Chapter 2
Developmental Origins of Hypoxic Pulmonary Hypertension and Systemic Vascular Dysfunction: Evidence from Humans

Claudio Sartori, Stefano F. Rimoldi, Hervé Duplain, Thomas Stuber, Sophie Garcin, Emrush Rexhaj, Yves Allemann, and Urs Scherrer

Abstract Epidemiological studies have shown an association between pathologic events occurring during fetal/perinatal life and the development of cardiovascular and metabolic disease in adulthood. These observations have led to the so-called developmental origin of adult disease hypothesis. More recently, evidence has been provided that the pulmonary circulation is also an important target for the developmental programming of adult disease in both experimental animal models and in humans. Here we will review this evidence and provide insight into mechanisms that may play a pathogenic role.

Keywords Barker hypothesis • Epigenetics • Perinatal insult

C. Sartori (✉) • H. Duplain • S. Garcin
Department of Internal Medicine, University Hospital, Lausanne, Switzerland
e-mail: claudio.sartori@chuv.ch

S.F. Rimoldi • E. Rexhaj
Department of Cardiology, Swiss Cardiovascular Center Bern, University Hospital, Bern, Switzerland
e-mail: stefano.rimoldi@insel.ch

T. Stuber
Imperial College Healthcare NHS Trust, St. Mary's Hospital, London, United Kingdom

Y. Allemann
Department of Cardiology, Swiss Cardiovascular Center Bern, University Hospital, Bern, Switzerland

U. Scherrer
Departamento de Biología, Universidad de Tarapacá, Arica, Chile

Department of Cardiology, Swiss Cardiovascular Center Bern, University Hospital, Bern, Switzerland

R.C. Roach et al. (eds.), *Hypoxia*, Advances in Experimental Medicine and Biology 903, DOI 10.1007/978-1-4899-7678-9_2

2.1 Introduction

2.1.1 The Barker Hypothesis

The initial observations made by Barker and colleagues [1], that individuals born with a low birth weight present increased cardiovascular mortality in adulthood, gave rise to the "Barker hypothesis." This hypothesis postulated that environmental factors, in particular nutritional, could act during the early phases of life and determine the risk to suffer from metabolic and/or cardiovascular disease later in life. Since then, many epidemiological studies have confirmed the association between impaired fetal growth (deduced from birth weight or body composition) and an increased incidence of cardiovascular diseases, type 2 diabetes mellitus, or their precursors: dyslipidemia, impaired glucose tolerance, or vascular endothelial dysfunction. The terms "fetal programming" and "developmental origin of adult diseases" were coined to describe these associations. Interestingly, this association is not only present in children with extremely low birth weight, since in children with normal birth weight the cardiovascular risk is also inversely related to birth weight. In some conditions, adverse developmental influences could also affect disease risk without birth size affected [12].

Developmental plasticity provides organisms with the ability to change structure and function in response to environmental cues. These changes usually take place during critical time windows, and then become permanent, and thereby permit a range of phenotypes to develop from a single genotype. The predictive developmental adaptive responses are thought to optimize the phenotype for the probable environment of the mature organism. Where there is a match between the predicted and actual mature environment, these predictive adaptive responses are appropriate and assist survival. Conversely, inappropriate predictions increase the risk of disease. Modeling suggests that such lagged responses aid the survival of the species [11].

To explain his observations, Barker postulated that when the fetal environment is low in nutrients, the fetus adapts its metabolism to increase its chances of survival after the birth in presumably similarly poor conditions. However, if the actual environment will be richer in food than predicted, then the adaptations programmed during the pregnancy might be deleterious and predispose to disease in adulthood [15].

In humans, such a situation occurred towards the end of World War II. A Dutch epidemiological study showed that an insufficient caloric intake in pregnant mothers during the period of famine of the winter 1944–1945 increased the risk of the offspring to develop cardiovascular or metabolic diseases in adulthood, and this even in the presence of a normal birth weight [30]. Noteworthily, the girls born from these pregnancies in period of famine gave themselves birth to children of lower than normal weight, suggesting the possibility of a transgenerational transmission of the consequences of a perinatal insult [28].

