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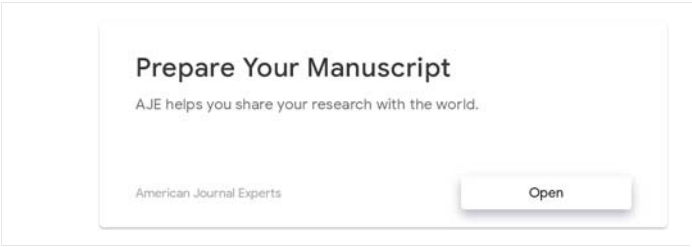

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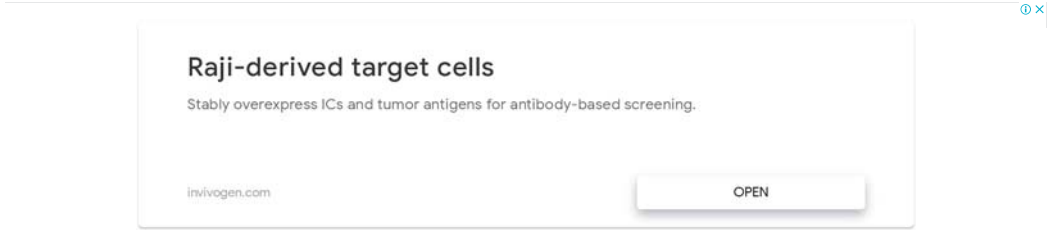

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Review

Developmental Origins of Disease - Crisis Precipitates Change

Christoph Reichetzeder[a,b] Sulistyo Emantoko Dwi Putra[a,c] Jian Li[d] Berthold Hocher[a,d,e]

[a]Institute for Nutritional Science, University of Potsdam, Nuthetal, Germany; [b]Center for Cardiovascular Research (CCR), Campus Charité Mitte, University Hospital Charité, Berlin, Germany; [c]Faculty of Biotechnology, University of Surabaya, Surabaya, Indonesia; [d]Department of Basic Medicine, Medical College of Hunan Normal University, Changsha, China; [e]Institut für Laboratoriumsmedizin, Berlin, Germany

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Abstract
The concept of developmental origins of diseases has gained a huge interest in recent years and is a constantly emerging scientific field. First observations hereof originated from epidemiological studies, linking impaired birth outcomes to adult chronic, noncommunicable disease. By now there is a considerable amount of both epidemiological and experimental evidence highlighting the impact of early life events on later life disease susceptibility. Albeit far from being completely understood, more recent studies managed to elucidate underlying mechanisms, with epigenetics having become almost synonymous with developmental programming. The aim of this review was to give a comprehensive overview of various aspects and mechanisms of developmental origins of diseases. Starting from initial research foci mainly centered on a nutritionally impaired intrauterine environment, more recent findings such as postnatal nutrition, preterm birth, paternal programming and putative interventional approaches are summarized. The review outlines general underlying mechanisms and particularly discusses mechanistic explanations for sexual dimorphism in developmental programming. Furthermore, novel hypotheses are presented emphasizing a non-mendelian impact of parental genes on the offspring's phenotype.

Introduction

Throughout the entire life of an individual, environmental factors play an important role for its state of health. However, at no stage in life the surrounding environment has a bigger impact than during embryonic and fetal life. Growth and development in utero are complex

Prof. Dr. Berthold Hocher
Department of Basic Medicine, Medical College of Hunan Normal University, Changsha, (China)
E-Mail hocher@uni-potsdam.de

and dynamic processes which require an orchestration of a variety of maternal, paternal and fetal factors for an optimal outcome. This complex interaction between mother, father, placenta and embryo/fetus ensures an optimal supply of nutrients, oxygen and endocrine signals, all fundamental elements for normal development. Disruptions in this supply system may not only have a direct impact on altering fetal growth patterns, but, as evidence suggests, can be associated with the occurrence of diseases in the later life of the offspring. In the current review, we will discuss exogenous (environmental) as well as endogenous factors (both parental and offspring genes) contributing to the complex interaction between mother, father, placenta and embryo/fetus.

Undernutrition

Epidemiological data unequivocally indicate that there is a connection between early life conditions, anthropometric measures at birth and disease susceptibility in later life [1, 2]. The “Barker Hypothesis”, also called the “Fetal Programming Hypothesis” or the theory of the “Developmental Origins of Health and Diseases (DOHaD)”, has become the foundation for this increasingly popular scientific field [2]. Barker et al. were not the first investigating this subject, but it was their groundbreaking epidemiological studies in England and Wales in the late 1980ies that inspired research worldwide. Barker et al. initially demonstrated a geographical relationship between cases of ischemic heart disease in the years 1968-1978 and child mortality rates between 1921-1925 [3]. A follow-up study showed that individuals born with a reduced birth weight had an increased risk for coronary heart disease in their adult life [4, 5]. Hales et al. demonstrated in another follow-up study that there is a similar inverse correlation between birth weight and later life glucose tolerance or insulin resistance [6]. In addition, they revealed that individuals with the lowest birth weight, in comparison to heavier newborns, displayed a six fold increased risk for impaired glucose tolerance or diabetes mellitus type 2 in late adulthood [6]. Until now, these findings have been replicated in several different study populations and in different ethnic groups [7]. Based on their observations, Hales and Barker formulated the "Thrifty Phenotype Hypothesis", a more detailed hypothesis trying to outline a putative mechanism of fetal programming. According to this explanation model, gestational under nutrition induces a series of adaptive processes in the fetus, trying to maximize the chances of survival in the given nutrient-poor environment. However, if a mismatch between pre- and postnatal nutrient supply exists fetal adaptation can be deleterious, increasing the risk for diseases later in life [7, 8].

The Thrifty Phenotype Hypothesis

Research stimulated by the thrifty phenotype hypothesis has improved the understanding of the plasticity of early human development, emphasizing an important role of developmental plasticity as a possible contributing factor to later human disease [9]. Until now, the thrifty phenotype hypothesis was confirmed by a number of human studies. The link between a poor intrauterine environment, restricted fetal growth and increased adult disease risk was well demonstrated in the "Dutch famine study". In this retrospective study, children born during a war-inflicted famine between December 1944 and April 1945 were analyzed [10, 11]. During the famine, the daily caloric intake for the general population was restricted to 400 - 800 kcal per day, about half as much as before and after this period. The comparison of individuals that were in utero during this time with individuals born a year before or after the famine showed that gestational caloric restriction was associated with a decreased birth weight and an increased prevalence of impaired glucose tolerance at an age of 50 years [10]. Moreover, twin studies were able to confirm the Thrifty Phenotype Hypothesis. A Danish study examined mono- and dizygotic twins which were discordant for the occurrence of type 2 diabetes. Results of the study revealed that the diabetic

twin was born with a significantly lower birth weight compared to the euglycemic twin sibling [12]. Other twin studies, especially studies on monozygotic twins, highlighted the importance of the intrauterine environment and developmental plasticity, regardless of the underlying genotype [13]. In addition to the connection between a sub-optimal intrauterine environment, disturbed fetal growth patterns and disease predisposition in adulthood, several more recent studies showed that postnatal nutrition is to be regarded as another critical component of the thrifty phenotype hypothesis. Crowther et al. investigated the impact of postnatal weight gain in a cohort of 7-year-old South African children [14]. Results of this study showed that children born with a reduced birth weight and rapid postnatal weight gain, displayed an impaired glucose tolerance already at an age of 7 years [14]. Further studies in Finland and India replicated these findings [15–17]. Various studies have demonstrated that rapid postnatal weight gain in newborns with an initial low birth weight is mainly due to fat accumulation and not due to an increase in muscle mass [18–20]. This specific phenotype was observed in several cohorts of small for gestational age newborns [21, 22]. In addition it was demonstrated that fat accumulation is more prominent in visceral than in subcutaneous fat depots [23, 24].

Parallel to the epidemiological studies outlined above, various animal studies have been conducted over the years in order to investigate the underlying mechanisms of developmental programming more thoroughly. Preclinical results substantiated findings from observational studies and gave more insight into involved mechanisms, also substantiating the thrifty phenotype hypothesis [25, 26]. It was demonstrated that restricting the maternal diet during gestation does not just result in low birth weight but induces disproportional growth. At the expense of organs such as liver, kidney, pancreas, lung and skeletal muscle, the development of brain, heart and adrenal gland is prioritized [25, 27]. Caloric restriction during gestation was shown to reduce pancreatic beta cell mass formation in the offspring, leading to a decreased production of insulin [28]. In a postnatal calorie-rich life, this lack of insulin production can predispose for the development of diabetes [29].

