Review

Prenatal Programming and Epigenetics in the Genesis of the Cardiorenal Syndrome

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Key Words

Albuminuria • Dyslipidemia • Fetal development • Hypertension • Insulin resistance • Malnutrition • Pediatric obesity

Abstract

The presence of a group of interacting maladaptive factors, including hypertension, insulin resistance, metabolic dyslipidemia, obesity, and microalbuminuria and/or reduced renal function, collectively constitutes the cardiorenal metabolic syndrome (CRS). Nutritional and other environmental cues during fetal development can permanently affect the composition, homeostatic systems, and functions of multiple organs and systems; this process has been referred to as 'programming'. Since the original formulation of the notion that low birth weight is a proxy for 'prenatal programming' of adult hypertension and cardiovascular disease, evidence has also emerged for programming of kidney disease, insulin resistance, obesity, metabolic dyslipidemia, and other chronic diseases. The programming concept was initially predicated on the notion that in utero growth restriction due to famine was responsible for increased hypertension, and cardiovascular and renal diseases. On the other hand, we are now more commonly exposed to increasing rates of maternal obesity. The current review will discuss the overarching role of maternal overnutrition, as well as fetal undernutrition, in epigenetic programming in relation to the pathogenesis of the CRS in children and adults.

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Introduction

The fetal/developmental origin of the disease hypothesis originally proposed by Barker and Osmond [1] and Barker [2] presaged numerous clinical and basic science observations implicating fetal undernutrition and/or low birth weight and associated epigenetic influences in the development of common chronic diseases such as hypertension, kidney disease, cardiovascular disease (CVD), liver disease, diabetes, and other metabolic abnormalities (fig. 1; table 1) [1–32]. However, emerging data suggest that persons who are exposed to adverse in utero conditions do not have to manifest low birth weights to develop adult chronic medical conditions [14, 33]. Indeed, recent studies have demonstrated strong associations between adult metabolic disorders and neonatal adiposity, and maternal malnutrition in addition to birth weight [33–36]. Further, since overweight and obesity have grown to pandemic proportions in industrialized countries during the past decade, it is of increasing relevance that children whose mothers are obese are at increased risk for developing metabolic disorders, including insulin resistance, diabetic dyslipidemia, hypertension, and kidney disease, all components of the cardiorenal metabolic syndrome (CRS; table 2) [32, 37–43]. Finally, recent evidence has indicated [44] that female rats can develop a diabetic phenotype due to a high fat content in their father's diet before they were conceived. It has been suggested that epigenetic modifications of the paternal sperm DNA may underlie this interesting observation. Thus, epigenetic influences can emanate from both parents during the perinatal period.

Epigenetic programming is mediated by molecular factors around DNA that alter gene expression independently of the DNA sequence [33]. Epigenetic modifications include DNA methylation, posttranslational histone modifications, and non-coding RNA-mediated silencing processes. DNA methylation patterns are predominantly affected in, and transmitted through, the germ cell line. DNA methylation involves the covalent addition of a methyl group to the 5'-position of cytosines within the CpG dinucleotides. This methyl group, which extends into the DNA, can recruit protein complexes that alter chromatin compaction or displace transcription factors and thus silence involved genomic regions. Posttranslational histone modifications, such as methylation, acetylation, and phosphorylation, covalently modify the N-terminal tail of histones and modulate chromatin condensation. RNA silencing is mediated by small, non-coding 19- to 25-nucleotide-long RNA molecules, termed microRNAs, which target up to one third of mRNAs in humans and negatively modulate gene expression.

The early postconceptional period is a seminal time for establishment of DNA methylation patterns. Indeed, the methylation profile of the genome is reprogrammed during early embryogenesis [45]. After fertilization, rapid demethylation changes in the paternal genome take place, except in paternally imprinted genes, heterochromatin around some centromeres, and some repetitive elements [33]. Differential timing of remethylation during gametogenesis may have implications for the relative paternal versus maternal epigenetic effect on the phenotype of the offspring. Animal models representing epigenetic origins of chronic metabolic disease have generally employed maternal or paternal alterations in nutrition (energy or protein intake) during the pre- and postconceptional period. For example, feeding a low-protein diet or creating utero-placental insufficiency in pregnant rats causes DNA methylation responses, which manifest as endothelial dysfunction, increased AT₁R (angiotensin II receptor type 1) expression in the kidney and adrenal gland, hypertension, reduced tissue expression of the membrane transporter GLUT4, and reduced numbers of pancreatic β cells and renal glomeruli in the progeny (table 1) [33, 46, 47].

There are considerable data suggesting that epigenetic changes associated with maternal malnutrition and stress are associated with fetal programming that promotes obesity,

Fig. 1. Prenatal programming and epigenetics in the genesis of CRS: mechanisms include the heritable changes in gene expression of the cell to its progeny without being encoded into the DNA sequence. Nutrients, oxidative and inflammatory stressors, toxins, and radiation can induce inhibitory or permissive gene expression resulting in chromatin epigenetic remodeling of genes, and ultimately the organism – offspring. Stressors such as excessive or inadequate nutrients (famine) can result in differential gene expression. Dissimilar to genetic changes, epigenetic changes may be more dynamic and reversible, depending on the presence or absence of future inducing factors in the environment. The focus of this image is directed toward cardiovascular and chronic kidney disease. Importantly, there are other clinical abnormalities such as: hypertension, obesity, insulin resistance, non-alcoholic fatty liver disease, and type 2 diabetes mellitus. ER = Endoplasmic reticulum; FFA = free fatty acids; IR = insulin resistance; NO = nitric oxide; NOO⁻ = peroxynitrite; PAI-1 = plasminogen activator inhibitor; ROS = reactive oxygen species; TNF = tumor necrosis factor; TPA = tissue plasminogen activator; # = number.

