maternal low-protein diet) engage both processes [25] at least via transcriptional [24,25] or epigenetic [19,20] regulation of genes encoding the proteins involved. At the same time, total antioxidant capacity is reduced in offspring of women with obesity [26], while NADPH oxidase activity for ROS production is increased in offspring of maternally diabetic rats [27].

The mitochondria are emerging as sensors that integrate not only metabolic and cell signaling cues but may in part explain the origins of poor developmental outcomes through heritable changes that lead to disease susceptibility. In offspring to mother exposed to high-fructose, the mRNA expression of peroxisome proliferator-activated receptor γ coactivator and mitochondrial transcription factor A, two nuclear-encoded mitochondrial regulatory genes for transcriptional activation and organization of mitochondrial DNA (mtDNA) are downregulated, resulting in reduced mitochondrial DNA copy number and impaired mitochondrial biogenesis [28]. Human studies also reported a decrease in mtDNA copy number in infants of mothers exposed to higher levels of environmental pollutants during pregnancy [29, 30]. Newborns of mothers with gestational diabetes exhibit reduced expression of mitochondrial-encoded electron transport chain genes, decreases in oxidative phosphorylation respiratory capacity and defects in mitochondrial bioenergetics [31]. Moreover, mitochondrial functions are modulated by fission and fusion, two dynamic processes that assist in maintaining mitochondria homeostasis. Female offspring born to obese mothers displays altered mitochondrial dynamic [32], which may persist through the female germ-line to pass down to the second and third generations, suggesting a key role for the inheritance of aberrant mitochondria in programming mitochondrial dysfunction that passes down generations. The defects in mitochondrial biogenesis, bioenergetic and dynamic lead to an elevated mitochondrial ROS production and cellular oxidative stress damage that impacts FPCS.

Oxidative stress plays an important role in FPCS. ROS are produced in cells, including renal, vascular, cardiac, liver, pancreatic, and adipose cells that are known to participate in the

pathogenesis of CMS. Other cells that are capable of producing ROS, such as immune and nerve cells, also possess the potential to participate in the pathogenesis of CMS. Since several recent reviews [6-10, 12, 14, 16-18] have discussed this topic in detail, only a few examples will be highlighted in this mini-review. In offspring to intrauterine growth retardation, ROS-dependent changes in the expression of renal transcriptomes and aberrant nitric oxide signals participate in FPCS by associating with low nephron number and impaired sodium chloride handling in renal cells [19, 20, 24]. Activations of matrix metallopeptidases and the RAAS by ROS are permissive to vascular remodeling associated with programmed CMS [12]. Fetal hearts of pregnant rats suffering from prenatal hypoxia develop oxidative stress-mediated cell proliferation and collagen accumulation which primes cardiac fibrosis and altered cardiac contractility associated with CMS in adulthood [33]. Trans-unsaturated fatty acids-enriched diet during pregnancy and lactation predisposes the adult offspring to metabolic changes via oxidative stress-associated elevations in liver bioenergetics and fatty acid profiles [34]. Progressive loss of pancreatic beta-cell function and eventual development of hyperinsulinemia and insulin resistance in adulthood because of FPCS due to intrauterine growth retardation is attributable to dysfunction of the mitochondrial electron transport chain in fetal beta-cell, leading to the production of ROS [35]. Developmental exposure to endocrine disruptor bisphenol A programs adipocyte hypertrophy and metabolic defects during adulthood that is associated with increased tissue oxidative stress in visceral adipocytes [36]. Likewise, exposure to excess maternal fuels during fetal life promotes ROS production and excess triglyceride storage, which together with altered immune function and epigenetic changes that prime the fetal liver for nonalcoholic fatty liver disease and CMS in the next generation [37]. In addition, excess ROS production and reduced antioxidant capacity in sympathetic premotor neurons in the brain contribute to fetal programming of sympathetic overactivation and traits of CMS in offspring to maternal high fructose exposure [28]. The observations that tissue oxidative stress persists in young adult suggests that tissue oxidative stress may continue throughout adulthood and contribute to the maintenance of FPCS.

In short, a wealth of evidence from both human and animal studies suggest that a compromised environment during pre- and postnatal development may prime tissues to oxidative stress damage, which in turn programs structural and functional changes in cardiometabolic-related organs, thereby contributing to FPCS (Figure 1).