Overnutrition

As worldwide obesity rates are constantly rising, the focus of research has moved from maternal undernutrition as a predisposing factor for reduced birth weight and adult disease susceptibility, to the impact of maternal overnutrition on offspring health. Interestingly, it was shown that maternal overnutrition and an increased birth weight of the newborn elicits similar effects on offspring health as observed in low birth weight offspring [30, 31]. Being born small for gestational age (SGA) usually is associated with deficits in placental function, placental blood flow and adverse environmental influences, such as maternal undernutrition, particularly if the diet lacks sufficient protein levels [32–35]. Furthermore, literature suggests a complex genetic association, as SGA offspring more commonly occurs in women themselves born SGA [32, 36]. Increases in birth weight are typically associated with maternal obesity and gestational or pre-gestational diabetes [37–39]. Moreover, a very recent study provided genetic evidence for a causal relationship between maternal obesity-related traits and offspring birth weight [37]. Large for gestational age (LGA) offspring usually displays an increased body fat mass and an increased risk for metabolic disease in later life [37, 40, 41]. Current evidence suggests that either being born with a reduced or an increased birth weight increases disease risk in later life. Meta-analysis have underlined this by demonstrating an U-shaped relationship between later life metabolic diseases and birth weight [42–44]. The overlap of the adult phenotype in SGA and LGA offspring raises the important question which mechanisms are affected in these conditions, and vice versa howthese mechanisms can be triggered by conditions producing extremely disparate early life phenotypes [32]. Interestingly, specific overnutrition by feeding an isocaloric high-protein diet to rats, was shown to elicit no effects on birth weight but cause an impaired phenotype in adult animals [45]. Furthermore, it was demonstrated in animal and human

models that the simultaneous presence of two gestational insults, maternal obesity and maternal stress, are associated with increased rates of both, SGA and LGA offspring [31, 32, 46]. Literature on this subject suggests that the variability in the observed outcomes is likely due to different dosage, timing and downstream effects of a maternal insult. Maternal obesity and pre-pregnancy high-fat intake was on one hand shown to increase the risk for SGA and preeclampsia. On the other hand, this combination of maternal insults was associated with maternal gestational overeating which is associated with gestational diabetes and LGA [30, 32, 47]. Animal stress models revealed that the timing of the maternal stressor during gestation is a key factor for the offspring to be born SGA or LGA [48]. Furthermore, placental development and function, especially an impairment of the placental barrier which normally limits fetal exposure to maternal stress hormones, is thought to play a central role in the severity of maternal stress effects [49, 50]. Taken together, both over and undernutrition are associated with developmental programming. Future studies will give a more precise picture of the complex interaction between nutrition and developmental programming. More recent studies already aimed to discern the role of micronutrient deficiency or excess in regards to developmental origins of disease [51–55]. Furthermore there are also novel approaches to integrate the role of the microbiome and its interaction with nutrition into developmental programming studies [56].

Critical Periods for Nutritional Programming

Experimental and epidemiological data show that effects of developmental programming can be triggered throughout gestation. However, the nature of adult disease can vary according to the timing of a gestational insult [57]. Analysis of the "Dutch Hunger Winter" cohort demonstrated that offspring exposed to famine during early periods of gestation displayed an increased risk for coronary heart disease in later life, which could not be observed if famine exposure happened during later stages of pregnancy [58]. Interestingly, caloric restriction during late gestation was associated with disturbances in glucose-insulin homeostasis, clinically reflected by an increased risk of type 2 diabetes [58]. This finding could be replicated in animal models [59, 60]. Gardner et al. showed that maternal undernutrition in sheep in late gestation also led to impaired glucose-insulin homeostasis, highlighting the importance of late gestational periods in regards to programming effects on intermediary metabolism [60]. According to developmental processes in respective gestational periods, current literature suggests that nutritional insults during early gestation may influence organ development, altering fetal physiology in late gestation, and postnatal function, yet often without a measurable effect on birth weight [59, 61–64]. This was demonstrated by various studies investigating nutritional alteration in the periconceptual period, which is characterized by fertilisation, blastocystogenesis and the implantation process [61–65]. Nutritional insults set in later embryonic and early fetal life, a period which comprises intense organogenesis and placental development, display similar patterns of developmental programming [66–70]. Dietary modifications in later stages of gestation, characterized by very pronounced fetal growth and placental maturation, were shown to have a strong impact on birth weight and organ maturation with pronounced programming effects on intermediary metabolism and hormonal systems [71–75]. Furthermore, also postnatal nutrition plays an important role in developmental programming. A large body of studies have demonstrated that postnatal catch-up growth in low birth weight newborns is a crucial factor for increasing the risk of adult metabolic disturbances [20, 22, 76]. Intriguingly, also in postnatal developmental programming timing is of importance. It was shown that catch-up growth restricted to the first postnatal year did not have an effect on insulin levels, but sustained catch-up growth was associated with higher insulin levels in seven year old- and insulin resistance in eight year old children [77–79]. Next to postnatal periods, newer evidence highlights the importance of preconceptual nutrition of both the mother and the father on offspring health.

There is a growing amount of evidence, demonstrating that dietary challenges during oozyte development or spermatogenesis can induce permanent phenotypic changes in the offspring [80–84]. Taken together, available evidence highlights the importance of different time frames before, during and after gestation in regards to developmental origins of health and disease. However, given species differences in physiology, metabolism, placental structure and function, cautious interpretation of the available studies is warranted, especially when extrapolating to human situations [72].

Prematurity

More recent data showed that fetal adaptation causing persistent functional and structural changes of the fetal organism can be induced by factors that go beyond gestational nutrition and do not necessarily have to impact on anthropometric measures at birth [85]. A very important factor in this regard is preterm birth. As outlined before, initial studies on fetal programming focused on a 'deprived' intrauterine environment as a cause for low birth weight or SGA [10, 86]. Such anthropometric measurements were then used as surrogate parameters for association analyses with later life disease [10, 86]. However, many of these epidemiologic studies based their investigations on old birth records, sometimes assessing birth weight without considering gestational age at birth [87, 88]. Thus, it is possible that a considerable amount of individuals included in these epidemiologic studies, were preterm individuals and not small for gestational age [87]. De Jong et al. demonstrated in a systematic literature review followed by a meta-analysis, that preterm birth is associated with higher blood pressure in adulthood, suggesting a relevant role of gestational age in fetal programming [89]. There is an increasing body of evidence that prematurity is associated with an increased risk for various disease in adult life [53, 87, 89–91]. It is known that preterm birth causes an interruption of normal organogenesis, especially in organ systems that display a branching morphogenesis like kidney, lung, pancreas, and the vascular system [87, 92–94]. The developing kidney is particularly vulnerable to preterm birth which causes considerable deficits in organ structure and function [93]. Prematurity was shown to be associated with a lower nephron endowment [95, 96] potentially increasing the risk of hypertension, proteinuria and kidney disease in later life [97, 98]. Although underlying mechanisms of increasing adult disease susceptibility by prematurity on first glance seem to be more direct, there are similarities between being born SGA and preterm. Preterm birth cannot be simply seen as an abrupt termination of gestation, but rather as a pathologic, stressful and inflammatory event, influenced by numerous factors, ranging from ethnicity and socioeconomic status to dysfunctions in hormonal systems and gestational micronutrient deficiencies [53, 88, 99–101]. Similar to SGA infants preterm infants suffer from an adverse intrauterine environment and, by being born prematurely, are additionally exposed to an adverse neonatal environment [102]. Both, SGA and preterm born infants display similar postnatal growth patterns with about 80% of both groups exhibiting catch up growth [102]. Resembling observations in SGA newborns, prematurity predisposes to childhood adiposity, with data indicating a shift in adipose tissue distribution towards visceral fat depots [102]. Furthermore, similar to observations in SGA cohorts, a more rapid postnatal catch-up growth was shown to be associated with greater reductions in insulin sensitivity [103, 104]. A recent systematic review and meta-analysis showed that there is also an association between preterm birth and insulin sensitivity throughout life. However, the data in this regard are conflicting and observed associations might be affected by the overall heterogeneity of the study designs and analyzed populations [105]. Albeit conflicting findings, prematurity putatively increases the risk for insulin resistance which, at least in part, appears to be regulated by postnatal growth. This highlights the importance of an optimal nutritional strategy for preterm infants which yet remains to be determined [104, 106].

The Role of Insulin in Fetal Development and Adult Diseases

The developmental origins theory can be applied to all early life events including low birth weight and/or prematurity [107–109]. Adverse environmental exposures during fetal and neonatal life are thought to trigger compensatory persistent physiological responses. Such adaptations may modify set points of physiological systems involved in sustaining homeostasis. This can become maladaptive if a mismatch between anticipated and actual environment occurs. In this regard, a lot of research was focused on insulin resistance as the main culprit for both, altered anthropometric measurements at birth, and later life disease susceptibility. Divergent to the developmental origins theory first postulated by Barker et al., Hattersley and Tooke proposed in their "fetal insulin hypothesis" that genetically determined insulin resistance results in impaired insulin-mediated growth in the fetus as well as in an insulin resistant phenotype in adult life [110]. It is known that type 2 diabetes has a strong genetic component. Furthermore, insulin acts as key factor in fetal growth. Thus, any genetic variant that impairs insulin secretion and/or insulin sensitivity may reduce birth weight and concomitantly result in adult life type 2 diabetes. Put differently, the "fetal insulin hypothesis" postulated that the genotype, not low birth weight, increases the risk of adult diabetes [110, 111]. The hypothesis is supported by genetic evidence showing that single nucleotide polymorphisms associated with an increased risk for type 2 diabetes were associated with low birth weight [112]. Moreover, a study in Caucasian mothers revealed that there is a negative correlation between total glycated hemoglobin in cord blood (fetal) and birth weight [113]. The relationship between cord blood glycemia and birth weight is diametrically opposed to the well described positive correlation between maternal glycemia and birth weight which was also observed in this study [113]. When subjected to similar degrees of maternal glycemia (reflected by maternal total glycated hemoglobin), lighter fetuses appear incapable of lowering their blood glucose concentrations (reflected by the newborn's total glycated hemoglobin), as do heavier fetuses. Meanwhile, the findings of an inverse relationship between cord blood glycemia and birth weight were replicated in an Asian cohort, highlighting their validity [114]. Until now, fetal blood glucose concentrations were regarded as a passive reflection of maternal glycemia. However, the observed inverse correlation between cord blood and birth weight showed that the fetal response to similar maternal glucose levels might not behave as uniform as previously thought [113, 114]. From a hypothetical point of view such findings can be explained by both, genetics and the fetal environment, underlining that future research, integratively applying genetic and epigenetic methodology, is still needed to better characterize the association between early life and adult disease susceptibility.