insulin resistance, and diabetes [33]. Intrauterine growth restriction and/or low birth weight followed by accelerated growth and weight gain in infancy and childhood are associated with an increased risk of insulin resistance, obesity, diabetes, and renal and cardiovascular disease (fig. 1) [33, 48–61]. In this regard, the periconceptional period is one of substantial sensitivity to suboptimal nutrition, which can also lead to adverse epigenetic responses without causing any change in birth weight. Maternal and paternal overnutrition can also lead to transgenerational amplification of obesity in animal models and man [33]. In a model particularly relevant to contemporary western societies, a maternal high-fat diet in primates leads to impaired lipid metabolism in the fetus in association with increased histone acetylation and decreased histone deacetylase activity [62]. Moreover, these epigenetic changes may occur independent of maternal quantitative nutrient intake via alterations in cofactors and substrates of DNA methylation [62]. For example, in a study

Table 1. Epigenetic factors involved in the genesis of renal disease, hypertension, and other components of the CRS

Timing/site of exposure	Types of exposure	Effects
Perinatal	Maternal and paternal malnutrition (both under- and overnutrition), mitochondrial inheritance	Reduced number of nephrons leading to albuminuria, reduced GFR, hypertension, and finally chronic kidney disease
	Hypoxia	Altered vasoconstrictor and vasodilatory responses of vasculature
	Iron deficiency, ionizing radiation and trace metals, homocysteine, tobacco, alcohol	Increased apoptosis of myocytes and asymmetric hypertrophy of heart
	Yet to be identified factors that modify histone methylation and acetylation	Increase in coronary vasculature leads to increase in coronary conductance, aberrant DNA methylation of cytosines
Intrauterine	Insulin resistance, reduced β -cell mass, impaired glucose tolerance, obesity and diabetes mellitus	Heart and kidney abnormalities characteristic of CRS
	Hormones and methylated compounds (folate, methionine)	
Placenta	Hyperglycemia, excessive glucocorticoids, free fatty acids, oxidative stress, inflammation and enhanced renin-angiotensin-aldosterone system activity	Insulin resistance, reduced β -cell mass, impaired glucose tolerance, obesity and diabetes mellitus
	Insufficiency, monozygotic twins	Increased AT ₁ R expression, renal and cardiac structural abnormalities, myocardial and vascular structural changes, and hypertension
		Although direct effects on adult CRS have not been studied well, effects on intrauterine growth and birth weight could have potential effects on CRS as above

Table 2. CRS components

- (1) Obesity, especially central obesity
- (2) Insulin resistance and increased prevalence of type 2 diabetes
- (3) Hypertension (increased salt sensitivity, endothelial dysfunction and vascular stiffness)
- (4) Metabolic dyslipidemia (low HDL, high triglycerides, and increased small dense LDL particles)
- (5) Albuminuria and/or
- (6) Reduced GFR (<60 ml/min/1.73 m²)
- (7) Early onset of metabolic cardiomyopathy characterized by diastolic dysfunction

HDL = High-density lipoprotein; LDL = low-density lipoprotein.

in sheep, periconceptional deprivation of maternal folate, vitamin B₁₂, and methionine led to extensive changes in the fetal genome and offspring that, in spite of similar birth weights to controls, became more resistant to insulin, obese, and hypertensive [63]. Further, children whose mothers were vitamin B₁₂ deficient during pregnancy manifested insulin resistance [64]. These data emphasize the importance of maternal micronutrients in fetal programming.

Epigenetic Regulation of Renal Function and Blood Pressure

Maternal Undernutrition

A number of animal and human studies have shown an important relationship between maternal malnutrition, low birth weight of infants, and the development of kidney disease and hypertension in offspring (table 1) [43]. During the development of the kidney, various genetic and epigenetic factors program the number of nephrons, termed the ‘nephron endowment’ [65, 66]. In this regard, the number of nephrons per kidney varies considerably between individuals (ranging between 800,000 and 1,800,000) [43]. It has been reported that a lower number of nephrons is a predictor for the development of hypertension [65–69]. An important autopsy study [70] reported that the number of glomeruli was considerably lower in hypertensive than in normotensive persons that died in traffic accidents. In that study, the estimated filtration surface was considerably higher in hypertensive persons with low nephron numbers than in normotensive persons. In another histomorphometric study, researchers observed fewer glomeruli in babies with low birth weight than in those with normal birth weight [71]. In other animal models, investigators have noted increased abnormal glomeruli in offspring with low birth weights [72]. Low birth weight is associated with increased risk for elevated levels of albuminuria, decreased glomerular filtration rates (GFRs), and increased rates of renal disease progression and end-stage renal disease [43]. In the Dutch study [14] where mothers had been exposed to low caloric or low protein intake during pregnancy, urinary albumin excretion was higher in the offspring of these women, especially when they were exposed to malnutrition during mid-trimester [73]. In another large registry analysis, significant relationships were detected between low birth weight and reduced renal function [74], chronic kidney disease [75], and end-stage renal disease [76]. Further, low birth weight has been shown to accelerate primary kidney disease [77, 78]. This finding is consistent with animal studies which demonstrated that reduced nephron numbers at birth predispose to progression of renal disease related to primary immunological, hypertensive, and metabolic kidney diseases [79–82].

The results of a number of animal and human studies indicate that a low nephron number in the perinatal period is related to the risk of developing hypertension [30, 43, 66–70, 83–105]. Evidence in humans comes from observations in monozygotic and dizygotic female twins with a low birth weight (<2,500 g) [83]. In a follow-up study, 24-hour blood pressure in adults was substantially higher in twins with a birth weight <2,500 g. This observation was subsequently confirmed in another large cohort [106]. Results from experimental studies suggest that reduced nephron number in the perinatal period is related to the risk of development of hypertension in offspring [81–83]. The hypertension that develops in small-birth-weight offspring is often characterized by increased salt sensitivity (table 1) [83]. There is experimental evidence that this is related, in part, to increased AT₁R-mediated sodium/hydrogen exchanger 3 activity in the proximal tubules [84–87], increased mineralocorticoid-mediated distal tubule/collecting duct sodium reabsorption [88, 89], and increased renal sympathetic activity [90]. Moreover, the hypertension seen in these individuals is accompanied by endothelial dysfunction [98], vascular stiffness [99], and microvascular disease [102–104], as well as by the comorbid conditions of obesity and diabetes [30, 100].