2.2 Underlying Mechanisms

A diet restricted in caloric or protein intake is the most widely used experimental animal model to study underlying mechanisms by which environmental cues may influence the developmental program. These studies have indicated two potential candidate mechanisms.

2.2.1 Altered Tissue Differentiation

When the fetus does not have sufficient substrates for its development, differentiation and growth of certain tissues may be altered. For example, in the rat, a low caloric diet during pregnancy induces a reduction in the number of β cells in the pancreas. This may explain, at least in part, the increased risk of diabetes in the adult offspring.

Similarly, a reduction in the number of nephrons has been suggested to be responsible for the increased risk of hypertension, whereas a reduction of the quantity of cardiomyocytes may explain the increased risk of cardiovascular disease in the adult offspring of restrictive diet pregnancies [26].

2.2.2 Epigenetic Alterations

The term "epigenetic" indicates changes of gene expression that are not related to modifications of the DNA sequence.

Gene expression is controlled by the epigenome, which comprises chromatine structure and DNA methylation. Methylation at the 5′ position of cytosine occurs in 60–90 % of CpG dinucleotides within the vertebrate genome and is associated with stable variation in gene expression. Methylation of CpG-rich clusters, termed CpG islands, is associated with transcriptional repression, whereas hypomethylation is associated with transcriptional activation [6, 29]. DNA methylation inversely correlates with histone acetylation [22]. Acting mainly on promoters, these covalent changes in DNA and histone structure affect the extent to which the transcription machinery is able to access specific regions of the DNA over extended periods of time. These modifications are maintained during cell division, may persist throughout the life span of the individual [13, 21, 23] and transmitted to the next generation, although the mechanism for epigenetic inheritance is not yet well understood.

Recent studies have provided evidence for the potential role of epigenetic mechanisms underpinning the fetal origin of adult diseases. In rodents, uteroplacental insufficiency and hypoxia increase acetylated histone H3 and alter DNA methylation in vitro, and may cause DNA hypomethylation and increased histone acetylation in the postnatal rat liver [25].

In humans, individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944–45 had, 6 decades later, less DNA methylation of the imprinted *IGF2* gene compared with their unexposed, same-sex siblings. This association was specific for periconceptional exposure, reinforcing the concept that very early mammalian development is a crucial period for establishing epigenetic marks that may persist throughout life [17].

Until recently, the DNA methylation pattern was thought to be irreversible in adult post-mitotic cells. However, recent data suggest that histone deacetylase inhibitors are capable of inducing replication-independent demethylation of ectopically methylated genes by increasing histone acetylation [42]. Accordingly, supplementation of pregnant mice with methyl-donor and cofactors (folic acid, vitamin B12) increases CpG methylation in the offspring, and this pattern is retained into adulthood [40].

Epigenetic alterations may have important functional consequences later in life. For example, offspring of mothers that show increased pup licking/grooming and arched-back nursing (high LG-ABN mothers) exhibit reduced fearfulness, decreased hypothalamic CRF expression, and more modest hypothalamic–pituitary–adrenal responses to stress during the first week of postnatal life. As adults, offspring of high LG-ABN mothers show increased hippocampal glucocorticoid receptor expression and enhanced glucocorticoid feedback sensitivity compared to offspring of low LG-ABN mothers [7]. This protective maternal behavior during the first week of life is associated with global DNA demethylation, and increased histone acetylation in the hippocampus of the offspring [38].

In line with this concept, central infusion of the histone deacetylase inhibitor richostatin A normalized histone acetylation, DNA methylation, hippocampal glucocorticoid receptor expression, and hypothalamic–pituitary–adrenal responses to stress in the adult offspring of high LG-ABN dams [43].