Epigenetics

Although the underlying molecular mechanisms are incompletely understood so far, there is convincing evidence that developmental plasticity is mediated by epigenetic modifications of the DNA. Important epigenetic mechanisms are histone modifications, non coding RNAs and DNA methylation [115, 116]. These tools generally affect how accessible DNA is to transcription factor complexes, how efficiently transcription proceeds, and how stable already transcribed mRNA is [104]. Histone modifications consist of chemical alterations such as acetylation, phosphorylation and methylation [116] which can modulate chromatin structure, thus influencing the accessibility of the transcription machinery to the gene [117]. Non coding RNAs can trigger RNAse activity by RNA interference eliminating mRNA transcribed by target genes [38, 118]. The currently best studied epigenetic mechanism is DNA methylation [119]. DNA methylation is the addition of a methyl group at the C5 position of the cytosine pyrimidine ring via DNA methyl transferase activity [120]. Methylated cytosines are generally located in cytosine-phosphate-guanine (CpG) sequences [121, 122]. Although about 70% of all genomic CpGs are methylated, there are clusters of

CpGs, termed CpG islands, that remain unmethylated [102, 120, 123]. Such unmethylated CpG islands are associated with about 60% of all human genomic promoters [124]. Methylating a CpG site attracts methyl-binding proteins that trigger chromatin remodeling, leading to a more condensed chromatin, thus restricting access for the transcription machine [125]. Therefore, promoter regions of translated genes usually display low methylated CpG islands, whereas un-translated genes are heavily methylated.

In mammalian development, there are two main periods characterized by extensive epigenetic modifications. During the course of gametogenesis, genome-wide demethylation takes place followed by remethylation before fertilization. In early phases of embryogenesis, extensive epigenetic modifications occur, with phases of total demethylation alternating with phases of remethylation, ensuring the totipotency of the developing embryo [126]. Additionally, de- and remethylation processes after fertilization are thought to play a role in the removal of acquired epigenetic modifications, especially those acquired during gametogenesis [127–129]. However, some parental epigenetic modifications seem to escape the second wave of demethylation, underlining a potential inheritance of epigenetic modifications set during gametogenesis [102, 130].

Epigenetic mechanisms are not only important in early phases of pregnancy but throughout gestation [131, 132]. Current literature suggests that epigenetic modifications acquired during early developmental phases can be permanent [133]. It was demonstrated in a variety of experimental models and clinical studies of fetal programming that environmental conditions during gestation or shortly after birth can induce epigenetic alterations, stably changing the degree of promoter methylation and thereby permanently altering gene expression [54, 133]. Rat offspring of dams fed a low-protein diet during pregnancy exhibit decreases in promoter methylation of the glucuronid receptor and the peroxisome proliferator-activated receptor α (PPAR-α) gene in the liver [134]. Similar epigenetic changes were shown for p53 in the kidney [135], the suprarenal angiotensin II type-1b receptor [136], and for the hypothalamic glucocorticoid receptor [137]. More recent data underlined that an alteration of DNA methylation triggered by maternal undernutrition is not tissue specific but a global phenomenon, associated with widespread changes of gene expression [138]. It is not exactly known yet for how long the time window for stable epigenetic changes is opened, but current evidence suggests that the timeframe spans from conceptional to early postnatal stages [137, 139]. It has also been demonstrated that DNA methylation patterns can be transmitted from one generation to the following [140]. Moreover, it was shown that a gestational low-protein diet fed to F0 dams can still alter promoter methylation and gene expression of the F2 generation without any nutrient restriction in the F1 generation [141]. Another study even described a significant impact of a gestational/lactational low protein diet administered only to the F0 generation on the phenotype of F3 generation offspring [142].

Paternal Programming

Until now, the focus regarding fetal programming was mostly set on maternal programming. However, there is accumulating evidence that the father also plays a relevant role in epigenetic modifications of the offspring's phenotype [143, 144]. Epidemiological data showed that the grandchildren of men, who were exposed to a restricted caloric intake during the slow growth phase just before reaching puberty, lived significantly longer than grandchildren of men, who experienced overnutrition during this phase [82]. In a more detailed analysis of these data, it was demonstrated that an excess caloric intake of the paternal grandfather was associated with a fourfold increased risk of dying from diabetes associated disease in the grandchildren's generation [83]. There is also data from animal experiments confirming an influence in terms of fetal programming on the offspring. In a study by Anderson et al. it was shown that paternal fasting before mating was associated with reduced serum glucose levels in the F1 generation [145]. Ng et al. were able to demonstrate

that a preconceptional high fat diet of the father causes beta cell dysfunction of the pancreas in the F1 generation [146]. Apart from dietary influences, Bakke et al. demonstrated in a pioneer study that hypothyroidism of male rats before mating resulted in significant phenotypic changes of the F1 generation [147]. Paternal hypothyroidism was induced either by radiothyroidectomy or by large doses of neonatally injected thyroxine. Offspring of hypothyroid fathers displayed a slower postnatal development, reduced weaning weights and increased final body weights, and had enlarged pituitary and thyroid glands. Furthermore, female offspring from thyroidectomized fathers developed significantly smaller uteri and enlarged ovaries, whereas testes of male offspring were significantly smaller [147].

Sex Differences in Developmental Origins of Disease

The existence of sex specific differences in animal models of developmental programming is well described in currently available literature. The vast majority of non communicable diseases, which in many cases have developmental origins, often display some degree of sex bias [148]. Most developmental programming studies have shown that the same stimulus can elicit different long term effects, depending on the sex of the offspring. The underlying mechanism of this sexual dimorphism is not well understood [149]. It was demonstrated that gene expression shows sex specific differences, which are already detectable in the preimplanted embryo, long before any gonadal development and sex hormone production [150–152]. Thus, such early phenotypic differences can only be attributed to transcriptional differences resulting from different sex chromosomes, i.e. to Y-chromosomal genes and X-chromosomal genes that to a smaller or bigger extent escape X-chromosome inactivation [150]. Moreover, it was shown that sex chromosomal differences in gene expression can influence the transcription of autosomal genes, resulting in prominent sex specific transcriptional differences [150]. Analysis of bovine blastocysts demonstrated that one third of genes, most of them of autosomal origin, displays sex specific differences in expression [153]. Mechanistically, the imprinting of X-linked genes may be involved in sex specific expression differences. In females specific imprinting ensures that the paternal allele is uniquely or preferentially expressed. As male embryos are missing the paternally inherited X-chromosome, synergistic effects of double X dosage plus imprinting mechanisms may be responsible for sex specific transcriptional differences [150]. Early gestational sexual dimorphism in protein expression may influence several molecular pathways, including glucose and protein metabolism and impact on epigenetic mechanisms, particularly DNA methylation. This might be one underlying reason for a sex specific different susceptibility to environmental stressors, leading to distinct long-term effects in the offspring [150]. Furthermore, there is evidence in literature that the fetal sex as a major genetic variant of the fetal genome may influence maternal physiology during gestation in genetically susceptible pregnant women. It was demonstrated that depending on fetal sex certain maternal genetic variants (*ACE I/D; PPARG2 Pro 12 Ala; PROGINS* progesteron receptor polymorphism) are associated with different outcomes in regards to maternal glycemia and blood pressure regulation, both very influential factors in fetal development [154–156]. Another crucial factor for sexual dimorphism in developmental programming is the placenta [148, 149, 151]. Being the functional link between the maternal environment and the fetus, the placenta plays a central role as a buffer for environmental effects and is capable of modulating effects of adverse intrauterine conditions [151]. As this organ derives from embryonic trophoblast cells, it bears the same sex as the embryo/fetus [151]. Depending on the sex of the fetus, the placenta displays sexual dimorphism, with different growth rates and a varying responsiveness to fetal hormones [157]. In many species male placentas usually are larger or distinctively shaped, an observation that, at least in mice, seems to be independent of androgen effects [151, 158]. More importantly, current literature suggests that female and male placentas are characterized by different molecular mechanisms to optimize the outcome of the offspring, with distinct transcriptomes, perfectly