Reprogramming FPCS by Targeting Maternal Tissue Oxidative Stress

Investigations on the underlying pathophysiology of FPCS are towards the ultimate goal of developing preventative strategies and/or therapeutic interventions against adult CMS. Again, several excellent review articles on this topic are available [8,11,17,38,39], and only reprogramming strategies targeting maternal tissue oxidative stress on FPCS will be discussed below.

Beneficial effects on the outcomes of adult CMS by treatment schemes targeting maternal oxidative stress damage, via the reduction in ROS production and/or increase in antioxidant activity, have been reported in various animal models of FPCS, including at least maternal exposure to hypoxia, low protein diet, high fructose or fat diet, dexamethasone and intrauterine growth restriction [8,11,17,38,39]. Agents that show protection against oxidative stress damage in FPCS include at least ascorbic acid [40], resveratrol [14,28,41], lazaroid [42], melatonin [19,40,43], docosahexaenoic acid [44] and simvastatin [28]. These agents, when applied to mother or offspring, exert beneficial influences in traits of adult CMS;

among which are diabetes, cardiovascular disorders, dysregulated lipid profiles and obesity [27].

It is, however, noteworthy that antioxidant treatment has not always been successful in preventing FPCS. In some cases, antioxidant treatment causes nominal or even detrimental outcomes. For example, maternal resveratrol treatment alters fetal pancreatic development [45], and combined antioxidant treatment with vitamins C and E in undernourished pregnant rats prevents programming of vascular dysfunction but is unable to prevent programming of the reduction in glomerular number or glomerular filtration rate [46].

At the same time, it should be accentuated that the beneficial effects of antioxidant interventions demonstrated in various animal models of FPCS may not always be translated to clinical therapy. Pregnant women with fetal growth restriction have significantly reduced plasma levels of antioxidant vitamins C and E [47], but a meta-analysis showed that supplementation with these antioxidant vitamins does not improve fetal growth [48]. Randomized controlled trials in women with compromised pregnancies have also been performed to assess the potential benefits of antioxidant therapy but have failed to demonstrate improved pregnancy outcomes or neonatal mortality from antioxidant therapy [8]. Together, the inconsistency on the beneficial outcomes of maternal treatment, and the safety and efficacy of applying antioxidants during pregnancy prompted intervention strategies for FPCS to target tissue oxidative stress in offspring without directly interfering with fetal development is an attractive alternative. Towards this end, only a few animal studies have been reported. Postnatal resveratrol supplementation prevents the deleterious cardiovascular effects of high fat diet in offspring exposed to prenatal hypoxia [49]. Oral intake of resveratrol by young adult rats ameliorates brain oxidative stress and reduces reprogrammed hypertension to maternal high fructose exposure [28]. Although evidence from animal studies indicates the beneficial effect of postnatal antioxidant treatments on the FPCS, therapeutic use of agents targeting oxidative stress to prevent or alleviate adult human CMS of fetal origin has not been investigated despite their clinical relevance.

Perspectives

After more than three decades of investigations, the concept of DOHaD in adult CMS is well corroborated in animal and human studies. From the collective evidence it is clear that exposure to suboptimal intrauterine environment during fetal development primes long-term influence and exerts considerably impact on adult health. While there is an impressive collection of research studies that have markedly expanded our knowledge on the impact of FPCS in adult life, there still remain areas in which little is known or results are controversial. One area of critical importance in FPCS is the timing and duration of the insult to fetal development. Indeed, some research has been performed to identify the critical windows during which fetal development is at most vulnerable risk of undergoing oxidative stress-induced adverse adaptations. Greater understanding of the time course of the oxidative stress damage will provide insight into the relative impact of various prenatal and postnatal factors on FPCS. These lines of information will then provide the opportunity for the identification of biomarkers to predict offspring affected by FPCS, and allow for early implementation of monitoring or treatment strategies. At the same time, further studies in the discovery of specific molecules and pathways affected by tissue oxidative stress during fetal development are required to drive the development of novel therapeutics.

Another aspect of FPCS research is that most animal studies have concentrated on the male and evidence from recent studies implicates gender differences in oxidative stress-associated dysfunctions in offspring [27,50]. Much remains to be determined in delineating how and

why the responses are sex-dependent, which will be critical in determining the most advantageous personalized therapeutic options. Furthermore, intervention strategies to offspring during pre-CMS or CMS conditions are not systemically investigated despite their clinical relevance. Therefore, future study on the antioxidant reprogramming strategy may need to be diverted from treating the mother to normalize fetal growth and birth weight, but rather emphasize the ability of antioxidants to prevent FPCS in offspring. Particularly, studies designed to evaluate the efficacy and safety of antioxidant interventions on FPCS at different ages of offspring are required. It is also invaluable if long-term longitudinal follow-ups of infants born to mother exposure to oxidative stress could be conducted to test the oxidative stress programming hypothesis in FPCS. Finally, although there have been clinical trials using antioxidants to treat neonatal and fetal diseases, the reprogramming strategies aiming at oxidative stress for various adult non-communicable diseases, especially CMS, still awaits further clinical translation.