Interestingly, although the effects of maternal care or Trichostatin A administration involve a large number of genes, these effects were quite specific and limited to a small number of genes suggesting that these interventions did not result in a general collapse of gene expression programming.

Although the basis for this specificity remains unknown, these observations may have important implications for the potential use of such interventions for the treatment of diseases associated with epigenetic alterations (Fig. 2.1).

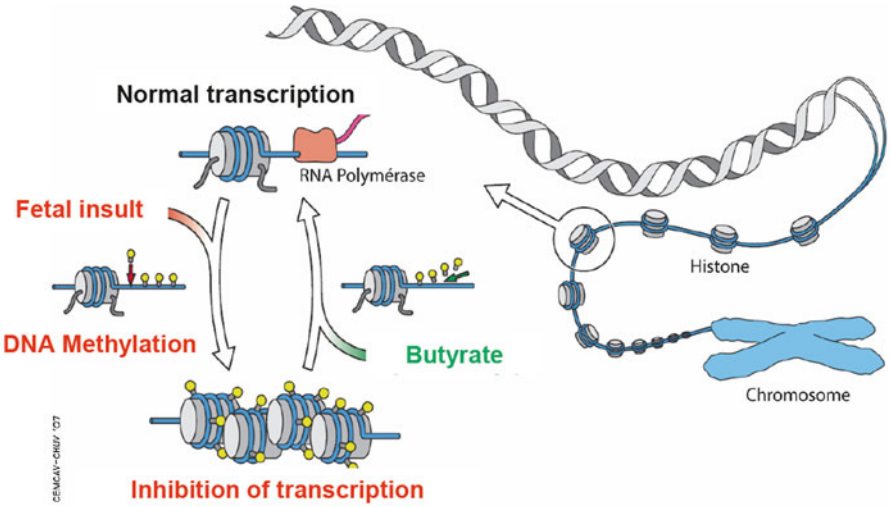

Fig. 2.1 Fetal/perinatal insults may induce epigenetic alterations (DNA methylation, histone deacetylation) that can alter transcription. Despite being stable and maintained during cell division throughout the life span, epigenetic alteration may be reversed by pharmacological agents, such as histone deacetylase inhibitors (Sodium Butyrate, Trichostatin A, Valproic Acid)

2.3 Pulmonary Arterial Hypertension and Fetal Programming

Very recently, we provided evidence, in both experimental animal models and in humans, that the pulmonary circulation is also an important target for the developmental programming of adult disease.

2.3.1 Environmental Insult During the Perinatal Period

During the perinatal period, the pulmonary circulation undergoes important structural and functional changes to allow the sudden transition from gas exchange by the placenta to gas exchange by the lungs. During this period, the pulmonary circulation is particularly vulnerable to noxious stimuli.

In line with this concept, in rats, exposure to hypoxia during the first days of life induces a transient increase of pulmonary artery pressure, and predisposes to exaggerated pulmonary vasoconstrictor responses to hypoxia and monocrotaline in adulthood [14].

During studies at the high-altitude research laboratory Capanna Regina Margherita in the Alps (4559 m), we have demonstrated a similar phenomenon in young healthy adults who had suffered from transient lack of oxygen during the first few days after birth [31]. Indeed, in these subjects, the altitude-induced