shaped for a proper development of the given sex [151, 159]. Concomitantly, this results in a different susceptibility to perturbations in the intrauterine environment and the ability to cope with them. The molecular mechanisms underlying this sexually distinct adaptive responses are largely unknown, however, current data indicates that the sex specific genome and epigenome are key factors [150, 151]. Finally, regarding disease susceptibility in later life, the impact of sex hormones during development and over the course of life has to be taken into account. However, only a few studies so far have examined the contribution of sex hormones in later life disease susceptibility due to developmental programming. Ojeda et al. demonstrated in a rat model of placental insufficiency that intrauterine growth retardation (IUGR) was associated with hypertension in male offspring [160, 161]. Furthermore, serum testosterone levels were twofold higher in IUGR males than in healthy controls, indicating a connection to the observed hypertension in male IUGR offspring. Castration at an age of 10 weeks abolished hypertension in male IUGR offspring with intrauterine growth retardation. No effects of castration on blood pressure were observed in healthy controls [161]. Female growth retarded offspring also developed hypertension, however this increase in blood pressure returned to normotensive values once the animals reached puberty and displayed increasing levels of estradiol [162]. Ovariectomy at an age of 10 weeks blunted this decrease in blood pressure compared to intact IUGR females. In a third group that received 17β-estradiol replacement, ovariectomy induced increases in blood pressure were attenuated [162]. Results from these and similar studies indicate that sex hormones can influence the long term consequences of developmental programming [161–163]. However, until now there is a lack of studies that evaluated this matter in different animal models with other outcomes than hypertension in a similar extensive fashion as Ojeda et al. Taken together, sexual dimorphism is tightly connected to developmental programming. The influence of sex hormones and differences in placental function are important factors in this regard. Moreover, disparities in the sex specific genome and epigenome, leading to a transcriptional sexual dimorphism which is already present in the preimplanting embryo, may play a relevant role in the varying susceptibility to environmental stressors among the sexes.

Interaction of Parental Genes, Parental Environment and Fetal Programming

As outlined before, maternal and paternal environmental factors can influence the phenotype of the offspring by inducing epigenetic adaptive mechanisms. Another factor responsible for developmental programming during intrauterine life might be related to parental genes that impact on the fetal phenotype independent of their presence in the fetal genome [164, 165]. About 25 years ago, Parkhurst et al. described a wimp mutation in Drosophila that resulted in a lethal phenotype, although the mutation was not transmitted to the offspring [166]. Hocher et al. translated this finding to mammalian/human development. They showed that a single nucleotide polymorphism (SNP) in the maternal G protein beta3-subunit gene, which is involved in regulation of blood supply to the uterus, is associated with a substantial reduction in birth weight without actually being transmitted to the offspring (Fig. 1) [167]. Other studies later demonstrated similar independent associations between specific maternal genes and offspring phenotype without any transmission of the particular gene [168–179]. It was shown that maternal mutations of relevant genes involved in folate metabolism are associated with an increased risk for neural tube or congenital heart defects [170–172]. Similar findings were demonstrated for maternal polymorphisms involved in glucose metabolism [173]. Such drastic teratogenic consequences highlight the possible impact maternal genetic deficiencies can have, regardless of any transmission to the offspring. Not as drastic alterations on the offspring phenotype, that better fit to the concept of the developmental origins hypothesis were observed for maternal polymorphisms in the monoamine oxidase A, the peroxisome proliferator activated receptor gamma and cytochrome P enzyme genes controlling sex steroid biosynthesis and metabolism [174–176]. Additionally, it was demonstrated that the maternal genotype plays an important role

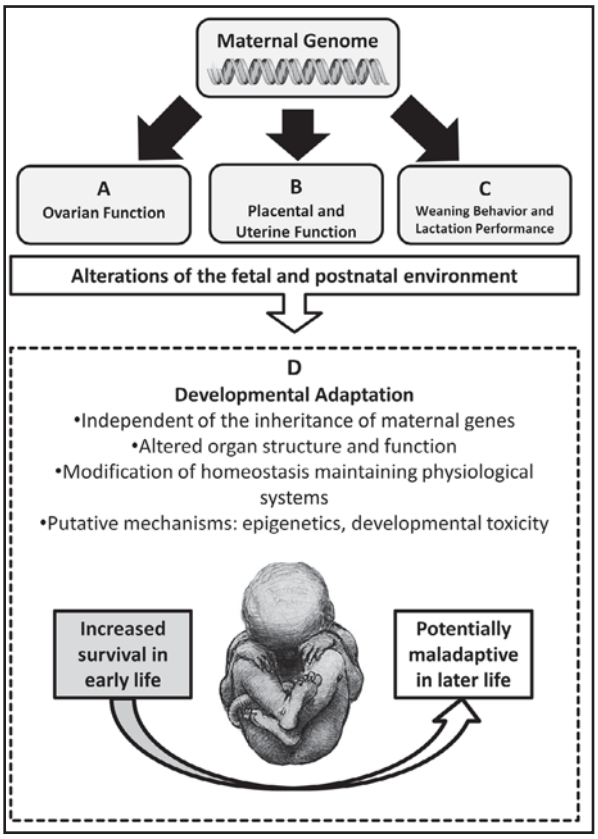

Fig. 1. The Advanced Fetal Programming Hypothesis. (A) Maternal gene dysfunction may influence ovary function. Physiological ovarian function, oocyte development and maturation, including the establishment of epigenetic patterns could potentially be affected by altered maternal gene function [193–196]. (B) Maternal gene dysfunction can impact on the placenta and the embryonic/fetal environment by altering decidual function [181, 182, 197–199]. (C) Maternal gene dysfunction may alter weaning behavior and lactation performance and thus influence the early postnatal environment [200–203]. (D) The impact of maternal gene dysfunction on embryonal/fetal/neonatal environmental factors listed in A-C may trigger stable, long lasting epigenetic adaptation in the offspring or result in developmental toxicity [204–206]. Regardless of the underlying mechanism, the phenotype of the offspring may be modified by altered maternal gene function without any transmission of the affected maternal gene.

in modifying adverse intrauterine conditions [180]. Studies showed that polymorphisms of genes encoding for xenobiotic metabolizing enzymes, such as *GSTT1*, and *GSTM1* gene or phase I/phase II enzymes such as *CYP1A1*or *EPHX1* can elicit a modifying effect on birth weight among actively or passively smoking mothers [177–179]. Taken together, there is an increasing amount of evidence indicating that parental genes may influence offspring physiology independent of the inheritance of these genes.

In a very recent study, Hocher et al. aimed to better characterize this biological phenomenon in an animal experiment. Therefore, female heterozygous endothelial nitric oxide synthase (*eNOS*) knockout mice were mated with male wildtype mice and their wildtype offspring was compared to wildtype offspring from wildtype mice. A heterozygous knock out in the *eNOS* gene was chosen because of the central role *eNOS* plays in controlling vascular and placental function, negatively affecting the interuterine environment [181, 182]. The partial lack of the maternal *eNOS* gene resulted in a reduced birth weight and a steatotic liver phenotype of wildtype offspring. Sex specific differences regarding the phenotype were observed [183]. Using a similar study design, Costantine et al. had previously also demonstrated a sex specific transgenerational effect of a maternal heterozygous *eNOS* deficiency on the vascular phenotype of wildtype offspring [184]. Results of both studies suggest a non-environmentally mediated mechanism of developmental programming driven by altered parental gene function. Without any transmittance of the specific gene, maternal and putatively also paternal gene dysfunction might influence oocyte or sperm maturation and later embryonic and fetal development by the induction of epigenetic modifications or developmental toxicity, finally resulting in an altered phenotype ("The Advanced Fetal Programming Hypothesis"; see Fig. 1) [165, 183]. Next to the general implications of these findings for the field of developmental programming, they also suggest to reassess murine knock out or transgenic animal models, one of the most important tools currently used in studying gene function. The presumed causality between a genetic manipulation and a resulting phenotype should be reconsidered in regards to potential confounding by

an induction of epigenetic changes due to parental gene dysfunction that is absent in the offspring [183].

Interventional Approaches

Some studies already investigated if it is possible to ameliorate deleterious effects of fetal programming by interventional approaches. Lillycrop et al. showed in a rat model of fetal programming that a high-protein diet of pregnant dams lead to a hypomethylation of different genes in the offspring. However, if folate was supplemented simultaneous to the low protein diet, the previously observed epigenetic modifications were absent [134]. Until now these or similar results were observed by other studies [138, 185]. It was demonstrated that the DNA methylation machinery relies on ingested methyl group donors and other essential micronutrients [185]. A restriction of these factors may have far-reaching consequences on the phenotype of offspring [139, 185].

