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Chapter 17

Epigenetic Programming of Cardiovascular Disease by Perinatal Hypoxia and Fetal Growth Restriction

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Abstract

Most of the worldwide deaths in patients with non-communicable diseases are due to cardiovascular and metabolic diseases, which are determined by a mix of environmental, genetic and epigenetic factors, and by their interactions. The aetiology of most cardiovascular diseases has been partially linked with *in utero* adverse conditions that may increase the risk of developing diseases later in life, known as Developmental Origins of Health and Disease (DOHaD). Perinatal hypoxia can program the fetal and postnatal developmental patterns, resulting in permanent modifications of cells, organs and systems function. In spite of the vast evidence obtained from human and animal studies linking development under adverse intrauterine conditions with increased cardiovascular risk, still few is known about the specific effects of intrauterine oxygen deficiency and the related pathogenic mechanisms. Currently, the most accepted processes that program cellular function are epigenetic mechanisms which determine gene expression in a cell-specific fashion. In this chapter we will review the current literature regarding the perinatal exposure to chronic hypoxia and Fetal Growth Restriction (FGR) in humans and animals and how this impinges the cardiovascular physiology through epigenetic, biochemical, morphologic and pathophysiologic modifications that translate into diseases blasting at postnatal life.

Keywords: hypoxia, programming, vascular function, oxidative stress, epigenetics, chronic diseases

1. Introduction

The worldwide prevalence of cardiovascular diseases (CVDs) and metabolic syndrome ranges between 20 and 40%. These figures are likely to rise over the next decades [1, 2]. Genetic changes associated with the traits of the metabolic syndrome and cardiovascular diseases are

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able to explain a small proportion of cases [3], suggesting the presence of other contributory factors in these conditions. Epidemiologic studies in the late 1980s in the UK revealed a strong correlation with perinatal and fetal growth patterns. Fetal growth restriction (FGR) is thus associated with an increased risk of developing adult cardiometabolic diseases [4]. Multiple reports from across the world have documented the association between intrauterine growth mediators in early life with lifelong health. These are now recognized to be important risks in the development of non-communicable diseases in adult life. This concept so-called "Fetal Programming" has evolved into "Developmental Origins of Health and Disease" (DOHaD), which we refer as Intrauterine Programming (IUP) [5] for the purpose of this chapter. The present efforts in this field are focused on unveiling the physiological and molecular mechanisms, which drive IUP, and exploring opportunities to prevent or revert the long-term consequences. The physiologic and biochemical changes that explain IUP relate to the timing and stage of development when the insult takes place; the earlier in development, the stronger the long-term effects [5]. Conversely, the long-term consequences of IUP and reproducibility of the related phenotypes suggest that epigenetic mechanisms may underlay the altered "cell programming" [6].

2. Fetal growth restriction

Fetal growth restriction (FGR) is clinically defined by a fetal weight below the 10th percentile of normal for gestational age, but in a generic manner, FGR is a condition in which the potential growth of the fetus is negatively influenced by environmental and maternal factors [7]. The short-term consequences of FGR are LBW and the corresponding phenotype, which is associated with increased perinatal morbidity and mortality [8]. The long-term effects include a two- to threefold increase in the risk of developing cardiovascular disease (hypertension and coronary heart disease) in adult life [9]. The higher CVD risk in adults resulting from FGR can be traced back to a reduced arterial compliance in pre-pubertal subjects [10] and a decreased peripheral endothelial-dependent vascular relaxation at birth [11]. Moreover, studies in human placentae show that FGR-related endothelial dysfunction can also be detected in chorionic and umbilical arteries [12, 13]. Notably, we have recently demonstrated the presence of functional and epigenetic markers of endothelial dysfunction in systemic and umbilical arteries from FGR guinea pigs. The presence of these comparable markers suggests that umbilical artery endothelial cells (ECs) may be useful to explore the endothelial function of the fetus. The etiology of FGR in humans is not fully understood; however, there are known maternal risk factors such as living at high altitude, malnutrition, smoking, stress, and vascular dysfunction [14] which induce placental dysfunction and consequently fetal growth restriction. Presently, oxygen, glucose, free radicals, amino acids, and hormones have been shown to play an important role in modulating fetal growth and development. These factors are dynamically regulated throughout gestation [15]. In the earlier stages, limitations in oxygen supply promote trophoblast proliferation; however, persistence in a hypoxic environment as occurs in FGR harms trophoblast invasion and the transformation of spiral arteries leading to a vascular dysfunction of the placenta and impaired fetal growth. Thus, chronic hypoxia and oxidative stress have an important role in the placental

dysfunction observed in FGR [15]. Several studies on humans confirm the presence of molecular markers of oxidative stress in the FGR placentae, the fetus, and the mother [16–19]. Impaired placental vascular function has also been proposed to play a role in FGR, conditioned by augmented synthesis and response to vasoconstrictors [20] and limited action of vasodilators [13], as well as by an increased inhibition of endothelial-dependent relaxation mediated by prooxidants [21].

Appropriate maternal nutrient supply to the fetus is key for its development. Several approaches limiting maternal supply (i.e., diet restriction) and placental nutrient transfer have been used to alter the normal fetal growth rate and development. In order to address this issue, various animal models (sheep, rat, rabbit, and guinea pig) have been developed, where placental dysfunction is induced by a reduction in uterine blood flow [22, 23]. We have recently developed a novel model of FGR in guinea pigs, by a progressive bilateral occlusion of the uterine arteries during the second half of gestation that gradually alters placental vascular resistance [24]. Several aspects suggest that this model is relevant to human clinical significance. For instance, guinea pigs present a decreased fetal abdominal growth and impaired placental blood flow adaptation during gestation, with a preserved brain blood flow and development, translating into an asymmetric FGR. Additionally, higher resistance to blood flow in the umbilical arteries can be observed. These are relevant clinical markers of FGR. However, most of mammalian models that develop placental insufficiency present a mixed effect of undernutrition, hypoxia, and oxidative stress [22]. Therefore, complementary models on chick embryos have been used to isolate the unique fetal effects of hypoxia during development from maternal responses [22]. Interestingly, the follow-up of the chickens gestated under hypoxia has shown important insights into the pathophysiological mechanisms that impair the cardiovascular function. For instance, Tintu et al. showed that developmental hypoxia induces cardiomyopathy associated with left ventricular dilatation, reduced ventricular wall mass, and increased apoptosis [25]. These responses were coupled with pump dysfunction, decreased ejection fractions, and diastolic dysfunction, which persisted in adulthood. Further, Salinas et al. showed marked cardiovascular morphostructural changes in high-altitude chicks, which were reverted either by incubation at low altitude or by oxygen supplementation [26]. Notably, Herrera et al. followed up these chicks to adulthood describing cardiac impairment in the capacity to response to pressor challenges [27]. In addition to the cardiovascular system, several organs/functions are affected during developmental hypoxia such as central nervous system, lung, and systemic metabolism. As well as in mammalian physiology, it seems that oxidative stress might be key in establishing the impairments induced by developmental hypoxia [28].