Maternal Overnutrition

While in utero nutrient restriction has been shown to promote hypertension, CVD, and chronic kidney disease in offspring, we are more commonly faced with maternal overnutrition. In this regard, high birth weight is associated with increased propensity for the development of CRS (table 2) [33–42, 106–127]. In westernized industrialized societies, up to 25% of mothers are obese, and in relatively recent studies >40% of women gained excessive weight with their pregnancies [128, 129]. Excessive weight gain in the mother is associated with ex-

cessive obesity and metabolic disease in offspring [130–133]. For example, children from Brazil with high birth weight (as well as those with a low birth weight) had high blood pressure levels [134]. In a recent study, high maternal pre-pregnancy body mass index and a high birth weight were the most powerful predictors of a higher blood pressure in childhood [42]. Factors which may predispose to the development of CRS in offspring of overweight mothers include both circulating maternal biochemical factors and local placental factors. In this respect, higher relative weights in Pima Indian offspring at the age of 5–24 years [135], and increased risk of childhood obesity and diabetes in a broad-based US population [41, 136, 137] were observed across increasing levels of maternal glucose concentration.

The impact of placental exposure to excessive glucocorticoids on offspring has been termed ‘glucocorticoid programming’ [138–147]. Indeed, epigenetic changes associated with stress can cause indelible changes in the transcriptome. These epigenetic changes are associated with subsequent abnormal physiological function in cardiomyocytes [148, 149], an abnormality seen in CRS (table 2) [106–108]. Indeed, the exposure to excess endogenous or exogenous glucocorticoids during the perinatal period may program the kidney and other organs of the offspring for hypertension, glucose intolerance, and other CRS components in adulthood (table 1). Because of reduced activity of the 11 β -hydroxysteroid dehydrogenase type 2 enzyme in maternal diseases such as preeclampsia, placental cortisol availability may be endogenously increased [144]. It is quite likely that other hormones such as aldosterone, angiotensin II, and catecholamines will have important roles in regulating placental growth, function, and blood supply, and thus exert important roles in fetal programming [146, 147]. Future investigation in this area should parcel out the respective roles of different nutritional and hormonal factors in the epigenetic regulation of the various CRS components.

Conclusion

Epigenetic modulation of adult CRS is an active area of investigation. Traditionally, maternal undernutrition was considered to underlie fetal programming. However, evidence is emerging that overnutrition in both mothers and fathers may predispose the fetus and future adult to CRS. The epigenetic mechanisms underlying fetal programming are only beginning to be understood. Future studies will define the molecular pathways leading up to this phenomenon. Importantly, little is understood what effects nutritional and hormonal factors exert on the fetal genome. Specifically, studies should include the assessment of the different mechanisms in conjunction with one another. Further, the studies should include diverse populations with long-term follow-up. Prevention/intervention strategies in fetal and early life should be developed.

Acknowledgments

The authors would like to acknowledge Stacy Turpin for her illustration and Brenda Hunter for her assistance with this paper. This research was supported by NIH (R01 HL73101-01A1 and R01 HL107910-01) and the Veterans Affairs Merit System 0018 (J.R.S.).