An interesting explanation model of epigenetic modifications due to environmental influences provides the "Free Radical Theory of Developement" [186, 187]. This theory is based on the biochemical link between redox buffer systems, such as glutathione, and the methyl group metabolism. It was demonstrated that unfavorable intrauterine conditions, triggered for example by gestational protein restriction, can impact on the capacity of redox buffer systems and expose the organism to increased oxidative stress [186]. As an opposing measure, the production of glutathione can be increased which requires methyl group metabolites. This increased demand for methyl group donors can result in a reduced availability of the essential methyl group donator S-adenosylmethionine (SAM), thus affecting epigenetic mechanisms including DNA and histone methylation [186]. Camboine et al. were able to show in a protein restriction model that the simultaneous feeding of a lipidperoxidation inhibitor during pregnancy and lactation is able to prevent the effects of the low protein diet on blood pressure regulation, vascular function and microvascular rarefaction and counteracts a reduction of glutathione [188]. Similar results were generated employing other antioxidants [189–192]. In summary, nutritional interventions during pregnancy affecting the methyl group metabolism might be able to prevent or alter a developmentally programmed phenotype. Future studies are needed to assess, whether such approaches could be translatable therapeutic options targeting the developmental origins of diseases.

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Review

Developmental Origins of Disease - Crisis Precipitates Change

Christoph Reichetzeder[a,b] Sulistyo Emantoko Dwi Putra[a,c] Jian Li[d] Berthold Hocher[a,d,e]

[a]Institute for Nutritional Science, University of Potsdam, Nuthetal, Germany; [b]Center for Cardiovascular Research (CCR), Campus Charité Mitte, University Hospital Charité, Berlin, Germany; [c]Faculty of Biotechnology, University of Surabaya, Surabaya, Indonesia; [d]Department of Basic Medicine, Medical College of Hunan Normal University, Changsha, China; [e]Institut für Laboratoriumsmedizin, Berlin, Germany

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Abstract
The concept of developmental origins of diseases has gained a huge interest in recent years and is a constantly emerging scientific field. First observations hereof originated from epidemiological studies, linking impaired birth outcomes to adult chronic, noncommunicable disease. By now there is a considerable amount of both epidemiological and experimental evidence highlighting the impact of early life events on later life disease susceptibility. Albeit far from being completely understood, more recent studies managed to elucidate underlying mechanisms, with epigenetics having become almost synonymous with developmental programming. The aim of this review was to give a comprehensive overview of various aspects and mechanisms of developmental origins of diseases. Starting from initial research foci mainly centered on a nutritionally impaired intrauterine environment, more recent findings such as postnatal nutrition, preterm birth, paternal programming and putative interventional approaches are summarized. The review outlines general underlying mechanisms and particularly discusses mechanistic explanations for sexual dimorphism in developmental programming. Furthermore, novel hypotheses are presented emphasizing a non-mendelian impact of parental genes on the offspring's phenotype.

Introduction

Throughout the entire life of an individual, environmental factors play an important role for its state of health. However, at no stage in life the surrounding environment has a bigger impact than during embryonic and fetal life. Growth and development in utero are complex

Prof. Dr. Berthold Hocher

Department of Basic Medicine, Medical College of Hunan Normal University, Changsha, (China)
E-Mail hocher@uni-potsdam.de

and dynamic processes which require an orchestration of a variety of maternal, paternal and fetal factors for an optimal outcome. This complex interaction between mother, father, placenta and embryo/fetus ensures an optimal supply of nutrients, oxygen and endocrine signals, all fundamental elements for normal development. Disruptions in this supply system may not only have a direct impact on altering fetal growth patterns, but, as evidence suggests, can be associated with the occurrence of diseases in the later life of the offspring. In the current review, we will discuss exogenous (environmental) as well as endogenous factors (both parental and offspring genes) contributing to the complex interaction between mother, father, placenta and embryo/fetus.

Undernutrition

Epidemiological data unequivocally indicate that there is a connection between early life conditions, anthropometric measures at birth and disease susceptibility in later life [1, 2]. The "Barker Hypothesis", also called the "Fetal Programming Hypothesis" or the theory of the "Developmental Origins of Health and Diseases (DOHaD)", has become the foundation for this increasingly popular scientific field [2]. Barker et al. were not the first investigating this subject, but it was their groundbreaking epidemiological studies in England and Wales in the late 1980ies that inspired research worldwide. Barker et al. initially demonstrated a geographical relationship between cases of ischemic heart disease in the years 1968-1978 and child mortality rates between 1921-1925 [3]. A follow-up study showed that individuals born with a reduced birth weight had an increased risk for coronary heart disease in their adult life [4, 5]. Hales et al. demonstrated in another follow-up study that there is a similar inverse correlation between birth weight and later life glucose tolerance or insulin resistance [6]. In addition, they revealed that individuals with the lowest birth weight, in comparison to heavier newborns, displayed a six fold increased risk for impaired glucose tolerance or diabetes mellitus type 2 in late adulthood [6]. Until now, these findings have been replicated in several different study populations and in different ethnic groups [7]. Based on their observations, Hales and Barker formulated the "Thrifty Phenotype Hypothesis", a more detailed hypothesis trying to outline a putative mechanism of fetal programming. According to this explanation model, gestational under nutrition induces a series of adaptive processes in the fetus, trying to maximize the chances of survival in the given nutrient-poor environment. However, if a mismatch between pre- and postnatal nutrient supply exists fetal adaptation can be deleterious, increasing the risk for diseases later in life [7, 8].

The Thrifty Phenotype Hypothesis

Research stimulated by the thrifty phenotype hypothesis has improved the understanding of the plasticity of early human development, emphasizing an important role of developmental plasticity as a possible contributing factor to later human disease [9]. Until now, the thrifty phenotype hypothesis was confirmed by a number of human studies. The link between a poor intrauterine environment, restricted fetal growth and increased adult disease risk was well demonstrated in the "Dutch famine study". In this retrospective study, children born during a war-inflicted famine between December 1944 and April 1945 were analyzed [10, 11]. During the famine, the daily caloric intake for the general population was restricted to 400 - 800 kcal per day, about half as much as before and after this period. The comparison of individuals that were in utero during this time with individuals born a year before or after the famine showed that gestational caloric restriction was associated with a decreased birth weight and an increased prevalence of impaired glucose tolerance at an age of 50 years [10]. Moreover, twin studies were able to confirm the Thrifty Phenotype Hypothesis. A Danish study examined mono- and dizygotic twins which were discordant for the occurrence of type 2 diabetes. Results of the study revealed that the diabetic

twin was born with a significantly lower birth weight compared to the euglycemic twin sibling [12]. Other twin studies, especially studies on monozygotic twins, highlighted the importance of the intrauterine environment and developmental plasticity, regardless of the underlying genotype [13]. In addition to the connection between a sub-optimal intrauterine environment, disturbed fetal growth patterns and disease predisposition in adulthood, several more recent studies showed that postnatal nutrition is to be regarded as another critical component of the thrifty phenotype hypothesis. Crowther et al. investigated the impact of postnatal weight gain in a cohort of 7-year-old South African children [14]. Results of this study showed that children born with a reduced birth weight and rapid postnatal weight gain, displayed an impaired glucose tolerance already at an age of 7 years [14]. Further studies in Finland and India replicated these findings [15–17]. Various studies have demonstrated that rapid postnatal weight gain in newborns with an initial low birth weight is mainly due to fat accumulation and not due to an increase in muscle mass [18–20]. This specific phenotype was observed in several cohorts of small for gestational age newborns [21, 22]. In addition it was demonstrated that fat accumulation is more prominent in visceral than in subcutaneous fat depots [23, 24].

Parallel to the epidemiological studies outlined above, various animal studies have been conducted over the years in order to investigate the underlying mechanisms of developmental programming more thoroughly. Preclinical results substantiated findings from observational studies and gave more insight into involved mechanisms, also substantiating the thrifty phenotype hypothesis [25, 26]. It was demonstrated that restricting the maternal diet during gestation does not just result in low birth weight but induces disproportional growth. At the expense of organs such as liver, kidney, pancreas, lung and skeletal muscle, the development of brain, heart and adrenal gland is prioritized [25, 27]. Caloric restriction during gestation was shown to reduce pancreatic beta cell mass formation in the offspring, leading to a decreased production of insulin [28]. In a postnatal calorie-rich life, this lack of insulin production can predispose for the development of diabetes [29].