2.1. Hypoxia and oxidative stress in FGR

Hypoxia is defined as a limited oxygen (O_2) supply relative to the physiological demands of a tissue, organ, or organism. This is a restrictive condition frequently seen in the hypobaric environment (hypoxia of high altitude) or by a diminished oxygen delivery. At lowlands, hypoxia is a restrictive condition often faced during fetal life, either by maternal, umbilical-placental, or fetal conditions. Placental insufficiency leads to fetal growth restriction due to a chronic decrease in fetoplacental perfusion. This situation affects simultaneously O_2 and

nutrient supply to the fetus [29], overlapping conditions that become difficult to isolate in order to assess the specific effect of O_2 deficiency in determining vascular impairment. Using avian models of FGR has served to establish that chronic hypoxia, independent of nutrition, plays a crucial role in vascular programming [30, 31]. Studies of vascular function during fetal life show remarkable similarities between the effect of hypoxia in chick embryos and placental insufficiency in mammals [26, 28]; they have also served to assess the long-term consequences [27]. In both cases (chick embryos and mammalian fetuses), the presence of endothelial dysfunction and vascular remodeling is observed mainly in peripheral arteries. The mechanism by which hypoxia induces cell damage in either case is the result of an increased generation of reactive oxygen species (ROS) due to an incomplete reduction of oxygen [15, 32].

The imbalance between endogenous antioxidant defenses and reactive oxygen species, where ROS overwhelms the antioxidant capacity, has been termed "oxidative stress" [33]. ROS includes a wide variety of highly reactive molecules, such as superoxide anion ($\cdot O_2^-$), hydrogen peroxide (H_2O_2), ·NO, peroxynitrite (ONOO-), organic hydroperoxide (ROOH), hypochlorous acid (HOCl), and hydroxyl (·OH), alkoxy (RO·), and peroxy radicals (ROO·) [34]. Superoxide is the main ROS acting at the vascular level; it derives from the enzymatic activity of NOX (NADPH oxidases), XOR (xanthine oxidases), mitochondrial complexes I and III, uncoupled eNOS, and iNOS. In the case of NOS, ROS generation can occur because of reduced L-arginine (substrate) or BH_4 (cofactor) availability [33], uncoupling eNOS enzymes. Consequently, NOS-derived $\cdot O_2^-$ rapidly reacts with NO generating ONOO-, which reduces NO levels and modifies the structure of proteins, lipids, and DNA, causing endothelial dysfunction. Thus, increased oxidative stress exerts a negative effect on eNOS activity and NO bioavailability at multiple levels [33].

In FGR, compelling data show that oxidative stress in parallel to chronic hypoxia contributes to vascular dysfunction in the mother, placenta, and fetus [14]. In fact, short-term hypoxia induces eNOS expression and activation in human umbilical artery endothelial cells (HUAECs) [35], while in FGR HUAEC, there is reduced eNOS activation [13]. Conversely, FGR subjects present at birth increased levels of lipid peroxidation and decreased the activity of antioxidant enzymes and circulating mediators [36]. Additionally, markers of oxidative stress have been positively associated with increased umbilical artery pulsatility index, particularly in pregnancies affected by FGR [37]. We recently addressed the role of oxidative stress in FGR by treating pregnant guinea pigs with N-acetyl cysteine, a glutathione precursor, during the second half of gestation. Our results show that maternal treatment with NAC restores fetal growth by increasing placental efficiency and reverses endothelial dysfunction in FGR guinea pigs [38]. Similarly, *in ovo* melatonin administration to chronic hypoxic chick embryos reduces the levels of oxidative stress markers (i.e., lipid peroxidation and protein nitration), by increasing the expression of glutathione peroxidase (GPx), an antioxidant enzyme [28]. This effect is associated with improved endothelial function and reversal of fetal hypoxia-induced vascular remodeling; however, melatonin does not prevent FGR. Even more, in a chronic hypoxic sheep model, melatonin decreased maternal oxidative stress but simultaneously enhanced fetal growth restriction [39]. In summary, these data suggest that hypoxia and oxidative stress participate in the genesis of FGR-induced vascular dysfunction.

However, there is a need for further studies addressing the precise molecular mechanisms and effective treatments for hypoxic FGR and IUP.

At a molecular level, transcription factors nuclear factor kappa B (NFκB) [34] and nuclear factor E2-related factor 2 (Nrf2) implicated in oxidative stress [34, 40] participate in promoting and reducing cellular oxidative stress, respectively. Interestingly, Nrf2 presents the suggested properties of an oxidative stress sensor. Nrf2 is normally bound to Keap1, which targets the complex to proteasome degradation; however, a prooxidant milieu induces the oxidation of two cysteine residues in Keap1 and the release of Nrf2 that subsequently translocate to the nucleus [34]. The antioxidant response triggered by Nrf2 includes the expression of NAD(P)H dehydrogenase quinone 1 (NQO1), heme-oxygenase (HO), and other antioxidant enzymes [40]. Studies show that Nrf2-induced expression of NQO1 and HO-1 improves endothelial dysfunction increasing eNOS efficiency. However, there is no information addressing whether changes in the expression of genes involved in the antioxidant defense are present in early stages of endothelial dysfunction in FGR and whether they can be modulated during gestation.

3. Epigenetics and endothelial programming in FGR

Alteration in fetal development and IUP results in permanent changes in the physiological responses to different stressors across the life course. Undoubtedly, this represents a potential "handicap" for long-term health. Growing evidence in humans from individuals with altered fetal growth, and from animal models associated with the development of later cardiometabolic alterations, confirms the presence of epigenetic markers in different cell types [41]. Epigenetics can be considered as "chromosome-based mechanisms that modify the phenotypic plasticity of a cell or organism" [6]. Development itself is controlled by epigenetic mechanisms, which regulate cell differentiation and record environmental signals under physiologic [42] and/or pathologic conditions [43]. These epigenetic mechanisms include DNA methylation, a plethora of histone posttranslational modifications (PTM) (acetylation, methylation, phosphorylation, and others), ATP-dependent chromatin modifications, and noncoding RNAs [44].