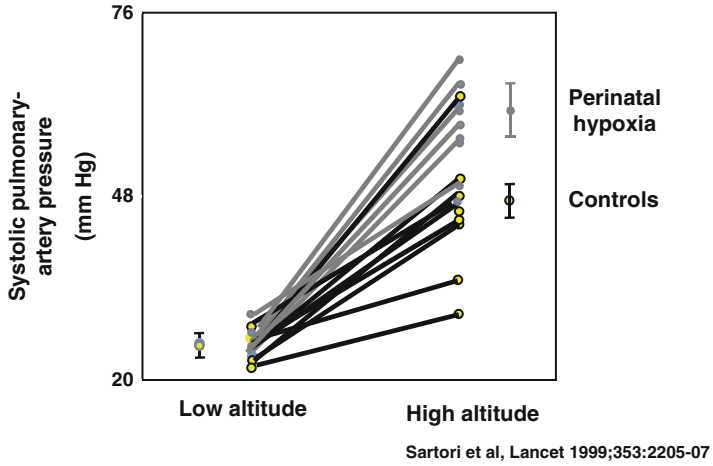

Fig. 2.2 Pulmonary-artery pressure measured at low (560 m) and at high altitude (4550 m) in young adults having suffered from transient perinatal hypoxia and control subjects

increase in pulmonary artery pressure was more than 50 % larger than in control subjects (Fig. 2.2).

The mechanism underlying this exaggerated vasoconstrictor response is not known yet, but there is evidence that this pathologic response is related to a functional rather than a structural defect. Data in rats show that transient hypoxia during the first few days leads to decreased eNOS expression in the lungs [36]. Thus, impaired NO synthesis may represent a potential mechanism. In line with this hypothesis, NO inhalation caused a substantially larger decrease in pulmonary artery pressure in the subjects with a perinatal insult than in control subjects.

These findings provided the first evidence in humans that a transient insult to the pulmonary circulation during the perinatal period leaves a persistent imprint (possibly defective NO synthesis) which, when activated later in the life, predisposes to a pathological response. This observation also suggests that survivors of perinatal pulmonary hypertension may be at risk of developing this disorder later in life.

Based on these findings, we wondered whether an insult occurring earlier during gestation may have similar long-term effects on the pulmonary circulation and, if so, may predispose to chronic hypoxic pulmonary hypertension.

To answer these questions, in collaboration with Bolivian researchers at the Instituto Boliviano de Biologia de Altura, we studied cardiopulmonary adaptation in high-altitude dwellers living in La Paz, Bolivia (3600–4000 m).

2.3.2 *Environmental Insults During Late Fetal Period*

Preeclampsia is the most frequent complication of pregnancy, and its prevalence is particularly high in high-altitude populations. Preeclampsia refers to the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman. It occurs in approximately 5–15 % of pregnancies worldwide and is associated with endothelial dysfunction in the mother which is related to the release of circulating vasculotoxic factors and the induction of augmented oxidative stress by the diseased placenta [16, 20, 24, 39]. We speculated that these circulating factors may pass the placental barrier and leave a persistent imprint in the pulmonary circulation of the offspring that may predispose to a pathological response later in life. Accordingly, we found that offspring of preeclampsia had exaggerated pulmonary hypertension. These important observations provide the first evidence in humans that a pathological event during late fetal development predisposes the offspring to pulmonary vascular dysfunction.

The preeclampsia-induced predisposition for exaggerated hypoxic pulmonary hypertension may have clinical consequences. Exaggerated hypoxic pulmonary hypertension is an important underlying mechanism of high-altitude pulmonary edema [32, 33]. Offspring of preeclampsia may be at risk for this problem. In line with this speculation, several offspring of preeclampsia had suffered from re-entry high-altitude pulmonary edema. Moreover, offspring of preeclampsia living at high altitude, or living at low altitude and suffering from disease states associated with chronic hypoxemia, may be at greater risk for developing sustained pulmonary hypertension and right heart failure.

The underlying mechanisms are not known.

Augmented oxidative stress may represent a candidate mechanism. Fetal insults are associated with a persistent increase of oxidative stress in the offspring in humans and experimental animals [9, 10]. Oxidative stress causes endothelial dysfunction and facilitates hypoxic pulmonary vasoconstriction in experimental animal models [8, 19]. Exaggerated oxidative stress during the fetal period may induce endothelial dysfunction in the offspring by causing epigenetically-induced alterations of the expression of genes involved in the regulation of endothelial function [44].