References

- 1 Barker DJ, Osmond C: Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986;1:1077–1081.
- 2 Barker DJ: The fetal and infant origins of disease. *Eur J Clin Invest* 1995;25:457–463.
- 3 Gillman MW: Developmental origins of health and disease. *N Engl J Med* 2005;353:1848–1850.
- 4 Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ: Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation* 1996;94:3246–3250.
- 5 Hoy WE, Rees M, Kile E, Mathews JD, Wang Z: A new dimension to the Barker hypothesis: low birth weight and susceptibility to renal disease. *Kidney Int* 1999;56:1072–1077.
- 6 Davies AA, Smith GD, Ben-Shlomo Y, Litchfield P: Low birth weight is associated with higher adult total cholesterol concentration in men: findings from an occupational cohort of 25,843 employees. *Circulation* 2004;110:1258–1262.
- 7 Fan ZJ, Lackland DT, Lipsitz SR, Nicholas JS: The association of low birthweight and chronic renal failure among Medicaid young adults with diabetes and/or hypertension. *Public Health Rep* 2006;121:239–244.
- 8 Nelson RG, Morgenstern H, Bennett PH: Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. *Am J Epidemiol* 1998;148:650–656.
- 9 Lackland DT, Bendall HE, Osmond C, Egan BM, Barker DJ: Low birth weights contribute to high rates of early rates of early-onset chronic renal failure in the Southeastern United States. *Arch Intern Med* 2000;160:1472–1476.
- 10 Irving RJ, Belton NR, Elton RA, Walker BR: Adult cardiovascular risk factors in premature babies. *Lancet* 2000;355:2135–2136.
- 11 De Prins FA, Van Assche FA: Intrauterine growth retardation and development of endocrine pancreas in the experimental rat. *Biol Neonate* 1982;41:16–21.
- 12 Godfrey K: The 'developmental origins' hypothesis: epidemiology; in Gluckman PD, Hanson MA (eds): *Developmental Origins of Health and Disease*. Cambridge, 2006, Cambridge University Press, pp 6–32.
- 13 Hales CN, Barker DJ: Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992;35:595–601.
- 14 Painter RC, Roseboom TJ, Bleker OP: Prenatal exposure to the Dutch famine and disease in later life: an overview. *Reprod Toxicol* 2005;20:345–352.
- 15 Johansson S, Iliadou A, Bergvall N, Tuvemo T, Norman M, Cnattingius S: Risk of high blood pressure among young men increases with the degree of immaturity at birth. *Circulation* 2005;112:3430–3436.
- 16 Keijzer-Veen MG, Finken MJ, Nauta J, Dekker FW, Hille ET, Frölich M, Wit JM, van der Heijden AJ, Dutch POPS-19 Collaborative Study Group: Is blood pressure increased 19 years after intrauterine growth restriction and preterm birth? A prospective follow-up study in The Netherlands. *Pediatrics* 2005;116:725–731.
- 17 Kistner A, Celsi G, Vanpée M, Jacobson SH: Increased systolic daily ambulatory blood pressure in adult women born preterm. *Pediatr Nephrol* 2005;20:232–233.
- 18 Rotteveel J, van Weissenbruch MM, Twisk JW, Delemarre-Van de Waal HA: Infant and childhood growth patterns, insulin sensitivity, and blood pressure in prematurely born young adults. *Pediatrics* 2008;122:313–321.
- 19 Haynes A, Bower C, Bulsara MK, Finn J, Jones TW, Davis EA: Perinatal risk factors for childhood type 1 diabetes in Western Australia: a population-based study (1980–2002). *Diabet Med* 2007;24:564–570.
- 20 Cardwell CR, Carson DJ, Patterson CC: Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood type 1 diabetes: UK regional retrospective cohort study. *Diabet Med* 2005;22:200–206.
- 21 Petry CJ, Dorling MW, Pawlak DB, Ozanne SE, Hales CN: Diabetes in old male offspring of rat dams fed a reduced protein diet. *Int J Exp Diabetes Res* 2001;2:139–143.
- 22 Hofman PL, Regan F, Jackson WE, Jefferies C, Knight DB, Robinson EM, Cutfield WS: Premature birth and later insulin resistance. *N Engl J Med* 2004;351:2179–2186.
- 23 Lawlor DA, Davey Smith G, Clark H, Leon DA: The associations of birthweight, gestational age and childhood BMI with type 2 diabetes: findings from the Aberdeen Children of the 1950s cohort. *Diabetologia* 2006;49:2614–2617.
- 24 Hovi P, Andersson S, Eriksson JG, Jarvenpää AL, Strang-Karlsson S, Makitie O, Kajantie E: Glucose regulation in young adults with very low birth weight. *N Engl J Med* 2007;356:2053–2063.
- 25 Jansson SP, Andersson DK, Svärdsudd K: Prevalence and incidence rate of diabetes mellitus in a Swedish community during 30 years of follow-up. *Diabetologia* 2007;50:703–710.
- 26 Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, Barrett-Connor E, Bhargava SK, Birgisdottir BE, Carlsson S, de Rooij SR, Dyck RF, Eriksson JG, Falkner B, Fall C, Forsén T, Grill V, Gudnason V, Hulman S, Hyppönen E, Jeffreys M, Lawlor DA, Leon DA, Minami J, Mishra G, Osmond C, Power C, Rich-Edwards JW, Roseboom TJ, Sachdev HS, Syddall H, Thorsdottir I, Vanhala M, Wadsworth M, Yarbrough DE: Birth weight and risk of type 2 diabetes: a systematic review. *JAMA* 2008;300:2886–2897.
- 27 Kaijser M, Bonamy AK, Akre O, Cnattingius S, Granath F, Norman M, Ekblom A: Perinatal risk factors for diabetes in later life. *Diabetes* 2009;58:523–526.
- 28 Willemsen RH, Leunissen RW, Stijnen T, Hokken-Koelega AC: Prematurity is not associated with reduced insulin sensitivity in adulthood. *J Clin Endocrinol Metab* 2009;94:1695–1700.