Overnutrition

As worldwide obesity rates are constantly rising, the focus of research has moved from maternal undernutrition as a predisposing factor for reduced birth weight and adult disease susceptibility, to the impact of maternal overnutrition on offspring health. Interestingly, it was shown that maternal overnutrition and an increased birth weight of the newborn elicits similar effects on offspring health as observed in low birth weight offspring [30, 31]. Being born small for gestational age (SGA) usually is associated with deficits in placental function, placental blood flow and adverse environmental influences, such as maternal undernutrition, particularly if the diet lacks sufficient protein levels [32–35]. Furthermore, literature suggests a complex genetic association, as SGA offspring more commonly occurs in women themselves born SGA [32, 36]. Increases in birth weight are typically associated with maternal obesity and gestational or pre-gestational diabetes [37–39]. Moreover, a very recent study provided genetic evidence for a causal relationship between maternal obesity-related traits and offspring birth weight [37]. Large for gestational age (LGA) offspring usually displays an increased body fat mass and an increased risk for metabolic disease in later life [37, 40, 41]. Current evidence suggests that either being born with a reduced or an increased birth weight increases disease risk in later life. Meta-analysis have underlined this by demonstrating an U-shaped relationship between later life metabolic diseases and birth weight [42–44]. The overlap of the adult phenotype in SGA and LGA offspring raises the important question which mechanisms are affected in these conditions, and vice versa howthese mechanisms can be triggered by conditions producing extremely disparate early life phenotypes [32]. Interestingly, specific overnutrition by feeding an isocaloric high-protein diet to rats, was shown to elicit no effects on birth weight but cause an impaired phenotype in adult animals [45]. Furthermore, it was demonstrated in animal and human

models that the simultaneous presence of two gestational insults, maternal obesity and maternal stress, are associated with increased rates of both, SGA and LGA offspring [31, 32, 46]. Literature on this subject suggests that the variability in the observed outcomes is likely due to different dosage, timing and downstream effects of a maternal insult. Maternal obesity and pre-pregnancy high-fat intake was on one hand shown to increase the risk for SGA and preeclampsia. On the other hand, this combination of maternal insults was associated with maternal gestational overeating which is associated with gestational diabetes and LGA [30, 32, 47]. Animal stress models revealed that the timing of the maternal stressor during gestation is a key factor for the offspring to be born SGA or LGA [48]. Furthermore, placental development and function, especially an impairment of the placental barrier which normally limits fetal exposure to maternal stress hormones, is thought to play a central role in the severity of maternal stress effects [49, 50]. Taken together, both over and undernutrition are associated with developmental programming. Future studies will give a more precise picture of the complex interaction between nutrition and developmental programming. More recent studies already aimed to discern the role of micronutrient deficiency or excess in regards to developmental origins of disease [51–55]. Furthermore there are also novel approaches to integrate the role of the microbiome and its interaction with nutrition into developmental programming studies [56].

Critical Periods for Nutritional Programming

Experimental and epidemiological data show that effects of developmental programming can be triggered throughout gestation. However, the nature of adult disease can vary according to the timing of a gestational insult [57]. Analysis of the "Dutch Hunger Winter" cohort demonstrated that offspring exposed to famine during early periods of gestation displayed an increased risk for coronary heart disease in later life, which could not be observed if famine exposure happened during later stages of pregnancy [58]. Interestingly, caloric restriction during late gestation was associated with disturbances in glucose-insulin homeostasis, clinically reflected by an increased risk of type 2 diabetes [58]. This finding could be replicated in animal models [59, 60]. Gardner et al. showed that maternal undernutrition in sheep in late gestation also led to impaired glucose-insulin homeostasis, highlighting the importance of late gestational periods in regards to programming effects on intermediary metabolism [60]. According to developmental processes in respective gestational periods, current literature suggests that nutritional insults during early gestation may influence organ development, altering fetal physiology in late gestation, and postnatal function, yet often without a measurable effect on birth weight [59, 61–64]. This was demonstrated by various studies investigating nutritional alteration in the periconceptual period, which is characterized by fertilisation, blastocystogenesis and the implantation process [61–65]. Nutritional insults set in later embryonic and early fetal life, a period which comprises intense organogenesis and placental development, display similar patterns of developmental programming [66–70]. Dietary modifications in later stages of gestation, characterized by very pronounced fetal growth and placental maturation, were shown to have a strong impact on birth weight and organ maturation with pronounced programming effects on intermediary metabolism and hormonal systems [71–75]. Furthermore, also postnatal nutrition plays an important role in developmental programming. A large body of studies have demonstrated that postnatal catch-up growth in low birth weight newborns is a crucial factor for increasing the risk of adult metabolic disturbances [20, 22, 76]. Intriguingly, also in postnatal developmental programming timing is of importance. It was shown that catch-up growth restricted to the first postnatal year did not have an effect on insulin levels, but sustained catch-up growth was associated with higher insulin levels in seven year old- and insulin resistance in eight year old children [77–79]. Next to postnatal periods, newer evidence highlights the importance of preconceptual nutrition of both the mother and the father on offspring health.

There is a growing amount of evidence, demonstrating that dietary challenges during oozyte development or spermatogenesis can induce permanent phenotypic changes in the offspring [80–84]. Taken together, available evidence highlights the importance of different time frames before, during and after gestation in regards to developmental origins of health and disease. However, given species differences in physiology, metabolism, placental structure and function, cautious interpretation of the available studies is warranted, especially when extrapolating to human situations [72].

Prematurity

More recent data showed that fetal adaptation causing persistent functional and structural changes of the fetal organism can be induced by factors that go beyond gestational nutrition and do not necessarily have to impact on anthropometric measures at birth [85]. A very important factor in this regard is preterm birth. As outlined before, initial studies on fetal programming focused on a 'deprived' intrauterine environment as a cause for low birth weight or SGA [10, 86]. Such anthropometric measurements were then used as surrogate parameters for association analyses with later life disease [10, 86]. However, many of these epidemiologic studies based their investigations on old birth records, sometimes assessing birth weight without considering gestational age at birth [87, 88]. Thus, it is possible that a considerable amount of individuals included in these epidemiologic studies, were preterm individuals and not small for gestational age [87]. De [65]g et al. demonstrated in a systematic literature review followed by a meta-analysis, that preterm birth is associated with higher blood pressure in adulthood, suggesting a relevant role of gestation[64]ge in fetal programming [89]. There is an increasing body of evidence that prematurity is associated with an increased risk for various disease in adult life [53, 87, 89–91]. It is known that preterm birth causes an interruption of normal organogenesis, especially in organ systems that display a branching morphogenesis like kidney, lung, pancreas, and the vascular system [87, 92–94]. The developing kidney is particularly vulnerable to preterm birth which causes considerable deficits in organ structure and function [93]. Prematurity was sho[31] to be associated with a lower nephron endowment [95, 96] potentially increasing the risk of hypertension, proteinuria and kidney disease in later life [97, 98]. Although underlying mechanisms of increasing adult disease susceptibility by prematurity on first glance seem to be more direct, there are similarities between being born SGA and preterm. Preterm birth cannot be simply seen as an abrupt termination of gestation, but rather as a pathologic, stressful and inflammatory event, influenced by numerous factors, ranging from ethnicity and socioeconomic status to dysfunctions in hormonal systems and gestational micronutrient deficiencies [53, 88, 99–101]. Similar to SGA infants preterm infants suffer from an adverse intrauterine environment and, by being born prematurely, are additionally exposed to an adverse neonatal environment [102]. Both, SGA and preterm born infants display similar postnatal growth patterns with about 80% of both groups exhibiting catch up growth [102]. Resembling observations in SGA newborns, prematurity predisposes to childhood adiposity, with data indicating a shift in adipose tissue distribution towards visceral fat depots [102]. Furthermore, similar to observations in SGA cohorts, a more rapid postnatal catch-up growth was shown to be associated with greater reductions in insulin sensitivity [103, 104]. A recent systematic review and meta-analysis showed that there is also an association between preterm birth and insulin sensitivity throughout life. However, the data in this regard are conflicting and observed associations might be affected by the overall heterogeneity of the study designs and analyzed populations [105]. Albeit conflicting findings, prematurity putatively increases the risk for insulin resistance which, at least in part, appears to be regulated by postnatal growth. This highlights the importance of an optimal nutritional strategy for preterm infants which yet remains to be determined [104, 106].

The Role of Insulin in Fetal Development and Adult Diseases

The developmental origins theory can be applied to all early life events including low birth weight and/or prematurity [107–109]. Adverse environmental exposures during fetal and neonatal life are thought to trigger compensatory persistent physiological responses. Such adaptations may modify set points of physiological systems involved in sustaining homeostasis. This can become maladaptive if a mismatch between anticipated and actual environment occurs. In this regard, a lot of research was focused on insulin resistance as the main culprit for both, altered anthropometric measurements at birth, and later life disease susceptibility. Divergent to the developmental origins theory first postulated by Barker et al., Hattersley and Tooke proposed in their "fetal insulin hypothesis" that genetically determined insulin resistance results in impaired insulin-mediated growth in the fetus as well as in an insulin resistant phenotype in adult life [110]. It is known that type 2 diabetes has a strong genetic component. Furthermore, insulin acts as key factor in fetal growth. Thus, any genetic variant that impairs insulin secretion and/or insulin sensitivity may re[10]e birth weight and concomitantly result in adult life type 2 diabetes. Put differently, the "fetal insulin hypothesis" postulated that the genotype, not low birth weight, increases the risk of adult diabetes [110, 111]. The [33]othesis is supported by genetic evidence showing that single nucleotide polymorphisms associated with an increased risk for type 2 diabetes were associated with low birth weight [112]. Moreover, a study in Caucasian mothers revealed that there is a negative correlation between total glycated hemoglobin in cord blood (fetal) and birth weight [113]. The relationship between cord blood glycemia and birth weight is diametrically opposed to the well described positive correlation between maternal glycemia and birth weight which was also observed in this study [113]. When subjected to similar degrees of maternal glycemia (reflected by maternal total glycated hemoglobin), lighter fetuses appear incapable of lowering their blood glucose concentrations (reflected by the newborn's total glycated hemoglobin), as do heavier fetuses. Meanwhile, the findings of an inverse relationship between cord blood glycemia and birth weight were replicated in an Asian cohort, highlighting their validity [114]. Until now, fetal blood glucose concentrations were regarded as a passive reflection of maternal glycemia. However, the observed inverse correlation between cord blood and birth weight showed that the fetal response to similar maternal glucose levels might not behave as uniform as previously thought [113, 114]. From a hypothetical point of view such findings can be explained by both, genetics and the fetal environment, underlining that future research, integratively applying genetic and epigenetic methodology, is still needed to better characterize the association between early life and adult disease susceptibility.