Consistent with this hypothesis, adult offspring of restrictive diet pregnancies, a mouse model of exaggerated oxidative stress during gestation [9] display pulmonary endothelial dysfunction in vitro and exaggerated hypoxia-induced pulmonary hypertension and right ventricular hypertrophy in vivo. This pulmonary vascular dysfunction was related, at least in part, to augmented oxidative stress, because Tempol normalized acetylcholine-induced vasodilation in vitro in offspring of restrictive diet pregnancy, and its administration during restrictive diet pregnancy prevented the pulmonary vascular dysfunction and exaggerated hypoxia-induced right ventricular hypertrophy in the offspring.

Furthermore, preliminary data from our group show that in offspring of preeclampsia exaggerated hypoxic pulmonary hypertension was related, at least in

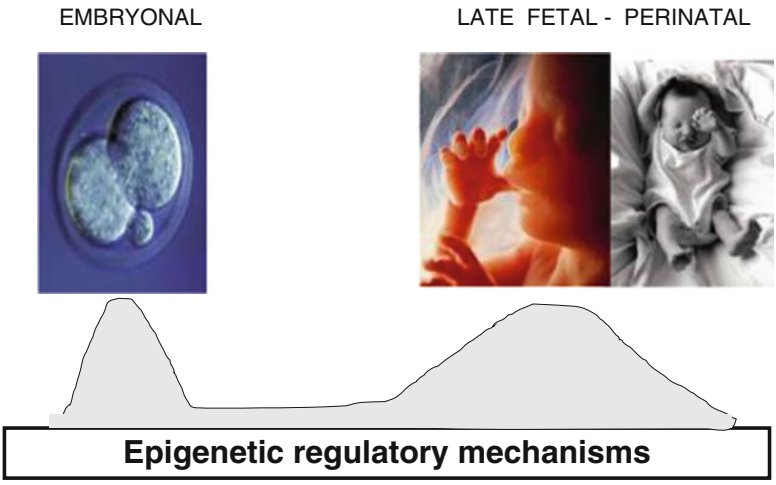

Fig. 2.3 Activity of epigenetic regulatory mechanisms during development

part, to increased oxidative stress, because TBARS plasma levels were increased and treatment with the antioxidant Vitamin C almost normalized pulmonary-artery pressure.

To test for the role of epigenetic mechanisms, we assessed pulmonary DNA methylation and examined the effects of the deacetylation inhibitor sodium butyrate on DNA methylation [3, 5, 18] and pulmonary vascular responsiveness in the offspring of restrictive diet pregnacies.

In very preliminary experiments, we observed that restrictive diet during gestation in mice was associated with altered global DNA methylation in the lung. Furthermore, administration of the histone deacetylatase inhibitor Butyrate during pregnancy prevented the alteration of DNA methylation in lung tissue of the offspring. Prevention of these pulmonary DNA methylation alterations in the offspring was associated with prevention of pulmonary endothelial dysfunction in vitro and exaggerated hypoxic pulmonary hypertension in vivo. This very interesting observation suggests that epigenetic alterations may be involved in the restrictive diet-induced impairment of pulmonary endothelial function in mice.

Epigenetic regulatory mechanisms play an important role not only during the fetal/perinatal period but also around conception during gametogenesis (Fig. 2.3).

Primordial germ cells undergo epigenetic erasure as they migrate along the genital ridge, and epigenetic marks are reestablished during gametogenesis. For example, after fertilization, there is active demethylation of the paternal pronucleus, and then a second wave of passive demethylation of the zygote genome. Imprinted genes are protected from this erasure. We therefore wondered whether environmental insults occurring during this period may have similar long-term effects in the offspring.