3.1. DNA methylation

In higher animals, DNA is methylated via an enzymatic activity that transfers a methyl group to the 5′ position of cytosine ring on CpG dinucleotide generating 5-methyl-cytosine, a reaction catalyzed by two different families of DNA methyltransferases (DNMTs), named DNMT1 and DNMT3 (DNMT3a and DNMT3b) encoded by three different genes [45]. The role of DNMT1 is to preserve the DNA methylation pattern after DNA replication during mitotic cell division as well as after fertilization [46], a process guided by the presence of hemi-methylated CpGs, which are recognized by DNMT1 in dsDNA [47]. Additionally, DNMT3a and DNMT3b catalyze *de novo* methylation allowing the establishment of new DNA methylation patterns during gametogenesis, embryonic development, and cell differentiation [46, 48]. Interestingly, the genome of different cell types from a single subject presents a high DNA methylation density;

however, larger differences occur in the promoter regions of genes representing less than 5% of the total genomic DNA methylation [49]. Nonetheless, these subtle differences are likely controlling most cell-specific proteins expression at the whole organism level [50]. It is commonly accepted that DNA methylation represents a hallmark of reduced gene expression and long-term gene silencing [51, 52]; however, it is worth noting that growing evidence suggests a more dynamic role for this mechanism in the regulation of gene expression [51].

3.2. Histone posttranslational modifications

The protein structural unit of the chromosomes, the nucleosome, is formed by two copies of four histones proteins named H2A, H2B, H3, and H4. Additionally, these proteins present a globular domain to interact with other histones, and a flexible tail that participates actively in the interaction with DNA. Unlike DNA methylation, histone posttranslational modifications (PTMs) are more dynamic and do not give a straight idea regarding gene silencing or activation [52]. Moreover, histone PTMs are closely related with the context in which they take place and the presence of additional PTMs, suggesting the existence of a "histone code." Up to date, more than 50 enzymes that catalyze diverse histone modifications have been identified and classified according to the reaction they carry out [53]. **Histone acetylation** occurs in lysine residues (K) and involves the transference of an acetyl group from acetyl-CoA. In mammals, this reaction is carried out by three families of histone acetyl-transferases (HAT) named GNAT, MYST, and CBP/p300 [54]. This modification is considered an activator of gene expression, due to the fact that it stabilizes the positive charge of the lysine in the histone, reducing its affinity for DNA, avoiding the formation of highly compacted chromatin. The best characterized acetylations are those that take place in lysine 9 (K9), K14, K18, and K56 in histone 3 (H3) and K5, K8, K13, and K16 in H4 [55]. At least four types of **histone deacetylases** (HDAC I, II, III y IV) have been identified, which catalyze the reverse reaction of that done by the **histone acetyl-transferase**. This enzymatic reaction is related to gene silencing, progression of cell cycle, differentiation, and the response induced by DNA damage [56]. HDAC activity can be induced in response to DNA methylation, once repressor proteins that bind CpGs (MCP) are recruited. The latter have a site of interaction with several HDACs, suggesting that gene silencing could result from a combined action of DNA and histone modifications [51, 57].

3.3. Noncoding RNAs

The idea that noncoding RNAs could regulate the expression of genes was first proposed in the early 1960s [58], with a substantial progress in this field during the last decade. Less than 5% of the transcribed RNA encodes proteins; thus, most of them correspond to noncoding RNAs (ncRNAs) involved mainly in the regulation of gene expression [59, 60]. "Long" ncRNA (lncRNA), small interfering RNA (siRNA), and micro-RNA (miRNA) are the main regulatory ncRNAs. The lncRNA regulates the expression of a specific gene complementary either through chromatin remodeling, alternative mRNA processing (splicing), or siRNA generation [59]. Conversely, siRNA and miRNAs are interference RNA-based epigenetic mechanisms,

which silence genes via noncoding RNAs of ~21 bp. To date, more than a thousand noncoding miRNAs have been reported. These are transcribed by the RNA polymerase II and encoded by specific genes (~70%) or, in lesser amounts, within the intronic regions of gene encoding proteins. Micro-RNAs are transcribed as pre-miRNA and initially processed in the nucleus by the DROSHA-DGCR8 complex. Subsequently, they are exported to the cytoplasm for miRNA maturation by the action of the complex formed by the DICER1 protein and RNase IIIa IIIb [61]. This processing leads to a single-strand RNA, which is incorporated into the "protein-induced silencing complex miRNA" (miRISC), which binds to a complementary region in a target mRNA. It has been proposed that a full complementarity between the miRNA and mRNA leads to degradation of the mRNA, while partial complementarity suppresses translation [62]. Notably, a single miRNA can regulate the expression of multiple mRNAs often associated signaling pathways or metabolic processes, while several miRNAs may converge in the regulation of a single mRNA constituting a complex mechanism for gene expression regulation [61, 62].

3.4. Epigenetics in endothelial physiology

Vascular development and endothelial differentiation and function require a fine epigenetic tuning, suggesting that epigenetic mechanisms play a key role in the IUP-associated vascular dysfunction [6]. The first stages of vascular development are determined by genetic factors, while the next processes that take place (i.e., blood vessel structure, identity, and function) are influenced/determined by hemodynamic factors, ROS, and oxygen levels [63, 64]. Considering that the effect of endothelial-specific transcription factors such as KLF2 and HoxA9 does not explain the protein expression levels present in this cell type [65], an "endothelial epigenetic code" regulating the expression of crucial genes has been suggested [52, 66]. Growing evidence shows that DNA methylation, histone PTM, and miRNAs [67] play an important role in the embryonic origins of endothelial cells (EC), as well as their homeostasis during life. The epigenetic regulation of *NOS3* gene has been extensively studied in EC and non-EC, showing that ECs have a distinctive pattern of DNA methylation and histone PTMs [65]. Conversely, the decreased expression of eNOS in HUVEC exposed to acute hypoxia is controlled by the overexpression of a natural cis-antisense noncoding RNA called sONE [68] and changes in histone PTM which occur specifically at the promoter of eNOS [69]. Similarly, in the endothelium, hypoxia and oxidative stress regulate the expression of several miRNAs that modify the expression of eNOS and other enzymes related to its short- and long-term function [70]. In support of this notion, we have recently demonstrated that eNOS-induced NO enhances arginase-2 expression by epigenetic modifications in the histones residing at *ARG2* gene promoter [71]. In summary, these data show that EC-specific eNOS expression, as well as other genes related with the L-arginine/NO pathway, is effectively controlled by multiple epigenetic mechanisms which are strongly influenced by hypoxia.