- 29 Pilgaard K, Faerch K, Carstensen B, Poulsen P, Pisinger C, Pedersen O, Witte DR, Hansen T, Jørgensen T, Vaag A: Low birthweight and premature birth are both associated with type 2 diabetes in a random sample of middle-aged Danes. *Diabetologia* 2010;53:2526–2530.
- 30 Kajantie E, Osmond C, Barker DJ, Eriksson JG: Preterm birth: a risk factor for type 2 diabetes? The Helsinki Birth Cohort Study. *Diabetes Care* 2010;33:2623–2625.
- 31 Hult M, Tornhammar P, Ueda P, Chima C, Bonamy AK, Ozumba B, Norman M: Hypertension, diabetes and overweight: looming legacies of the Biafran famine. *PLoS One* 2010;5:e13582.
- 32 Crump C, Winkeby MA, Sundquist K, Sundquist J: Risk of diabetes among young adults born preterm in Sweden. *Diabetes Care* 2011;34:1109–1113.
- 33 Gluckman PD, Hanson MA, Buklijas T, Low FM, Beedle AS: Epigenetic mechanisms that underpin metabolic and cardiovascular diseases. *Nat Rev Endocrinol* 2009;5:401–408.
- 34 Kuzawa CW, Adair LS: Lipid profiles in adolescent Filipinos: relation to birth weight and maternal energy status during pregnancy. *Am J Clin Nutr* 2003;77:960–966.
- 35 Yajnik CS: Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. *J Nutr* 2004;134:205–210.
- 36 Al Salmi I, Hoy WE, Kondalsamy-Chennakesavan S, Wang Z, Gobe GC, Barr ELM, Shaw JE: Disorders of glucose regulation in adults and birth weight: results from the Australian Diabetes, Obesity and Lifestyle (AUSDIAB) Study. *Diabetes Care* 2008;31:159–164.
- 37 Boney CM, Verma A, Tucker R, Vohr BR: Metabolic syndrome in childhood: association with birthweight, maternal obesity, and gestational diabetes. *Pediatrics* 2005;115:290–296.
- 38 Howie GJ, Sloboda DM, Kamal T, Vickers MH: Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. *J Physiol* 2009;587:905–915.
- 39 Heerwagen MRJ, Miller MR, Barbour LA, Friedman JE: Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. *Am J Regul Integr Comp Physiol* 2010;299:R711–R722.
- 40 Freeman DJ: Effects of maternal obesity on fetal growth and body composition: implications for programming and future health. *Semin Fetal Neonatal Med* 2010;15:113–118.
- 41 Deierlein AL, Chantala K, Siega-Riz AM, Herring AH: The association between maternal glucose concentration and child BMI at age 3 years. *Diabetes Care* 2011;34:480–484.
- 42 Filler G, Yasin A, Kesarwani P, Garg A, Lindsay R, Sharma AP: Big mother or small baby: which predicts hypertension? *J Clin Hypertens* 2011;13:35–41.
- 43 Ritz E, Amann K, Koleganova N, Benz K: Prenatal programming-effects on blood pressure and renal function. *Nat Rev Nephrol* 2011;7:137–144.
- 44 Ng SF, Lin RCY, Laybutt DR, Barres R, Owens JA, Morris MJ: Chronic high-fat diet in fathers programs β -cell dysfunction in female rat offspring. *Nature* 2010;467:963–966.
- 45 Reik W: Stability and flexibility of epigenetic gene regulation in mammalian development. *Nature* 2007;447:425–432.
- 46 Bogdarina I, Welham S, King PJ, Burns SP, Clark AJ: Epigenetic modification of the renin-angiotensin system in fetal programming of hypertension. *Circ Res* 2007;100:520–526.
- 47 Raychaudhuri N, Raychaudhuri S, Thamocharan M, Devaskar SU: Histone code modifications repress glucose transporter 4 expression in the intra-uterine growth-restricted offspring. *J Biol Chem* 2008;283:13611–13626.
- 48 Ozanne SE, Hales CN: Lifespan: catch-up growth and obesity in male mice. *Nature* 2004;427:411–412.
- 49 Zambrano E, Bautista CJ, Deás M, Martínez-Samayoá PM, González-Zamorano M, Ledesma H, Morales J, Larrea F, Nathanielsz PW: A low maternal protein diet during pregnancy and lactation has sex- and window of exposure-specific effects on offspring growth and food intake, glucose metabolism and serum leptin in the rat. *J Physiol* 2006;571:221–230.
- 50 Eriksson M, Tynelius P, Rasmussen F: Associations of birthweight and infant growth with body composition at age 15: the COMPASS study. *Paediatr Perinat Epidemiol* 2008;22:379–388.
- 51 Zeltser LM: Increased adiposity programmed by catch-up growth: requirement for leptin signals? *Endocrinology* 2011;152:337–339.
- 52 Matveyenko AV, Singh I, Shin BC, Georgia S, Devaskar SU: Differential effects of prenatal and postnatal nutritional environment on β -cell mass development and turnover in male and female rats. *Endocrinology* 2010;151:5647–5656.
- 53 Oak SA, Tran C, Pan G, Thamocharan M, Devaskar SU: Perturbed skeletal muscle insulin signaling in the adult female intrauterine growth-restricted rat. *Am J Physiol Endocrinol Metab* 2006;290:E1321–E1330.
- 54 Phillips DI, Barker DJ, Hales CN, Hirst S, Osmond C: Thinness at birth and insulin resistance in adult life. *Diabetologia* 1994;37:150–154.
- 55 Thamocharan M, Garg M, Oak S, Rogers LM, Pan G, Sangiorgi F, Lee PW, Devaskar SU: Transgenerational inheritance of the insulin-resistant phenotype in embryo-transferred intrauterine growth-restricted adult female rat offspring. *Am J Physiol Endocrinol Metab* 2007;292:E1270–E1279.
- 56 Stanger BZ, Tanaka AJ, Melton DA: Organ size is limited by the number of embryonic progenitor cells in the pancreas but not the liver. *Nature* 2007;445:886–891.
- 57 Simmons RA, Templeton LJ, Gertz SJ: Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. *Diabetes* 2001;50:2279–2286.