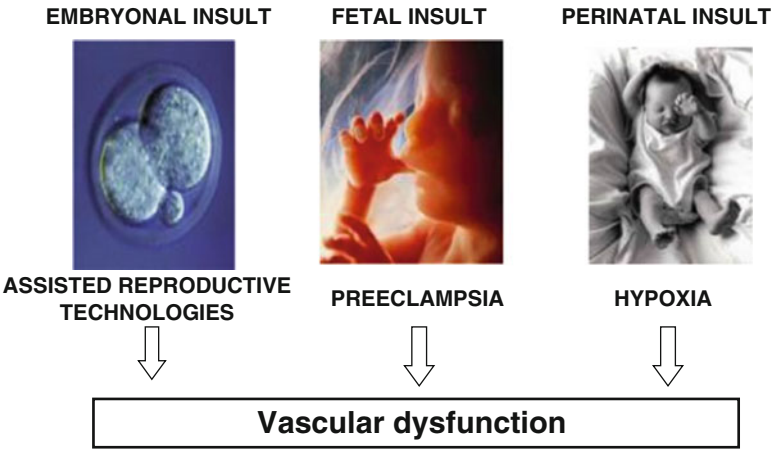

Fig. 2.4 Fetal/perinatal insults that have been shown to predispose to systemic and pulmonary vascular dysfunction in human offspring

2.3.3 Environmental Insults During Gametogenesis

Assisted reproductive technologies (ART) involve the manipulation of early embryos at a time when they may be particularly vulnerable to external disturbances. ART is a modulator of the epigenome in several animal species and in humans [2, 45]. In humans, this method is associated with a higher than expected frequency of rare imprinting disorders (i.e. Beckwith-Wiedeman and Angelman syndrome) [4]. The safety of ART for long-term health is therefore of utmost importance, but there is little information [27, 37]. This may be related at least in part to the young age of the progeny, since clinically manifest chronic disease may not yet have had time to develop.

Based on our previous observations in offspring of preeclampsia [34] and in young adults who had suffered from transient perinatal hypoxia [31] (see above), we speculated that ART might predispose to vascular dysfunction (Fig. 2.4).

Consistent with this speculation, recent studies in normal mice suggest that ART is associated with alterations of the activity of enzymes involved in the regulation of metabolic and cardiovascular homeostasis as well as arterial hypertension in the adult offspring [41]. No information was available in humans.

Data from our group now demonstrate that children born after ART present systemic and pulmonary vascular dysfunction on high-altitude exposure (a condition known to facilitate detection of vascular dysfunction in subjects with endothelial dysfunction) (See chap. 4).

2.4 Conclusion

Cardiovascular and metabolic diseases were thought to result from the interaction between the behavior of an individual and his genetic inheritance. Recent data indicate, however, that fetal programming also plays an important pathogenic role.

Among the underlying mechanisms by which fetal programming may lead to cardiovascular dysfunction, augmented oxidative stress and/or epigenetic alterations appear to play a major role. Fetal programming may occur at various stages of development and there is evidence that fetal programming-induced alterations are transmissible from cell to cell throughout life and then also to the next generation.

More importantly from a medical therapeutic standpoint, epigenetic alterations may be reversed by pharmacological interventions opening a window for the potential prevention and treatment of cardiovascular and metabolic diseases associated with fetal programming.