3.5. Epigenetics and endothelial dysfunction

Diverse studies show that epigenetic mechanisms can increase the risk or directly participate in the development of vascular diseases. In humans, ECs from atherosclerotic

plaques have decreased levels of estrogen receptor-β along with increased DNA methylation at the promoter region of this gene, compared with nonatherosclerotic plaques cells [72]. Further studies in mice [73] and swine [74] have demonstrated that disturbed flow induces genome-wide changes in the DNA methylation of EC in vivo and in vitro, an effect that would be dependent on DNMT1 expression and that mainly affects genes related to oxidative stress. Conversely, abrogation of *Nos3* promoter DNA methylation increases basal eNOS mRNA expression in vitro and protects against hind limb ischemia injury in vivo [75]. Similarly, growing evidence suggests a central role of miRNAs in the genesis of cardiometabolic dysfunction, also proposed as sensitive molecular markers of vascular disease [76]. In fact, we recently reported that circulating levels of miRNA Let-7 and miR-126 are associated with different traits of cardiometabolic dysfunction in children as well as have a predictive value for metabolic syndrome in these subjects [77]. Comparable results in adults with type 2 diabetes have been reported, where increased levels of miR-21 and decreased levels of miR-126 correlated with cardiovascular and inflammatory complications [78].

In the context of IUP of endothelial dysfunction in rats, it has been shown that brief exposure to hypoxia at the end of gestation induces pulmonary vascular dysfunction in the newborn, which associates with increased eNOS expression accompanied by decreased DNA methylation in *Nos3* gene promoter [79]. Similarly, we reported a few years ago for the first time the presence of an altered epigenetic programming of eNOS expression in EC derived from human umbilical arteries of FGR patients [12]. Notably, the altered expression of eNOS was reversed by silencing DNMT1 expression in FGR EC, which restored the DNA methylation pattern at *NOS3* promoter, as well as the regulation of eNOS expression induced by hypoxia [12]. Furthermore, using a guinea pig model of FGR, we compared the eNOS expression and DNA methylation pattern at *Nos3* promoter to clarify whether these epigenetic changes occurring in umbilical EC would represent changes that take place in systemic arteries (i.e., aorta and femoral) [38]. We found comparable changes in eNOS expression which were associated with specific changes in DNA methylation of *Nos3* promoter in the different FGR EC studied, suggesting the presence of a common programming of endothelial dysfunction in the umbilical-placental and systemic circulation. Of note, maternal treatment with an antioxidant (NAC) prevented this epigenetic programming, restoring the eNOS mRNA levels to values observed in control fetuses. Similar studies have shown the beneficial effects of antioxidants during development, showing clear evidences that ROS have causal roles in cardiovascular programming [32]. In addition, several authors have shown that ROS may induce important epigenetic modifications that determined cardiovascular dysfunction later in life. Hypoxia and oxidative stress have been shown to be present in several conditions during pregnancy, such as preeclampsia, placental insufficiency, and high-altitude pregnancies [80]. In addition, assisted reproductive technologies induce hypoxic conditions at very early stages of development. All of the above studies have suggested epigenetic modifications of the eNOS gene [80, 81]. Conversely, the response to hypoxia and oxidative stress is primarily mediated by the hypoxia-inducible transcription factor (HIF), which is regulated by the oxygen-sensing HIF hydroxylases, members of the 2-oxoglutarate (2OG)-dependent oxygen-

ase family. Similarly, there are demethylases from the same family modulating methylation levels. Both systems, a transcription factor and an epigenetic regulator, are being regulated by hypoxia [82]. Further, HIF-1α has been suggested as an epigenetic modulator determining chromatin remodeling of hypoxia-responsive elements (HREs) sites [83]. Interestingly, in this report, a marked hyperacetylation of histones H3 and H4 was observed in the placental growth factor (Plgf) intron in hypoxic conditions. Further studies are needed to determine the interaction of transcription factors and epigenetic regulation, which might be an efficient way of controlling gene expression.

Another epigenetic regulatory mechanism is the miRNAs in the IUP. Present evidence suggests that miRNAs could be transferred across the placenta [84] with important consequences on fetal and maternal physiology. In humans, circulating levels of miR-21 during gestation in the mother positively correlate with evidence of fetal hypoxia [85] and evidence from in vitro studies show the participation of miR-21 in the FGR placental vascular dysfunction [86, 87]. By contrast, placental miR-126 levels negatively correlate with the FGR severity [88]. Studies in umbilical endothelium from swine fetuses have shown that the expression of miRNA that targets eNOS and VEGF pathways can be modulated by maternal supplementation with an L-arginine precursor [89]. Similarly, undernutrition decreases and programs at long term the expression of an anti-remodeling miRNA and this effect is prevented by the *in utero* inhibition of corticosteroid synthesis in pregnant rats [90].

4. Potential role of hypoxia-induced miRNAs, miR-21 and miR-126, on the endothelial dysfunction in FGR

As previously discussed, ncRNAs constitute an important epigenetic mechanism, which mainly regulates RNA translation; notably miR-21 and miR-126 represent two potential miRNAs with a crucial role in the endothelium. In fact, both miRNAs are abundantly expressed in cultured endothelium [91] and respond to hypoxia with a substantial increase in miR-21 and miR-126 levels, representing ~40% of all the miRNAs present in this cell type [92]. In contrast to most miRNAs, miR-126 and miR-21 are encoded within the intronic region of genes coding for proteins. MiR-126 is encoded in the seventh intron of the gene for the endothelial-specific protein epidermal growth factor-like domain 7 (Egfl7) and its expression is partially (~30%) dependent on transcription factors that bind to the promoter region of this Egfl7 [93]. Additionally, miR-126 expression is regulated, independently of Egfl7, by the DNA methylation status of a miR-126-specific promoter located in intron 7 of Egfl7 [94], as well as the binding of Nrf2 to this region in response to oxidative stress [95]. Preliminary data from our group show that FGR human endothelial cells present increased levels of DNA methylation in miR-126 promoter, suggesting an epigenetic programming of this miRNA in FGR endothelium. Conversely, miR-21 is encoded in the 11th intron of the stress-induced protein TMEM49, but its expression is completely controlled by a specific promoter in the intron 10 of TMEM49 with predicted binding sites for transcription factors that respond to oxidative

stress and inflammation [96, 97]. This suggests that the expression of miR-21 and miR-126 could be regulated by epigenetic modifications present in their specific intronic promoters.

It has been proposed that miR-126 is an endothelial-specific miRNA which promotes angiogenic activation in progenitor cells during early development, as well as vascular repair in adult subjects, while in mature endothelial cells, it has an anti-atherogenic effect maintaining endothelial quiescence and preventing inflammation [67]. In ob/ob mice, antioxidant treatment induces a miR-126-dependent anti-inflammatory and antioxidant vascular response [98], an effect also observed in HUVEC [99]. Both miRNAs, miR-21 and miR-126, are upregulated by unidirectional shear stress, protecting EC from apoptosis and increasing the activation of eNOS [100]. However, in oscillatory shear stress conditions, increased levels of miR-21 promote the expression of pro-inflammatory mediators [101]. Thus, it has been proposed that miR-21 has a dual effect on vascular function: over a short time, it protects against hypoxia and ischemia [70, 102–104], and over the longer term, leads to endothelial dysfunction, apoptosis [70, 102, 105, 106], and eNOS dysfunction. The latter would occur by targeting the expression of antioxidant enzymes [70], as well as enhancing the levels of the endogenous eNOS inhibitor asymmetric dimethyl arginine (ADMA) by downregulating the expression of the enzyme dimethyl arginine dimethylaminohydrolase 1 (DDAH1) [105, 107, 108]. These data suggest that the dynamic regulation of miR-21 and miR-126 could participate in the early defense of the endothelium to hypoxia and oxidative stress; nonetheless, they prime endothelial dysfunction over the long term. Thus, increased levels of miR-21 and decreased expression of miR-126 observed in FGR placentae at term could represent a consequence rather than a cause of the hypoxia-induced endothelial dysfunction.