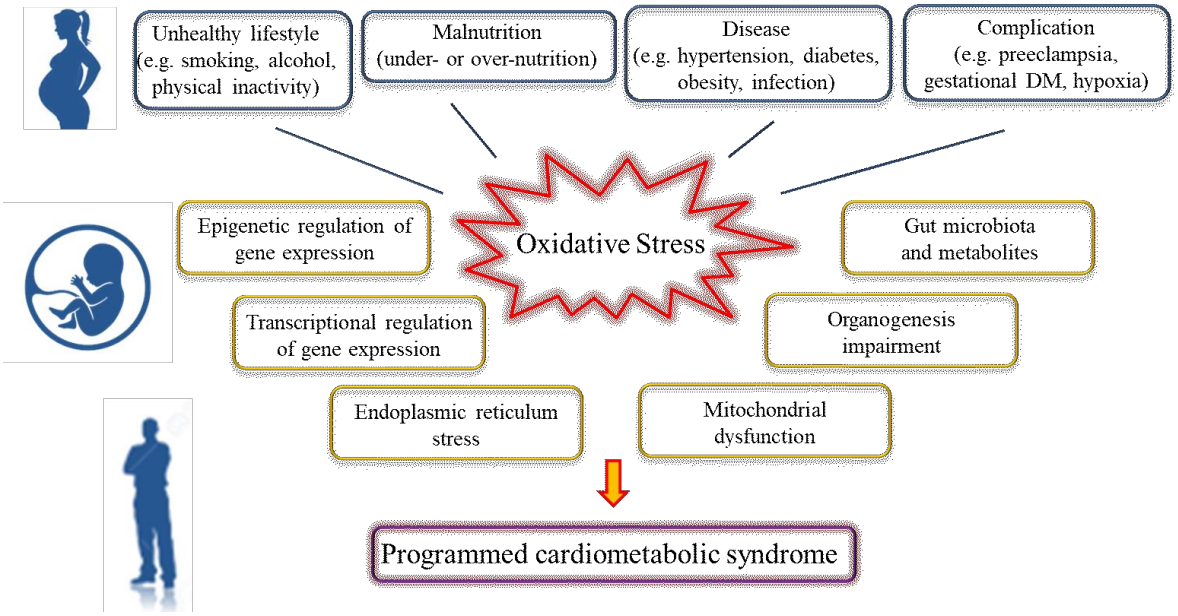

Figure 1. Overview schematics of the role of oxidative stress in fetal programming of cardiometabolic syndrome. Both maternal (lifestyle and disease) and placental factors (malnutrition, complication) prime oxidative stress damage in fetus, which in turn programs structural and functional changes in cardiometabolic-related organs via at least transcriptional and epigenetic regulation of genes, endoplasmic reticulum stress, mitochondrial dysfunction, impairment of organogenesis and changes in gut microbiota and metabolites, thereby influence the in utero and postnatal environment of the offspring to increase the risks for cardiometabolic syndrome later in adult life.

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Julie Y. H. Chan received her PhD in Neuroscience from Washington State University, in the field of central neural control of cardiovascular functions. Following one year postdoctoral training at the same university, she returned to Taiwan in 1990 to join the Department of Medical Education and Research at the Taipei Veterans General Hospital as a principal investigator and was promoted to senior (professorial) principal investigator in 1996. In 1998, Julie moved to the Veterans General Hospital in Kaohsiung, Taiwan, where she served as the Head of the Basic Medical Research Division until 2010 when she joined the Kaohsiung Chang Gung Memorial Hospital to chair the Department of Medical Research. She is currently a Distinguished Chair Professor in the Institute for Translational Research in Biomedicine and the President of the International Union of Physiological Sciences. Julie Chan's laboratory has a long-standing research interest in brain stem cardiovascular regulatory mechanisms. Her current research focuses on molecular and cellular mechanisms underlying oxidative stress-mediated cardiovascular disorders, particularly with reference to neurogenic hypertension and fetal programming of metabolic syndromes.