References

1. Barker DJP. Mothers, babies, and disease in later life. London: BMJ Books; 1994.
2. Bowdin S, Allen C, Kirby G, Brueton L, Afnan M, Barratt C, Kirkman-Brown J, Harrison R, Maher ER, Reardon W. A survey of assisted reproductive technology births and imprinting disorders. Hum Reprod. 2007;22:3237–40.
3. Dashwood RH, Ho E. Dietary histone deacetylase inhibitors: from cells to mice to man. Semin Cancer Biol. 2007;17:363–9.
4. DeBaun MR, Niemitz EL, Feinberg AP. Association of in vitro fertilization with Beckwith-Wiedemann syndrome and epigenetic alterations of LIT1 and H19. Am J Hum Genet. 2003;72:156–60.
5. Deutsch SI, Rosse RB, Long KD, Gaskins BL, Burket JA, Mastropaolo J. Sodium butyrate, an epigenetic interventional strategy, attenuates a stress-induced alteration of MK-801's pharmacologic action. Eur Neuropsychopharmacol. 2008;18:565–8.
6. Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. Nature. 2004;429:457–63.
7. Fish EW, Shahrokh D, Bagot R, Caldji C, Bredy T, Szyf M, Meaney MJ. Epigenetic programming of stress responses through variations in maternal care. Ann N Y Acad Sci. 2004;1036:167–80.
8. Fortuno A, Jose GS, Moreno MU, Diez J, Zalba G. Oxidative stress and vascular remodelling. Exp Physiol. 2005;90:457–62.
9. Franco Mdo C, Dantas AP, Akamine EH, Kawamoto EM, Fortes ZB, Scavone C, Tostes RC, Carvalho MH, Nigro D. Enhanced oxidative stress as a potential mechanism underlying the programming of hypertension in utero. J Cardiovasc Pharmacol. 2002;40:501–9.
10. Franco MC, Akamine EH, Reboucas N, Carvalho MH, Tostes RC, Nigro D, Fortes ZB. Long-term effects of intrauterine malnutrition on vascular function in female offspring: implications of oxidative stress. Life Sci. 2007;80:709–15.
11. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science. 2004;305:1733–6.
12. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359:61–73.

13. Godfrey KM. The role of the placenta in fetal programming-a review. Placenta. 2002;23 Suppl A: S20–27.
14. Hakim TS, Mortola JP. Pulmonary vascular resistance in adult rats exposed to hypoxia in the neonatal period. Can J Physiol Pharmacol. 1990;68:419–24.
15. Hales CN, Barker DJ. The thrifty phenotype hypothesis. Br Med Bull. 2001;60:5–20.
16. Hayman R, Brockelsby J, Kenny L, Baker P. Preeclampsia: the endothelium, circulating factor(s) and vascular endothelial growth factor. J Soc Gynecol Investig. 1999;6:3–10.
17. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008;105:17046–9.
18. Hitchler MJ, Oberley LW, Domann FE. Epigenetic silencing of SOD2 by histone modifications in human breast cancer cells. Free Radic Biol Med. 2008;45(11):1537–80.
19. Hoshikawa Y, Ono S, Suzuki S, Tanita T, Chida M, Song C, Noda M, Tabata T, Voelkel NF, Fujimura S. Generation of oxidative stress contributes to the development of pulmonary hypertension induced by hypoxia. J Appl Physiol. 2001;90:1299–306.
20. Hubel CA. Oxidative stress in the pathogenesis of preeclampsia. Proc Soc Exp Biol Med. 1999;222:222–35.
21. Ingelfinger JR. Pathogenesis of perinatal programming. Curr Opin Nephrol Hypertens. 2004;13:459–64.
22. Jones PL, Wolffe AP. Relationships between chromatin organization and DNA methylation in determining gene expression. Semin Cancer Biol. 1999;9:339–47.
23. Langley-Evans SC. Developmental programming of health and disease. Proc Nutr Soc. 2006;65:97–105.
24. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF, Thadhani R, Sachs BP, Epstein FH, Sibai BM, Sukhatme VP, Karumanchi SA. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350:672–83.
25. MacLennan NK, James SJ, Melnyk S, Piroozi A, Jernigan S, Hsu JL, Janke SM, Pham TD, Lane RH. Uteroplacental insufficiency alters DNA methylation, one-carbon metabolism, and histone acetylation in IUGR rats. Physiol Genomics. 2004;18:43–50.
26. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev. 2005;85:571–633.
27. Niemitz EL, Feinberg AP. Epigenetics and assisted reproductive technology: a call for investigation. Am J Hum Genet. 2004;74:599–609.
28. Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI, Roseboom TJ. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. BJOG. 2008;115:1243–9.
29. Razin A. CpG methylation, chromatin structure and gene silencing-a three-way connection. Embo J. 1998;17:4905–8.
30. Roseboom TJ, van der Meulen JH, Osmond C, Barker DJ, Ravelli AC, Schroeder-Tanka JM, van Montfrans GA, Michels RP, Bleker OP. Coronary heart disease after prenatal exposure to the Dutch famine, 1944–45. Heart. 2000;84:595–8.
31. Sartori C, Allemann Y, Trueb L, Delabays A, Nicod P, Scherrer U. Augmented vasoreactivity in adult life associated with perinatal vascular insult. Lancet. 1999;353:2205–7.
32. Sartori C, Allemann Y, Scherrer U. Pathogenesis of pulmonary edema: learning from high-altitude pulmonary edema. Respir Physiol Neurobiol. 2007;159:338–49.
33. Scherrer U, Sartori C, Lepori M, Allemann Y, Duplain H, Trueb L, Nicod P. High-altitude pulmonary edema: from exaggerated pulmonary hypertension to a defect in transepithelial sodium transport. Adv Exp Med Biol. 1999;474:93–107.
34. Scherrer U, Turini P, Thalmann S, Hutter D, Salmon CS, Stuber T, Shaw S, Jayet PY, Sartori-Cucchial C, Villena M, Allemann Y, Sartori C. Pulmonary hypertension in high-altitude dwellers: novel mechanisms, unsuspected predisposing factors. Adv Exp Med Biol. 2006;588:277–91.