- 58 Brufani C, Grossi A, Fintini D, Tozzi A, Nocerino V, Patera PI, Ubertaini G, Porzio O, Barbetti F, Cappa M: Obese children with low birth weight demonstrate impaired β -cell function during oral glucose tolerance test. *J Clin Endocrinol Metab* 2009;94:4448–4452.
- 59 Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, Rodford J, Slater-Jefferies JL, Garratt E, Crozier SR, Emerald BS, Gale CR, Inskip HM, Cooper C, Hanson MA: Epigenetic gene promoter methylation at birth is associated with child's later adiposity. *Diabetes* 2011;60:1528–1534.
- 60 Augustyniak RA, Singh K, Zeldes D, Singh M, Rossi NF: Maternal protein restriction leads to hyperresponsiveness to stress and salt-sensitive hypertension in male offspring. *Am J Physiol Regul Integr Comp Physiol* 2010;298:R1375–R1382.
- 61 Villar-Martini VC, Carvalho JJ, Neves MF, Aguila MB, Mandarim-de-Lacerda CA: Hypertension and kidney alterations in rat offspring from low protein pregnancies. *J Hypertens Suppl* 2009;27:S47–S51.
- 62 Waterland RA, Travisano M, Tahiliani KG, Rached MT, Mirza S: Methyl donor supplementation prevents transgenerational amplification of obesity. *Int J Obes (Lond)* 2008;32:1373–1379.
- 63 Aagaard-Tillery KM, Grove K, Bishop J, Ke X, Fu Q, McKnight R, Lane RH: Developmental origins of disease and determinants of chromatin structure: maternal diet modifies the primate fetal epigenome. *J Mol Endocrinol* 2008;41:91–102.
- 64 Sinclair KD, Allegrucci C, Singh R, Gardner DS, Sebastian S, Bispham J, Thurston A, Huntley JF, Rees WD, Maloney CA, Lea RG, Craigon J, McEvoy TG, Young LE: DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status. *Proc Natl Acad Sci USA* 2007;104:19351–19356.
- 65 Luyckx VA, Brenner BM: Low birth weight, nephron number, and kidney disease. *Kidney Int Suppl* 2005;97:S68–S77.
- 66 Zandi-Nejad K, Luyckx VA, Brenner BM: Adult hypertension and kidney disease: the role of fetal programming. *Hypertension* 2006;47:502–508.
- 67 Franco MC, Casarini DE, Carneiro-Ramos MS, Sawaya AL, Barreto-Chaves ML, Sesso R: Circulating renin-angiotensin system and catecholamines in childhood: is there a role for birthweight? *Clin Sci (Lond)* 2008;114:375–380.
- 68 Li L, Law C, Power C: Body mass index throughout the life-course and blood pressure in mid-adult life: a birth cohort study. *J Hypertens* 2007;25:1215–1223.
- 69 Franco MC, Christofalo DM, Sawaya AL, Ajzen SA, Sesso R: Effects of low birth weight in 8- to 13-year-old children: implications in endothelial function and uric acid levels. *Hypertension* 2006;48:45–50.
- 70 Keller G, Zimmer G, Mall G, Ritz E, Amann K: Nephron number in patients with primary hypertension. *N Engl J Med* 2003;348:101–108.
- 71 Manalich R, Reyes L, Herrera M, Melendi C, Fundora I: Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int* 2000;58:770–773.
- 72 Gubhaju L, Sutherland MR, Yoder BA, Zulli A, Bertram JF, Black MJ: Is nephrogenesis affected by preterm birth? Studies in a non-human primate model. *Am J Physiol Renal Physiol* 2009;297:F1668–F1677.
- 73 Painter RC, Roseboom TJ, van Montfrans GA, Bossuyt PM, Krediet RT, Osmond C, Barker DJ, Bleker OP: Microalbuminuria in adults after exposure to the Dutch famine. *J Am Soc Nephrol* 2005;16:189–194.
- 74 Hallan S, Euser AM, Irgens LM, Finken MJ, Holmen J, Dekker FW: Effect of intrauterine growth restriction on kidney function at young adult age: the Nord Trøndelag Health (HUNT 2) study. *Am J Kidney Dis* 2008;51:10–20.
- 75 Li S, Chen SC, Shlipak M, Bakris G, McCullough PA, Sowers J, Stevens L, Jurkovic C, McFarlane S, Norris K, Vassalotti J, Klag MJ, Brown WW, Narva A, Calhoun D, Johnson B, Obialo C, Whaley-Connell A, Becker B, Collins AJ, Kidney Early Evaluation Program Investigators: Low birth weight is associated with chronic kidney disease only in men. *Kidney Int* 2008;73:637–642.
- 76 Vikse BE, Irgens LM, Leivestad T, Hallan S, Iversen BM: Low birth weight increases risk for end-stage renal disease. *J Am Soc Nephrol* 2008;19:151–157.
- 77 Na YW, Yang HJ, Choi JH, Yoo KH, Hong YS, Lee JW, Kim SK: Effect of intrauterine growth retardation on the progression of nephrotic syndrome. *Am J Nephrol* 2002;22:463–467.
- 78 Zidar N, Cavic MA, Kenda RB, Koselj M, Ferluga D: Effect of intrauterine growth retardation on the clinical course and prognosis of IgA glomerulonephritis in children. *Nephron* 1998;79:28–32.
- 79 Nenov VD, Taal MW, Sakharova OV, Brenner BM: Multi-hit nature of chronic renal disease. *Curr Opin Nephrol Hypertens* 2000;9:85–97.
- 80 Plank C, Ostreicher I, Hartner A, Marek I, Struwe FG, Amann K, Hilgers KF, Rascher W, Dötsch J: Intrauterine growth retardation aggravates the course of acute mesangioproliferative glomerulonephritis in the rat. *Kidney Int* 2006;70:1974–1982.
- 81 Fassi A, Sangalli F, Maffi R, Colombi F, Mohamed EI, Brenner BM, Remuzzi G, Remuzzi A: Progressive glomerular injury in the MWF rat is predicted by inborn nephron deficit. *J Am Soc Nephrol* 1998;9:1399–1406.
- 82 Stewart T, Jung FF, Manning J, Vehaskari VM: Kidney immune cell infiltration and oxidative stress contribute to prenatally programmed hypertension. *Kidney Int* 2005;68:2180–2188.
- 83 Loos RJ, Fagard R, Beunen G, Derom C, Vlietinck R: Birth weight and blood pressure in young adults: a prospective twin study. *Circulation* 2001;104:1633–1638.
- 84 Hoy WE, Hughson MD, Bertram JF, Douglas-Denton R, Amann K: Nephron number, hypertension, renal disease, and renal failure. *J Am Soc Nephrol* 2005;16:2557–2564.