Epigenetics

Although the underlying molecular mechanisms are incompletely understood so far, there is convincing evidence that developmental plasticity is mediated by epigenetic modifications of the DNA. Important epigenetic mechanisms are histone modifications, non coding RNAs and DNA methylation [115, 116]. These tools generally affect how accessible DNA is to transcription factor complexes, how efficiently transcription proceeds, and how stable already transcribed mRNA is [104]. Histone modifications consist of chemical alterations such as acetylation, phosphorylation and methylation [116] which can modulate chromatin structure, thus influencing the accessibility of the transcription machinery to the gene [117]. Non coding RNAs can trigger RNAse activity by RNA interference eliminating mRNA transcribed by target genes [38, 118]. The current[17]best studied epigenetic mechanism is DNA methylation [119]. DNA methylation is the addition of a methyl group at the C5 position of the cytosine pyrimidine ring via DNA methyl transferase activity [120]. Methylated cytosines are generally located in cytosine-phosphate-guanine (CpG) sequences [121, 122]. Although about 70% of all genomic CpGs are methylated, there are clusters of

CpGs, termed CpG islands, that remain unmethylated [102, 120, 123]. Such unmethylated CpG islands are associated with about 60% of all human genomic promoters [124]. Methylating a CpG site attracts methyl-binding proteins that trigger chromatin remodeling, leading to a more condensed chromatin, thus restricting access for the transcription machine [125]. Therefore, promoter regions of translated genes usually display low methylated CpG islands, whereas un-translated genes are heavily methylated.

In mammalian development, there are two main periods characterized by extensive epigenetic modifications. During the course of gametogenesis, genome-wide demethylation takes place followed by remethylation before fertilization. In early phases of embryogenesis, extensive epigenetic modifications occur, with phases of total demethylation alternating with phases of remethylation, ensuring the totipotency of the developing embryo [126]. Additionally, de- and remethylation processes after fertilization are thought to play a role in the removal of acquired epigenetic modifications, especially those acquired during gametogenesis [127–129]. However, some parental epigenetic modifications seem to escape the second wave of demethylation, underlining a potential inheritance of epigenetic modifications set during gametogenesis [102, 130].

Epigenetic mechanisms are not only important in early phases of pregnancy but throughout gestation [131, 132]. Current literature suggests that epigenetic modifications acquired during early developmental phases can be permanent [133]. It was demonstrated in a variety of experimental models and clinical studies of fetal programming that environmental conditions during gestation or shortly after birth can induce epigenetic alterations, stably changing the degree of promoter methylation and thereby permanently altering gene expression [54, 133]. Rat offspring of dams fed a low-protein diet during pregnancy exhibit decreases in promoter methylation of the glucuronid receptor and the peroxisome proliferator-activated receptor α (PPAR-α) gene in the liver [134]. Similar epigenetic changes were shown for p53 in the kidney [135], the suprarenal angiotensin II type-1b receptor [136], and for the hypothalamic glucocorticoid receptor [137]. More recent data underlined that an alteration of DNA methylation triggered by maternal undernutrition is not tissue specific but a global phenomenon, associated with widespread changes of gene expression [138]. It is not exactly known yet for how long the time window for stable epigenetic changes is opened, but current evidence suggests that the timeframe spans from conceptional to early postnatal stages [137, 139]. It has also been demonstrated that DNA methylation patterns can be transmitted from one generation to the following [140]. Moreover, it was shown that a gestational low-protein diet fed to F0 dams can still alter promoter methylation and gene expression of the F2 generation without any nutrient restriction in the F1 generation [141]. Another study even described a significant impact of a gestational/lactational low protein diet administered only to the F0 generation on the phenotype of F3 generation offspring [142].

Paternal Programming

Until now, the focus regarding fetal programming was mostly set on maternal programming. However, there is accumulating evidence that the father also plays a relevant role in epigenetic modifications of the offspring's phenotype [143, 144]. Epidemiological data showed that the grandchildren of men, who were exposed to a restricted caloric intake during the slow growth phase just before reaching puberty, lived significantly longer than grandchildren of men, who experienced overnutrition during this phase [82]. In a more detailed analysis of these data, it was demonstrated that an excess caloric intake of the paternal grandfather was associated with a fourfold increased risk of dying from diabetes associated disease in the grandchildren's generation [83]. There is also data from animal experiments confirming an influence in terms of fetal programming on the offspring. In a study by Anderson et al. it was shown that paternal fasting before mating was associated with reduced serum glucose levels in the F1 generation [145]. Ng et al. were able to demonstrate

that a preconceptional high fat diet of the father causes beta cell dysfunction of the pancreas in the F1 generation [146]. Apart from dietary influences, Bakke et al. demonstrated in a pioneer study that hypothyroidism of male rats before mating resulted in significant phenotypic changes of the F1 generation [147]. Paternal hypothyroidism was induced either by radiothyroidectomy or by large doses of neonatally injected thyroxine. Offspring of hypothyroid fathers displayed a slower postnatal development, reduced weaning weights and increased final body weights, and had enlarged pituitary and thyroid glands. Furthermore, female offspring from thyroidectomized fathers developed significantly smaller uteri and enlarged ovaries, whereas testes of male offspring were significantly smaller [147].

Sex Differences in Developmental Origins of Disease

The existence of sex specific differences in animal models of developmental programming is well described in currently available literature. The vast majority of non communicable diseases, which in many cases have developmental origins, often display some degree of sex bias [148]. Most developmental programming studies have shown that the same stimulus can elicit different long term effects, depending on the sex of the offspring. The underlying mechanism of this sexual dimorphism is not well understood [149]. It was demonstrated that gene expression shows sex specific differences, which are already detectable in the preimplanted embryo, long before any gonadal development and sex hormone production [150–152]. Thus, such early phenotypic differences can only be attributed to transcriptional differences resulting from different sex chromosomes, i.e. to Y-chromosomal genes and X-chromosomal genes that to a smaller or bigger extent escape X-chromosome inactivation [150]. Moreover, it was shown that sex chromosomal differences in gene expression can influence the transcription of autosomal genes, resulting in prominent sex specific transcriptional differences [150]. Analysis of bovine blastocysts demonstrated that one third of genes, most of them of autosomal origin, displays sex specific differences in expression [153]. Mechanistically, the imprinting of X-linked genes may be involved in sex specific expression differences. In females specific imprinting ensures that the paternal allele is uniquely or preferentially expressed. As male embryos are missing the paternally inherited X-chromosome, synergistic effects of double X dosage plus imprinting mechanisms may be responsible for sex specific transcriptional differences [150]. Early gestational sexual dimorphism in protein expression may influence several molecular pathways, including glucose and protein metabolism and impact on epigenetic mechanisms, particularly DNA methylation. This might be one underlying reason for a sex specific different susceptibility to environmental stressors, leading to distinct long-term effects in the offspring [150]. Furthermore, there is evidence in literature that the fetal sex as a major genetic variant of the fetal genome may influence maternal physiology during gestation in genetically susceptible pregnant women. It was demonstrated that depending on fetal sex certain maternal genetic variants (*ACE I/D; PPARG2 Pro 12 Ala; PROGINS* progesteron receptor polymorphism) are associated with different outcomes in regards to maternal glycemia and blood pressure regulation, both very influential factors in fetal development [154–156]. Another crucial factor for sexual dimorphism in developmental programming is the placenta [148, 149, 151]. Being the functional link between the maternal environment and the fetus, the placenta plays a central role as a buffer for environmental effects and is capable of modulating effects of adverse intrauterine conditions [151]. As this organ derives from embryonic trophoblast cells, it bears the same sex as the embryo/fetus [151]. Depending on the sex of the fetus, the placenta displays sexual dimorphism, with different growth rates and a varying responsiveness to fetal hormones [157]. In many species male placentas usually are larger or distinctively shaped, an observation that, at least in mice, seems to be independent of androgen effects [151, 158]. More importantly, current literature suggests that female and male placentas are characterized by different molecular mechanisms to optimize the outcome of the offspring, with distinct transcriptomes, perfectly