35. Scherrer U, Vollenweider L, Delabays A, Savcic M, Eichenberger U, Kleger G-R, Fikrle A, Ballmer PE, Nicod P, Bärtsch P. Inhaled nitric oxide for high-altitude pulmonary edema. N Engl J Med. 1996;334:624–9.
36. Smith APL, Emery CJ, Higenbottam TW. Perinatal chronic hypoxia decreases endothelial nitric oxide synthase (NOS III) and increases preproendothelin-1 (ppET-1) mRNA levels in rat. Eur Respir J. 1997;10:433s. Abstract.
37. Sutcliffe AG, Ludwig M. Outcome of assisted reproduction. Lancet. 2007;370:351–9.
38. Szyf M, Weaver IC, Champagne FA, Diorio J, Meaney MJ. Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat. Front Neuroendocrinol. 2005;26:139–62.
39. Taylor RN, de Groot CJ, Cho YK, Lim KH. Circulating factors as markers and mediators of endothelial cell dysfunction in preeclampsia. Semin Reprod Endocrinol. 1998;16:17–31.
40. Waterland RA, Jirtle RL. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutrition. 2004;20:63–8.
41. Watkins AJ, Platt D, Papenbrock T, Wilkins A, Eckert JJ, Kwong WY, Osmond C, Hanson M, Fleming TP. Mouse embryo culture induces changes in postnatal phenotype including raised systolic blood pressure. Proc Natl Acad Sci U S A. 2007;104:5449–54.
42. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. Nat Neurosci. 2004;7:847–54.
43. Weaver IC, Meaney MJ, Szyf M. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. Proc Natl Acad Sci U S A. 2006;103:3480–5.
44. Weitzman SA, Turk PW, Milkowski DH, Kozlowski K. Free radical adducts induce alterations in DNA cytosine methylation. Proc Natl Acad Sci U S A. 1994;91:1261–4.
45. Weksberg R, Shuman C, Wilkins-Haug L, Mann M, Croughan M, Stewart D, Rakowsky C, Leader A, Hall J, Friedman JM, Simpson JL, Holmes L, Infante-Rivard C. Workshop report: evaluation of genetic and epigenetic risks associated with assisted reproductive technologies and infertility. Fertil Steril. 2007;88:27–31.

http://www.springer.com/978-1-4899-7676-5

Hypoxia
Translation in Progress
Roach, R.C.; Hackett, P.H.; Wagner, P.D. (Eds.)
2016, XIII, 772 p. 103 illus., 14 illus. in color., Hardcover
ISBN: 978-1-4899-7676-5