5. Conclusions

The programming of vascular, particularly endothelial dysfunction by hypoxia in FGR is an important issue in fetal-maternal medicine up to date. Currently, there is a serious need to undercover the real impact of hypoxia as a driving force to perinatal and postnatal cardiovascular and metabolic diseases, pointing out the main proposed mechanisms. The reviewed data support the notion that epigenetic mechanisms contribute to defining and regulating vascular responses to pathological stimuli (leading to FGR). However, evidence of how fetal exposure to hypoxia and oxidative stress lead to epigenetic modifications remains elusive.

Therefore, new knowledge on the role of epigenetic mechanisms involved in the long-term vascular function is crucial to understand and put into context adequate interventions. The timing of the vascular adaptations and epigenetic responses is one of the most relevant questions that need to be answered in order to prioritize clinical approaches to early diagnose and treat such perinatal conditions, limiting postnatal cardiometabolic risk in the progeny.

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References

[1] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr.: Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009, 120:1640–5.

[2] Escobedo J, Schargrodsky H, Champagne B, Silva H, Boissonnet CP, Vinueza R, Torres M, Hernandez R, Wilson E: Prevalence of the metabolic syndrome in Latin America and its association with sub-clinical carotid atherosclerosis: the CARMELA cross sectional study. Cardiovasc Diabetol 2009, 8:52.

[3] El Shamieh S, Visvikis-Siest S: Genetic biomarkers of hypertension and future challenges integrating epigenomics. Clin Chim Acta 2012, 414:259–65.

[4] Barker DJ: Birth weight and hypertension. Hypertension 2006, 48:357–8.

[5] Hanson MA, Gluckman PD: Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev 2014, 94:1027–76.

[6] Krause B, Sobrevia L, Casanello P: Epigenetics: new concepts of old phenomena in vascular physiology. Curr Vasc Pharmacol 2009, 7:513–20.

[7] Zhang J, Merialdi M, Platt LD, Kramer MS: Defining normal and abnormal fetal growth: promises and challenges. Am J Obstet Gynecol 2010, 202:522–8.

[8] Romo A, Carceller R, Tobajas J: Intrauterine growth retardation (IUGR): epidemiology and etiology. Pediatr Endocrinol Rev 2009, 6(Suppl 3):332–6.

[9] Cohen E, Wong FY, Horne RS, Yiallourou SR: Intrauterine growth restriction: impact on cardiovascular development and function throughout infancy. Pediatr Res 2016; 79(6):821–30.

[10] Martin H, Hu J, Gennser G, Norman M: Impaired endothelial function and increased carotid stiffness in 9-year-old children with low birthweight. Circulation 2000, 102:2739–44.

[11] Martin H, Gazelius B, Norman M: Impaired acetylcholine-induced vascular relaxation in low birth weight infants: implications for adult hypertension? Pediatr Res 2000, 47:457–62.

[12] Krause BJ, Costello PM, Munoz-Urrutia E, Lillycrop KA, Hanson MA, Casanello P: Role of DNA methyltransferase 1 on the altered eNOS expression in human umbilical endothelium from intrauterine growth restricted fetuses. Epigenetics: Official Journal of the DNA Methylation Society 2013, 8:944–52.

[13] Krause BJ, Carrasco-Wong I, Caniuguir A, Carvajal J, Farias M, Casanello P: Endothelial eNOS/arginase imbalance contributes to vascular dysfunction in IUGR umbilical and placental vessels. Placenta 2013, 34:20–8.

[14] Roberts JM: Pathophysiology of ischemic placental disease. Semin Perinatol 2014, 38:139–45.

[15] Herrera EA, Krause B, Ebensperger G, Reyes RV, Casanello P, Parra-Cordero M, Llanos AJ: The placental pursuit for an adequate oxidant balance between the mother and the fetus. Frontiers Pharmacol 2014, 5:149.

[16] Takagi Y, Nikaido T, Toki T, Kita N, Kanai M, Ashida T, Ohira S, Konishi I: Levels of oxidative stress and redox-related molecules in the placenta in preeclampsia and fetal growth restriction. Virchows Archiv: Int J Pathol 2004, 444:49–55.

[17] Biri A, Bozkurt N, Turp A, Kavutcu M, Himmetoglu O, Durak I: Role of oxidative stress in intrauterine growth restriction. Gynecol Obstet Invest 2007, 64:187–92.

[18] Bar-Or D, Heyborne KD, Bar-Or R, Rael LT, Winkler JV, Navot D: Cysteinylation of maternal plasma albumin and its association with intrauterine growth restriction. Prenatal Diag 2005, 25:245–9.

[19] Potdar N, Singh R, Mistry V, Evans MD, Farmer PB, Konje JC, Cooke MS: First-trimester increase in oxidative stress and risk of small-for-gestational-age fetus. Bjog 2009, 116:637–42.

[20] Wareing M, Greenwood SL, Fyfe GK, Baker PN: Reactivity of human placental chorionic plate vessels from pregnancies complicated by intrauterine growth restriction (IUGR). Biol Reprod 2006, 75:518–23.

[21] Schneider D, Hernandez C, Farias M, Uauy R, Krause BJ, Casanello P: Oxidative stress as common trait of endothelial dysfunction in chorionic arteries from fetuses with IUGR and LGA. Placenta 2015, 36:552–8.

[22] Swanson AM, David AL: Animal models of fetal growth restriction: Considerations for translational medicine. Placenta 2015, 36:623–30.

[23] Carter AM: Animal models of human placentation--a review. Placenta 2007, 28(Suppl A):S41–7.

[24] Herrera EA, Alegria R, Farias M, Diaz-Lopez F, Hernandez C, Uauy R, Regnault TR, Casanello P, Krause BJ: Assessment of in vivo fetal growth and placental vascular function in a novel intrauterine growth restriction model of progressive uterine artery occlusion in guinea pigs. J Physiol 2016, 594:1553–61.

[25] Tintu AN, Noble FA, Rouwet EV: Hypoxia disturbs fetal hemodynamics and growth. Endothelium 2007, 14:353–60.