- 85 Boudville N, Prasad GV, Knoll G, Muirhead N, Thiessen-Philbrook H, Yang RC, Rosas-Arellano MP, Housawi A, Garg AX, Donor Nephrectomy Outcomes Research (DONOR) Network: Meta-analysis: risk for hypertension in living kidney donors. *Ann Intern Med* 2006;145:185–196.
- 86 de Boer MP, Ijzerman RG, de Jongh RT, Eringa EC, Stehouwer CD, Smulders YM, Serné EH: Birth weight relates to salt sensitivity of blood pressure in healthy adults. *Hypertension* 2008;51:928–932.
- 87 Manning J, Beutler K, Knepper MA, Vehaskari VM: Upregulation of renal BSC1 and TSC in prenatally programmed hypertension. *Am J Physiol Renal Physiol* 2002;283:F202–F206.
- 88 Vehaskari VM, Stewart T, Lafont D, Soyey C, Seth D, Manning J: Kidney angiotensin and angiotensin receptor expression in prenatally programmed hypertension. *Am J Physiol Renal Physiol* 2004;287:F262–F267.
- 89 Houang M, Morineau G, le Bouc Y, Fiet J, Gourmelen M: The cortisol-cortisone shuttle in children born with intra-uterine growth retardation. *Pediatr Res* 1999;46:189–193.
- 90 Alexander BT, Hendon AE, Ferril G, Dwyer TM: Renal denervation abolishes hypertension in low-birth-weight offspring from pregnant rats with reduced uterine perfusion. *Hypertension* 2005;45:754–758.
- 91 Lurbe E, Garcia-Vicent C, Torro I, Fayos JL, Aguilar F, de Llano JM, Fuertes G, Redón J: First-year blood pressure increase steepest in low birthweight newborns. *J Hypertens* 2007;25:81–86.
- 92 Bhargava SK, Sachdev HS, Fall CH, Osmond C, Lakshmy R, Barker DJ, Biswas SK, Ramji S, Prabhakaran D, Reddy KS: Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *N Engl J Med* 2004;350:865–875.
- 93 Järvelin MR, Sovio U, King V, Lauren L, Xu B, McCarthy MI, Hartikainen AL, Laitinen J, Zitting P, Rantakallio P, Elliott P: Early life factors and blood pressure at age 31 years in the 1966 northern Finland birth cohort. *Hypertension* 2004;44:838–846.
- 94 Huxley RR, Shiell AW, Law CM: The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens* 2000;18:815–831.
- 95 Uiterwaal CS, Anthony S, Launer LJ, Witteman JC, Trouwborst AM, Hofman A, Grobbee DE: Birth weight, growth, and blood pressure: an annual follow-up study of children aged 5 through 21 years. *Hypertension* 1997;30:267–271.
- 96 Horta BL, Barros FC, Victora CG, Cole TJ: Early and late growth and blood pressure in adolescence. *J Epidemiol Community Health* 2003;57:226–230.
- 97 Spassov L, Curzi-Dascalova L, Clairambault J, Kauffmann F, Eiselt M, Médigue C, Peirano P: Heart rate and heart rate variability during sleep in small-for-gestational age newborns. *Pediatr Res* 1994;35:500–505.
- 98 Leeson CP, Whincup PH, Cook DG, Donald AE, Papacosta O, Lucas A, Deanfield JE: Flow-mediated dilation in 9- to 11-year-old children: the influence of intrauterine and childhood factors. *Circulation* 1997;96:2233–2238.
- 99 Ligi I, Grandvuillemin I, Andres V, Dignat-George F, Simeoni U: Low birth weight infants and the developmental programming of hypertension: a focus on vascular factors. *Semin Perinatol* 2010;34:188–192.
- 100 Varvarigou AA: Intrauterine growth restriction as a potential risk factor for disease onset in adulthood. *J Pediatr Endocrinol Metab* 2010;23:215–224.
- 101 Fagerudd J, Forsblom C, Pettersson-Fernholm K, Saraheimo M, Wadén J, Rönnback M, Rosengård-Bärlund M, Af Björkstén CG, Thorn L, Wessman M, Groop PH, Finn Diane Study Group: Birth weight is inversely correlated to adult systolic blood pressure and pulse pressure in type 1 diabetes. *Hypertension* 2004;44:832–837.
- 102 Antonios TF, Singer DR, Markandu ND, Mortimer PS, MacGregor GA: Structural skin capillary rarefaction in essential hypertension. *Hypertension* 1999;33:998–1001.
- 103 Antonios TF, Rattray FM, Singer DR, Markandu ND, Mortimer PS, MacGregor GA: Rarefaction of skin capillaries in normotensive offspring of individuals with essential hypertension. *Heart* 2003;89:175–178.
- 104 Mitchell P, Liew G, Rochtchina E, Wang JJ, Robaei D, Cheung N, Wong TY: Evidence of arteriolar narrowing in low-birth-weight children. *Circulation* 2008;118:518–524.
- 105 Chapman N, Mohamudally A, Cerutti A, Stanton A, Sayer AA, Cooper C, Barker D, Rauf A, Evans J, Wormald R, Sever P, Hughes A, Thom S: Retinal vascular network architecture in low-birth-weight men. *J Hypertens* 1997;15:1449–1453.
- 106 Sowers JR, Whaley-Connell A, Hayden MR: The role of overweight and obesity in the cardiorenal syndrome. *Cardiorenal Med* 2011;1:5–12.
- 107 Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM: Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006;295:1549–1555.
- 108 Ghandehari H, Le V, Kamal-Bahl S, Bassin SL, Wong ND: Abdominal obesity and the spectrum of global cardiometabolic risks in US adults. *Int J Obes (Lond)* 2009;33:239–248.
- 109 Sowers JR: Obesity as a cardiovascular risk factor. *Am J Med* 2003;115(suppl 8A):37S–41S.
- 110 Ogden CL, Carroll MD, Flegal KM: High body mass index for age among US children and adolescents, 2003–2006. *JAMA* 2008;299:2401–2405.
- 111 Allcock DM, Gardner JM, Sowers JR: Relation between childhood obesity and adult cardiovascular risk. *Int J Pediatr Endocrinol* 2009;2009:108187.
- 112 Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yockel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S: Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004;350:2362–2374.