shaped for a proper development of the given sex [151, 159]. Concomitantly, this results in a different susceptibility to perturbations in the intrauterine environment and the ability to cope with them. The molecular mechanisms underlying this sexually distinct adaptive responses are largely unknown, however, current data indicates that the sex specific genome and epigenome are key factors [150, 151]. Finally, regarding disease susceptibility in later life, the impact of sex hormones during development and over the course of life has to be taken into account. However, only a few studies so far have examined the contribution of sex hormones in later life disease susceptibility due to developmental programming. Ojeda et al. demonstrated in a rat model of placental insufficiency that intrauterine growth retardation (IUGR) was associated with hypertension in male offspring [160, 161]. Furthermore, serum testosterone levels were twofold higher in IUGR males than in healthy controls, indicating a connection to the observed hypertension in male IUGR offspring. Castration at an age of 10 weeks abolished hypertension in male IUGR offspring with intrauterine growth retardation. No effects of castration on blood pressure were observed in healthy controls [161]. Female growth retarded offspring also developed hypertension, however this increase in blood pressure returned to normotensive values once the animals reached puberty and displayed increasing levels of estradiol [162]. Ovariectomy at an age of 10 weeks blunted this decrease in blood pressure compared to intact IUGR females. In a third group that received 17β-estradiol replacement, ovariectomy induced increases in blood pressure were attenuated [162]. Results from these and similar studies indicate that sex hormones can influence the long term consequences of developmental programming [161–163]. However, until now there is a lack of studies that evaluated this matter in different animal models with other outcomes than hypertension in a similar extensive fashion as Ojeda et al. Taken together, sexual dimorphism is tightly connected to developmental programming. The influence of sex hormones and differences in placental function are important factors in this regard. Moreover, disparities in the sex specific genome and epigenome, leading to a transcriptional sexual dimorphism which is already present in the preimplanting embryo, may play a relevant role in the varying susceptibility to environmental stressors among the sexes.

Interaction of Parental Genes, Parental Environment and Fetal Programming

As outlined before, maternal and paternal environmental factors can influence the phenotype of the offspring by inducing epigenetic adaptive mechanisms. Another factor responsible for developmental programming during intrauterine life might be related to parental genes that impact on the fetal phenotype independent of their presence in the fetal genome [164, 165]. About 25 years ago, Parkhurst et al. described a wimp mutation in Drosophila that resulted in a lethal phenotype, although the mutation was not transmitted to the offspring [166]. Hocher et al. translated this finding to mammalian/human development. They showed that a single nucleotide polymorphism (SNP) in the maternal G protein beta3-subunit gene, which is involved in regulation of blood supply to the uterus, is associated with a substantial reduction in birth weight without actually being transmitted to the offspring (Fig. 1) [167]. Other studies later demonstrated similar independent associations between specific maternal genes and offspring phenotype without any transmission of the particular gene [168–170]. It was shown that maternal mutations of relevant genes involved in folate metabolism are associated with an increased risk for neural tube or congenital heart defects [170–172]. Similar findings were demonstrated for maternal polymorphisms involved in glucose metabolism [173]. Such drastic teratogenic consequences highlight the possible impact maternal genetic deficiencies can have, regardless of any transmission to the offspring. Not as drastic alterations on the offspring phenotype, that better fit to the concept of the developmental origins hypothesis were observed for maternal polymorphisms in the monoamine oxidase A, the peroxisome proliferator activated receptor gamma and cytochrome P enzyme genes controlling sex steroid biosynthesis and metabolism [174–176]. Additionally, it was demonstrated that the maternal genotype plays an important role

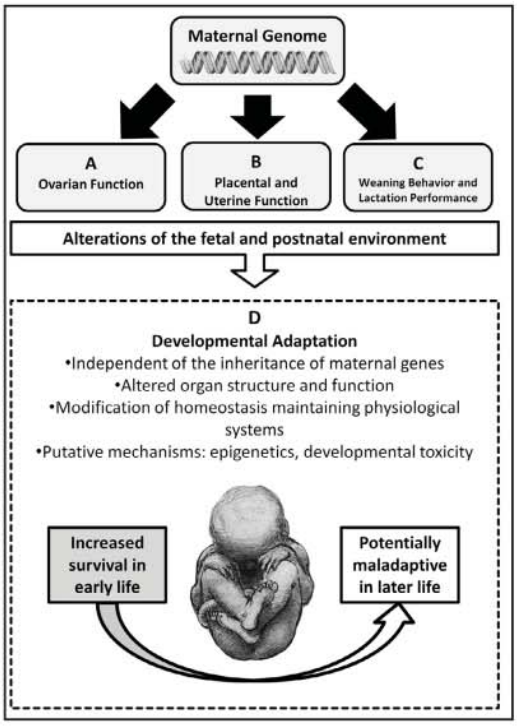

Fig. 1. The Advanced Fetal Programming Hypothesis. (A) Maternal gene dysfunction may influence ovary function. Physiological ovarian function, oocyte development and maturation, including the establishment of epigenetic patterns could potentially be affected by altered maternal gene function [193–196]. (B) Maternal gene dysfunction can impact on the placenta and the embryonic/fetal environment by altering decidual function [181, 182, 197–199]. (C) Maternal gene dysfunction may alter weaning behavior and lactation performance and thus influence the early postnatal environment [200–203]. (D) The impact of maternal gene dysfunction on embryonal/fetal/neonatal environmental factors listed in A-C may trigger stable, long lasting epigenetic adaptation in the offspring or result in developmental toxicity [204–206]. Regardless of the underlying mechanism, the phenotype of the offspring may be modified by altered maternal gene function without any transmission of the affected maternal gene.

in modifying adverse intrauterine conditions [180]. Studies showed that polymorphisms of genes encoding for xenobiotic metabolizing enzymes, such as *GSTT1*, and *GSTM1* gene or phase I/phase II enzymes such as *CYP1A1*or *EPHX1* can elicit a modifying effect on birth weight among actively or passively smoking mothers [177–179]. Taken together, there is an increasing amount of evidence indicating that parental genes may influence offspring physiology independent of the inheritance of these genes.

In a very recent study, Hocher et al. aimed to better characterize this biological phenomenon in an animal experiment. Therefore, female heterozygous endothelial nitric oxide synthase (*eNOS*) knockout mice were mated with male wildtype mice and their wildtype offspring was compared to wildtype offspring from wildtype mice. A heterozygous knock out in the *eNOS* gene was chosen because of the central role *eNOS* plays in controlling vascular and placental function, negatively affecting the interuterine environment [181, 182]. The partial lack of the maternal *eNOS* gene resulted in a reduced birth weight and a steatotic liver phenotype of wildtype offspring. Sex specific differences regarding the phenotype were observed [183]. Using a similar study design, Costantine et al. had previously also demonstrated a sex specific transgenerational effect of a maternal heterozygous *eNOS* deficiency on the vascular phenotype of wildtype offspring [184]. Results of both studies suggest a non-environmentally mediated mechanism of developmental programming driven by altered parental gene function. Without any transmittance of the specific gene, maternal and putatively also paternal gene dysfunction might influence oocyte or sperm maturation and later embryonic and fetal development by the induction of epigenetic modifications or developmental toxicity, finally resulting in an altered phenotype ("The Advanced Fetal Programming Hypothesis"; see Fig. 1) [165, 183]. Next to the general implications of these findings for the field of developmental programming, they also suggest to reassess murine knock out or transgenic animal models, one of the most important tools currently used in studying gene function. The presumed causality between a genetic manipulation and a resulting phenotype should be reconsidered in regards to potential confounding by

an induction of epigenetic changes due to parental gene dysfunction that is absent in the offspring [183].

Interventional Approaches

Some studies already investigated if it is possible to ameliorate deleterious effects of fetal programming by interventional approaches. Lillycrop et al. showed in a rat model of fetal programming that a high-protein diet of pregnant dams lead to a hypomethylation of different genes in the offspring. However, if folate was supplemented simultaneous to the low protein diet, the previously observed epigenetic modifications were absent [134]. Until now these or similar results were observed by other studies [138, 185]. It was demonstrated that the DNA methylation machinery relies on ingested methyl group donors and other essential micronutrients [185]. A restriction of these factors may have far-reaching consequences on the phenotype of offspring [139, 185].

An interesting explanation model of epigenetic modifications due to environmental influences provides the "Free Radical Theory of Developement" [186, 187]. This theory is based on the biochemical link between redox buffer systems, such as glutathione, and the methyl group metabolism. It was demonstrated that unfavorable intrauterine conditions, triggered for example by gestational protein restriction, can impact on the capacity of redox buffer systems and expose the organism to increased oxidative stress [186]. As an opposing measure, the production of glutathione can be increased which requires methyl group metabolites. This increased demand for methyl group donors can result in a reduced availability of the essential methyl group donator S-adenosylmethionine (SAM), thus affecting epigenetic mechanisms including DNA and histone methylation [186]. Camboine et al. were able to show in a protein restriction model that the simultaneous feeding of a lipidperoxidation inhibitor during pregnancy and lactation is able to prevent the effects of the low protein diet on blood pressure regulation, vascular function and microvascular rarefaction and counteracts a reduction of glutathione [188]. Similar results were generated employing other antioxidants [189–192]. In summary, nutritional interventions during pregnancy affecting the methyl group metabolism might be able to prevent or alter a developmentally programmed phenotype. Future studies are needed to assess, whether such approaches could be translatable therapeutic options targeting the developmental origins of diseases.

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