[26] Salinas CE, Blanco CE, Villena M, Camm EJ, Tuckett JD, Weerakkody RA, Kane AD, Shelley AM, Wooding FB, Quy M, Giussani DA: Cardiac and vascular disease prior to hatching in chick embryos incubated at high altitude. J Dev Orig Health Dis 2010, 1:60–6.

[27] Herrera EA, Salinas CE, Blanco CE, Villena M, Giussani DA: High altitude hypoxia and blood pressure dysregulation in adult chickens. J Dev Origins Health Dis 2013, 4:69–76.

[28] Itani N, Skeffington KL, Beck C, Niu YG, Giussani DA: Melatonin rescues cardiovascular dysfunction during hypoxic development in the chick embryo. J Pineal Res 2016, 60:16–26.

[29] Marsal K: Obstetric management of intrauterine growth restriction. Best Pract Res Clin Obstet Gynaecol 2009, 23:857–70.

[30] Giussani DA, Salinas CE, Villena M, Blanco CE: The role of oxygen in prenatal growth: studies in the chick embryo. J Physiol Lond 2007, 585:911–7.

[31] Miller SL, Green LR, Peebles DM, Hanson MA, Blanco CE: Effects of chronic hypoxia and protein malnutrition on growth in the developing chick. Am J Obstet Gynecol 2002, 186:261–7.

[32] Giussani DA, Camm EJ, Niu Y, Richter HG, Blanco CE, Gottschalk R, Blake EZ, Horder KA, Thakor AS, Hansell JA, Kane AD, Wooding FB, Cross CM, Herrera EA: Developmental programming of cardiovascular dysfunction by prenatal hypoxia and oxidative stress. PLoS One 2012, 7:e31017.

[33] Forstermann U: Nitric oxide and oxidative stress in vascular disease. Pflugers Arch 2010, 459:923–39.

[34] Brigelius-Flohe R, Flohe L: Basic principles and emerging concepts in the redox control of transcription factors. Antioxid Redox Signal 2011, 15:2335–81.

[35] Krause BJ, Prieto CP, Munoz-Urrutia E, San Martin S, Sobrevia L, Casanello P: Role of arginase-2 and eNOS in the differential vascular reactivity and hypoxia-induced endothelial response in umbilical arteries and veins. Placenta 2012, 33:360–6.

[36] Leduc L, Delvin E, Ouellet A, Garofalo C, Grenierd E, Morin L, Dube J, Bouity-Voubou M, Moutquin JM, Fouron JC, Klam S, Levy E: Oxidized low-density lipoproteins in cord blood from neonates with intra-uterine growth restriction. Eur J Obst Gynecol Rep Biol 2011, 156:46–9.

[37] Guven ESG, Karcaaltincaba D, Kandemir O, Kiykac S, Mentese A: Cord blood oxidative stress markers correlate with umbilical artery pulsatility in fetal growth restriction. J Matern-Fetal Neo M 2013, 26:576–80.

[38] Herrera EA, Cifuentes-Zuniga F, Figueroa E, Villanueva C, Hernandez C, Alegria R, Arroyo V, Penaloza E, Farias M, Uauy R, Casanello P, Krause BJ: N-acetyl cysteine, a glutathione precursor, reverts vascular dysfunction and endothelial epigenetic programming in intrauterine growth restricted guinea pigs. J Physiol 2016, doi: 10.1113/JP273396

[39] Gonzalez-Candia A, Veliz M, Araya C, Quezada S, Ebensperger G, Seron-Ferre M, Reyes RV, Llanos AJ, Herrera EA: Potential adverse effects of antenatal melatonin as a treatment for intrauterine growth restriction: findings in pregnant sheep. Am J Obstet Gynecol 2016, 215:245 e1–7.

[40] McSweeney SR, Warabi E, Siow RC: Nrf2 as an endothelial mechanosensitive transcription factor: going with the flow. Hypertension 2016, 67:20–9.

[41] Hanson M, Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD: Developmental plasticity and developmental origins of non-communicable disease: Theoretical considerations and epigenetic mechanisms. Prog Biophys Mol Biol 2011, 106:272–80.

[42] Ohtani K, Dimmeler S: Epigenetic regulation of cardiovascular differentiation. Cardiovasc Res 2011, 90:404–12.

[43] Ordovas JM, Smith CE: Epigenetics and cardiovascular disease. Nat Rev Cardiol 2010, 7:510–9.

[44] Kim JK, Samaranayake M, Pradhan S: Epigenetic mechanisms in mammals. Cell Mol Life Sci 2009, 66:596–612.

[45] Goll MG, Bestor TH: Eukaryotic cytosine methyltransferases. Annu Rev Biochem 2005, 74:481–514.

[46] Reik W: Stability and flexibility of epigenetic gene regulation in mammalian development. Nature 2007, 447:425–32.

[47] Buryanov YI, Shevchuk TV: DNA methyltransferases and structural-functional specificity of eukaryotic DNA modification. Biochemistry (Mosc) 2005, 70:730–42.

[48] Collas P, Noer A, Timoskainen S: Programming the genome in embryonic and somatic stem cells. J Cell Mol Med 2007, 11:602–20.

[49] Suzuki MM, Bird A: DNA methylation landscapes: provocative insights from epigenomics. Nat Rev Genet 2008, 9:465–76.

[50] Illingworth RS, Bird AP: CpG islands – 'a rough guide'. FEBS Lett 2009, 583:1713–20.

[51] Klose RJ, Bird AP: Genomic DNA methylation: the mark and its mediators. Trends Biochem Sci 2006, 31:89–97.

[52] Kimura A, Matsubara K, Horikoshi M: A decade of histone acetylation: marking eukaryotic chromosomes with specific codes. J Biochem 2005, 138:647–62.

[53] Jenuwein T, Allis CD: Translating the histone code. Science 2001, 293:1074–80.

[54] Wang GG, Allis CD, Chi P: Chromatin remodeling and cancer, Part I: covalent histone modifications. Trends Mol Med 2007, 13:363–72.

[55] Berger SL: The complex language of chromatin regulation during transcription. Nature 2007, 447:407–12.

[56] Thiagalingam S, Cheng KH, Lee HJ, Mineva N, Thiagalingam A, Ponte JF: Histone deacetylases: unique players in shaping the epigenetic histone code. Ann N Y Acad Sci 2003, 983:84–100.

[57] Matouk CC, Marsden PA: Epigenetic regulation of vascular endothelial gene expression. Circ Res 2008, 102:873–87.

[58] Britten RJ, Davidson EH: Gene regulation for higher cells: a theory. Science 1969, 165:349–57.

[59] Kaikkonen MU, Lam MT, Glass CK: Non-coding RNAs as regulators of gene expression and epigenetics. Cardiovasc Res 2011, 90:430–40.