- 113 Bakris G, Vassalotti J, Ritz E, Wanner C, Stergiou G, Molitch M, Nesto R, Kaysen GA, Sowers JR, CKD Consensus Working Group: National Kidney Foundation consensus conference on cardiovascular and kidney diseases and diabetes risk: an integrated therapeutic approach to reduce events. *Kidney Int* 2010;78:726–736.
- 114 Cruz ML, Weigensberg MJ, Huang TT, Ball G, Shaibi GQ, Goran MI: The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *J Clin Endocrinol Metab* 2004;89:108–113.
- 115 Sowers JR: Metabolic risk factors and renal disease. *Kidney Int* 2007;71:719–720.
- 116 Kurella M, Lo JC, Chertow GM: Metabolic syndrome and the risk of chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 2005;16:2134–2140.
- 117 Lucove J, Vupputuri S, Heiss G, North K, Russell M: Metabolic syndrome and the development of CKD in American Indians: the Strong Heart Study. *Am J Kidney Dis* 2008;51:21–28.
- 118 Whaley-Connell A, Pavey BS, McCullough PA, Saab G, Li S, McFarlane SI, Chen SC, Vassalotti JA, Collins AJ, Bakris G, Sowers JR, KEEP Investigators: Dysglycemia predicts cardiovascular and kidney disease in the Kidney Early Evaluation Program. *J Clin Hypertens (Greenwich)* 2010;12:51–58.
- 119 Wuerzner G, Pruijm M, Maillard M, Bovet P, Renaud C, Burnier M, Bochud M: Marked association between obesity and glomerular hyperfiltration: a cross-sectional study in an African population. *Am J Kidney Dis* 2010;56:303–312.
- 120 Levey AS, Kramer H: Obesity, glomerular hyperfiltration, and the surface area correction. *Am J Kidney Dis* 2010;56:255–258.
- 121 Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DL, Block ER, Herrera-Acosta J, Patel JM, Johnson RJ: A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol* 2006;290:F625–F631.
- 122 Sánchez-Lozada LG, Tapia E, Jiménez A, Bautista P, Cristóbal M, Nepomuceno T, Soto V, Avila-Casado C, Nakagawa T, Johnson RJ, Herrera-Acosta J, Franco M: Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats. *Am J Physiol Renal Physiol* 2007;292:F423–F429.
- 123 Bombard AS, Derebail VK, Shoham DA, Anderson CA, Steffen LM, Rosamond WD, Kshirsagar AV: Sugar-sweetened soda consumption, hyperuricemia, and kidney disease. *Kidney Int* 2010;77:609–616.
- 124 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM: Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251–259.
- 125 Zhou X, Ma L, Habibi J, Whaley-Connell A, Hayden MR, Tilmon RD, Brown AN, Kim JA, Demarco VG, Sowers JR: Nebivolol improves diastolic dysfunction and myocardial remodeling through reductions in oxidative stress in the Zucker obese rat. *Hypertension* 2010;55:880–888.
- 126 Pulakat L, DeMarco VG, Whaley-Connell A, Sowers JR: The impact of overnutrition on insulin metabolic signaling in the heart and the kidney. *Cardiorenal Med* 2011;1:102–112.
- 127 Pulakat L, DeMarco VG, Ardhanari S, Chockalingam A, Gul R, Whaley-Connell AT, Sowers JR: Adaptive mechanisms to compensate for overnutrition-induced cardiovascular abnormalities. *Am J Physiol Regul Integr Comp Physiol* 2011, E-pub ahead of print.
- 128 May R: Prepregnancy weight, inappropriate gestational weight gain, and smoking: relationships to birth weight. *Am J Hum Biol* 2007;19:305–310.
- 129 Olson CM: Achieving a healthy weight gain during pregnancy. *Annu Rev Nutr* 2008;28:411–423.
- 130 Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW: Gestational weight gain and child adiposity at age 3 years. *Am J Obstet Gynecol* 2007;196:322.e1–322.e8.
- 131 Taylor PD, Poston L: Developmental programming of obesity in mammals. *Exp Physiol* 2007;92:287–298.
- 132 Howie GJ, Sloboda DM, Kamal T, Vickers MH: Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. *J Physiol* 2009;587:905–915.
- 133 Ainge H, Thompson C, Ozanne SE, Rooney KB: A systemic review of animal models of maternal high fat feeding and offspring glycaemic control. *Int J Obes (Lond)* 2011;35:325–335.
- 134 Strufaldi MW, Silva EM, Franco MC, Puccini RF: Blood pressure levels in childhood: probing the relative importance of birth weight and current size. *Eur J Pediatr* 2009;168:619–624.
- 135 Pettitt DJ, Bennett PH, Saad MF, Charles MA, Nelson RG, Knowler WC: Abnormal glucose tolerance during pregnancy in Pima Indian women. Long-term effects on offspring. *Diabetes* 1991;40:126–130.
- 136 Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, Knowler WC: Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 2000;49:2208–2211.
- 137 Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ: Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care* 2007;30:2287–2292.
- 138 Doyle LW, Ford GW, Davis NM, Callanan C: Antenatal corticosteroid therapy and blood pressure at 14 years of age in preterm children. *Clin Sci (Lond)* 2000;98:137–142.
- 139 Seckl JR, Holmes MC: Mechanisms of disease: glucocorticoids, their placental metabolism and fetal ‘programming’ of adult pathophysiology. *Nat Clin Pract Endocrinol Metab* 2007;3:479–488.
- 140 Nuyt AM, Alexander BT: Developmental programming and hypertension. *Curr Opin Nephrol Hypertens* 2009;18:144–152.
- 141 Tang L, Carey LC, Bi J, Valeo N, Sun X, Deibel P, Perrott J, Figueroa P, Chappell MC, Rose JC: Gender differences in the effects of antenatal betamethasone exposure on renal function in adult sheep. *Am J Physiol Regul Integr Comp Physiol* 2009;296:R309–R317.

- 142 Dodic M, Moritz K, Wintour EM: Prenatal exposure to glucocorticoids and adult disease. *Arch Physiol Biochem* 2003; 111:61–69.
- 143 Tang L, Bi J, Valego N, Carey L, Figueroa J, Chappell M, Rose JC: Prenatal betamethasone exposure alters renal function in immature sheep: sex differences in effects. *Am J Physiol Regul Integr Comp Physiol* 2009;296:R309–R317.
- 144 Aufdenblatten M, Baumann M, Raio L, Dick B, Frey BM, Schneider H, Surbek D, Hoher B, Mohaupt MG: Prematurity is related to high placental cortisol in preeclampsia. *Pediatr Res* 2009;65:198–202.
- 145 Seckl JR, Meaney MJ: Glucocorticoid programming. *Ann NY Acad Sci* 2004;1032:63–84.
- 146 Gennari-Moser C, Khankin EV, Schüller S, Escher G, Frey BM, Portmann CB, Baumann MU, Lehmann AD, Surbek D, Karumanchi SA, Frey FJ, Mohaupt MG: Regulation of placental growth by aldosterone and cortisol. *Endocrinology* 2011;152:263–271.
- 147 Gwathmey TM, Shaltout HA, Rose JC, Diz DI, Chappell MC: Glucocorticoid-induced fetal programming alters the functional component of angiotensin receptor subtypes within the kidney. *Hypertension* 2011;57:620–626.
- 148 Kaneda R, Takada S, Yamashita Y, Choi YL, Nonaka-Sarukawa M, Soda M, Misawa Y, Isomura T, Shimada K, Mano H: Genome-wide histone methylation profile for heart failure. *Genes Cells* 2009;14:69–77.
- 149 Stein AB, Jones TA, Herron TJ, Patel SR, Day SM, Noujaim SF, Milstein ML, Klos M, Furspan PB, Jalife J, Dressler GR: Loss of H3K4 methylation stabilizes gene expression patterns and physiological functions in adult murine cardiomyocytes. *J Clin Invest* 2011;121:2641–2650.