[60] Deng K, Wang H, Guo X, Xia J: The cross talk between long, non-coding RNAs and microRNAs in gastric cancer. Acta Biochim Biophys Sin 2016;48(2):111–6.

[61] Lin S, Gregory RI: MicroRNA biogenesis pathways in cancer. Nat Rev Cancer 2015, 15:321–33.

[62] Afonso-Grunz F, Muller S: Principles of miRNA-mRNA interactions: beyond sequence complementarity. Cell Mol Life Sci 2015, 72:3127–41.

[63] le Noble F, Klein C, Tintu A, Pries A, Buschmann I: Neural guidance molecules, tip cells, and mechanical factors in vascular development. Cardiovasc Res 2008, 78:232–41.

[64] Ribatti D, Nico B, Crivellato E: Morphological and molecular aspects of physiological vascular morphogenesis. Angiogenesis 2009, 12:101–11.

[65] Fish JE, Marsden PA: Endothelial nitric oxide synthase: insight into cell-specific gene regulation in the vascular endothelium. Cell Mol Life Sci 2006, 63:144–62.

[66] Illi B, Colussi C, Rosati J, Spallotta F, Nanni S, Farsetti A, Capogrossi MC, Gaetano C: NO points to epigenetics in vascular development. Cardiovasc Res 2011, 90:447–56.

[67] Chistiakov DA, Orekhov AN, Bobryshev YV: The role of miR-126 in embryonic angiogenesis, adult vascular homeostasis, and vascular repair and its alterations in atherosclerotic disease. J Mol Cell Cardiol 2016, 97:47–55.

[68] Fish JE, Matouk CC, Yeboah E, Bevan SC, Khan M, Patil K, Ohh M, Marsden PA: Hypoxia-inducible expression of a natural cis-antisense transcript inhibits endothelial nitric-oxide synthase. J Biol Chem 2007, 282:15652–66.

[69] Fish JE, Yan MS, Matouk CC, St Bernard R, Ho JJ, Gavryushova A, Srivastava D, Marsden PA: Hypoxic repression of endothelial nitric-oxide synthase transcription is coupled with eviction of promoter histones. J Biol Chem 2010, 285:810–26.

[70] Marin T, Gongol B, Chen Z, Woo B, Subramaniam S, Chien S, Shyy JY: Mechanosensitive microRNAs-role in endothelial responses to shear stress and redox state. Free Radic Biol Med 2013, 64:61–8.

[71] Krause BJ, Hernandez C, Caniuguir A, Vasquez-Devaud P, Carrasco-Wong I, Uauy R, Casanello P: Arginase-2 is cooperatively up-regulated by nitric oxide and histone deacetylase inhibition in human umbilical artery endothelial cells. Biochem Pharmacol 2016, 99:53–9.

[72] Kim J, Kim JY, Song KS, Lee YH, Seo JS, Jelinek J, Goldschmidt-Clermont PJ, Issa JP: Epigenetic changes in estrogen receptor beta gene in atherosclerotic cardiovascular tissues and in-vitro vascular senescence. Biochim Biophys Acta 2007, 1772:72–80.

[73] Dunn J, Qiu H, Kim S, Jjingo D, Hoffman R, Kim CW, Jang I, Son DJ, Kim D, Pan C, Fan Y, Jordan IK, Jo H: Flow-dependent epigenetic DNA methylation regulates endothelial gene expression and atherosclerosis. J Clin Invest 2014, 124:3187–99.

[74] Jiang YZ, Manduchi E, Stoeckert CJ, Jr., Davies PF: Arterial endothelial methylome: differential DNA methylation in athero-susceptible disturbed flow regions in vivo. BMC Gen 2015, 16:506.

[75] Rao X, Zhong J, Zhang S, Zhang Y, Yu Q, Yang P, Wang MH, Fulton DJ, Shi H, Dong Z, Wang D, Wang CY: Loss of methyl-CpG-binding domain protein 2 enhances endothelial angiogenesis and protects mice against hind-limb ischemic injury. Circulation 2011, 123:2964–74.

[76] Navickas R, Gal D, Laucevicius A, Taparauskaite A, Zdanyte M, Holvoet P: Identifying circulating microRNAs as biomarkers of cardiovascular disease: a systematic review. Cardiovasc Res 2016.

[77] Krause BJ, Carrasco-Wong I, Dominguez A, Arnaiz P, Farias M, Barja S, Mardones F, Casanello P: Micro-RNAs Let7e and 126 in plasma as markers of metabolic dysfunction in 10 to 12 years old children. PLoS One 2015, 10:e0128140.

[78] Olivieri F, Spazzafumo L, Bonafe M, Recchioni R, Prattichizzo F, Marcheselli F, Micolucci L, Mensa E, Giuliani A, Santini G, Gobbi M, Lazzarini R, Boemi M, Testa R, Antonicelli R, Procopio AD, Bonfigli AR: MiR-21-5p and miR-126a-3p levels in plasma and circulating angiogenic cells: relationship with type 2 diabetes complications. Oncotarget 2015, 6:35372–82.

[79] Xu XF, Ma XL, Shen Z, Wu XL, Cheng F, Du LZ: Epigenetic regulation of the endothelial nitric oxide synthase gene in persistent pulmonary hypertension of the newborn rat. J Hypertens 2010, 28:2227–35.

[80] Sartori C, Rimoldi SF, Rexhaj E, Allemann Y, Scherrer U: Epigenetics in cardiovascular regulation. Adv Exp Med Biol 2016, 903:55–62.

[81] Rexhaj E, Paoloni-Giacobino A, Rimoldi SF, Fuster DG, Anderegg M, Somm E, Bouillet E, Allemann Y, Sartori C, Scherrer U: Mice generated by in vitro fertilization exhibit vascular dysfunction and shortened life span. J Clin Invest 2013, 123:5052–60.

[82] Hancock RL, Dunne K, Walport LJ, Flashman E, Kawamura A: Epigenetic regulation by histone demethylases in hypoxia. Epigenomics 2015, 7:791–811.

[83] Tudisco L, Della Ragione F, Tarallo V, Apicella I, D'Esposito M, Matarazzo MR, De Falco S: Epigenetic control of hypoxia inducible factor-1alpha-dependent expression of placental growth factor in hypoxic conditions. Epigen Off J DNA Meth Soc 2014, 9:600–10.

[84] Li J, Zhang Y, Li D, Liu Y, Chu D, Jiang X, Hou D, Zen K, Zhang CY: Small non-coding RNAs transfer through mammalian placenta and directly regulate fetal gene expression. Protein Cell 2015, 6:391–6.

[85] Whitehead CL, Teh WT, Walker SP, Leung C, Larmour L, Tong S: Circulating MicroRNAs in maternal blood as potential biomarkers for fetal hypoxia in-utero. PLoS One 2013, 8:e78487.

[86] Cindrova-Davies T, Herrera EA, Niu Y, Kingdom J, Giussani DA, Burton GJ: Reduced cystathionine gamma-lyase and increased miR-21 expression are associated with increased vascular resistance in growth-restricted pregnancies: hydrogen sulfide as a placental vasodilator. Am J Pathol 2013, 182:1448–58.

[87] Maccani MA, Padbury JF, Marsit CJ: miR-16 and miR-21 expression in the placenta is associated with fetal growth. PLoS One 2011, 6:e21210.

[88] Hromadnikova I, Kotlabova K, Hympanova L, Krofta L: Cardiovascular and cerebrovascular disease associated microRNAs are dysregulated in placental tissues affected with gestational hypertension, preeclampsia and intrauterine growth restriction. PLoS One 2015, 10:e0138383.

[89] Liu XD, Wu X, Yin YL, Liu YQ, Geng MM, Yang HS, Blachier F, Wu GY: Effects of dietary L-arginine or N-carbamylglutamate supplementation during late gestation of sows on the miR-15b/16, miR-221/222, VEGFA and eNOS expression in umbilical vein. Amino Acids 2012, 42:2111–9.

[90] Khorram O, Chuang TD, Pearce WJ: Long-term effects of maternal undernutrition on offspring carotid artery remodeling: role of miR-29c. J Dev Orig Health Dis 2015, 6:342–9.

[91] Guduric-Fuchs J, O'Connor A, Cullen A, Harwood L, Medina RJ, O'Neill CL, Stitt AW, Curtis TM, Simpson DA: Deep sequencing reveals predominant expression of miR-21 amongst the small non-coding RNAs in retinal microvascular endothelial cells. J Cell Biochem 2012, 113:2098–111.

[92] Voellenkle C, Rooij J, Guffanti A, Brini E, Fasanaro P, Isaia E, Croft L, David M, Capogrossi MC, Moles A, Felsani A, Martelli F: Deep-sequencing of endothelial cells exposed to hypoxia reveals the complexity of known and novel microRNAs. RNA 2012, 18:472–84.

[93] Harris TA, Yamakuchi M, Kondo M, Oettgen P, Lowenstein CJ: Ets-1 and Ets-2 regulate the expression of microRNA-126 in endothelial cells. Arterioscler Thromb Vasc Biol 2010, 30:1990–7.

[94] Watanabe K, Emoto N, Hamano E, Sunohara M, Kawakami M, Kage H, Kitano K, Nakajima J, Goto A, Fukayama M, Nagase T, Yatomi Y, Ohishi N, Takai D: Genome structure-based screening identified epigenetically silenced microRNA associated with invasiveness in non-small-cell lung cancer. Int J Cancer 2012, 130:2580–90.

[95] Kuosmanen SM, Viitala S, Laitinen T, Perakyla M, Polonen P, Kansanen E, Leinonen H, Raju S, Wienecke-Baldacchino A, Narvanen A, Poso A, Heinaniemi M, Heikkinen S, Levonen AL: The effects of sequence variation on genome-wide NRF2 binding – new target genes and regulatory SNPs. Nucl Acid Res 2016, 44:1760–75.

[96] Ribas J, Lupold SE: The transcriptional regulation of miR-21, its multiple transcripts, and their implication in prostate cancer. Cell Cycle 2010, 9:923–9.

[97] Kumarswamy R, Volkmann I, Thum T: Regulation and function of miRNA-21 in health and disease. RNA Biol 2011, 8:706–13.

[98] Togliatto G, Trombetta A, Dentelli P, Gallo S, Rosso A, Cotogni P, Granata R, Falcioni R, Delale T, Ghigo E, Brizzi MF: Unacylated ghrelin induces oxidative stress resistance in a glucose intolerance and peripheral artery disease mouse model by restoring endothelial cell miR-126 expression. Diabetes 2015, 64:1370–82.

[99] Sui XQ, Xu ZM, Xie MB, Pei DA: Resveratrol inhibits hydrogen peroxide-induced apoptosis in endothelial cells via the activation of PI3K/Akt by miR-126. J Atheroscler Thromb 2014, 21:108–18.

[100] Weber M, Baker MB, Moore JP, Searles CD: MiR-21 is induced in endothelial cells by shear stress and modulates apoptosis and eNOS activity. Biochem Biophys Res Commun 2010, 393:643–8.

[101] Zhou J, Wang KC, Wu W, Subramaniam S, Shyy JY, Chiu JJ, Li JY, Chien S. MicroRNA-21 targets peroxisome proliferators-activated receptor-{alpha} in an autoregulatory loop to modulate flow-induced endothelial inflammation. Proc Natl Acad Sci U S A 2011;108(25):10355-60.

[102] Xu X, Kriegel AJ, Jiao X, Liu H, Bai X, Olson J, Liang M, Ding X: miR-21 in ischemia/reperfusion injury: a double-edged sword? Physiol Gen 2014, 46:789–97.

[103] Ge X, Han Z, Chen F, Wang H, Zhang B, Jiang R, Lei P, Zhang J: MiR-21 alleviates secondary blood-brain barrier damage after traumatic brain injury in rats. Brain Res 2015, 1603:150–7.

[104] Qiao S, Olson JM, Paterson M, Yan Y, Zaja I, Liu Y, Riess ML, Kersten JR, Liang M, Warltier DC, Bosnjak ZJ, Ge ZD: MicroRNA-21 Mediates isoflurane-induced cardioprotection against ischemia-reperfusion injury via Akt/nitric oxide synthase/mitochondrial permeability transition pore pathway. Anesthesiology 2015, 123:786–98.

[105] Iannone L, Zhao L, Dubois O, Duluc L, Rhodes CJ, Wharton J, Wilkins MR, Leiper J, Wojciak-Stothard B: miR-21/DDAH1 pathway regulates pulmonary vascular responses to hypoxia. Biochem J 2014, 462:103–12.

[106] White K, Dempsie Y, Caruso P, Wallace E, McDonald RA, Stevens H, Hatley ME, Van Rooij E, Morrell NW, MacLean MR, Baker AH: Endothelial apoptosis in pulmonary hypertension is controlled by a microRNA/programmed cell death 4/caspase-3 axis. Hypertension 2014, 64:185–94.

[107] Chen L, Zhou JP, Kuang DB, Tang J, Li YJ, Chen XP: 4-HNE increases intracellular ADMA levels in cultured HUVECs: evidence for miR-21-dependent mechanisms. PLoS One 2013, 8:e64148.

[108] Zhao C, Li T, Han B, Yue W, Shi L, Wang H, Guo Y, Lu Z: DDAH1 deficiency promotes intracellular oxidative stress and cell apoptosis via a miR-21-dependent pathway in mouse embryonic fibroblasts. Free Radic Biol Med 2016, 92:50–60.

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