The Developmental Origins, Mechanisms, and Implications of Metabolic Syndrome¹⁻³

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Abstract

Metabolic syndrome (MetS) represents a combination of cardio-metabolic risk determinants, including central obesity, insulin resistance, glucose intolerance, dyslipidemia, hypertension, hyperinsulinemia, and microalbuminuria. The prevalence of MetS is rapidly increasing worldwide, largely as a consequence of the ongoing obesity epidemic. Environmental factors during periods early in development have been shown to influence the susceptibility to develop disease in later life. In particular, there is a wealth of evidence from both epidemiological and animal studies for greater incidence of features of MetS as a result of unbalanced maternal nutrition. The mechanisms by which nutritional insults during a period of developmental plasticity result in a MetS phenotype are now beginning to receive considerable scientific interest. This review focuses on recent data regarding these mechanisms, in particular the epigenetic and transcriptional regulation of key metabolic genes in response to nutritional stimuli that mediate persistent changes and an adult MetS phenotype. A continued and greater understanding of these mechanisms will eventually allow specific interventions, with a favorable impact on the global incidence of cardiovascular disease and type 2 diabetes in the future. J. Nutr. 140: 648–652, 2010.

Introduction

Just over 20 years ago 2 key biomedical concepts were created. In 1988 Reaven (1) first formulated the concept of the insulin resistance (IR) syndrome, which theorized that IR was the cause of glucose intolerance, hyperinsulinemia, increased VLDL, decreased HDL, and hypertension. Twenty years later, IR syndrome has graduated to become metabolic syndrome (MetS), a combination of cardiovascular risk determinants, including obesity (especially central adiposity), glucose intolerance and IR, dyslipidemia (including hypertriglyceridemia, increased FFA, and decreased HDL cholesterol), microalbuminuria, and hypertension. In addition, a number of other features have been recently associated with MetS onset, such as nonalcoholic fatty liver disease (NAFLD), polycystic ovarian syndrome, atherosclerosis, the proinflammatory state, and oxidative stress. The prevalence of MetS is rapidly increasing worldwide, largely as a consequence of the ongoing obesity epidemic. In many cases, the use of the MetS algorithm (particularly waist circumference measurements) presents a relatively simple method to calculate an increased risk for atherosclerotic cardiovascular disease with the potential to predict otherwise undetected clinical manifestations (2). Nevertheless, there is debate surrounding the etiology and pathogenesis of MetS, because a single unifying mechanism remains to be discovered (3). Recent analyses have pointed to obesity, ectopic fat accumulation, and an inflammatory state as central to MetS pathology. However, not all obese people develop MetS and not all people with MetS are obese. It is therefore likely that these features, and MetS itself, have a multi-factorial etiology, involving complex interactions among the genetic background, hormones, and nutrition. Indeed, studies viewing MetS as simply an imbalance between energy intake and expenditure have failed to elucidate useful therapeutic strategies (4). Consequently, the research focus has shifted to a biochemical and molecular approach that concentrates on key metabolic genes and their transcriptional control, which when disturbed lead to an increased risk of developing MetS and its clinical sequelae.

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4 Abbreviations used: A(vy), Agouti allele; IR, insulin resistance; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease.

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states that both these features could be beneficial adaptations for an organism developing in a poor nutritional environment, especially if this is sustained over the whole life course. Thus, a thrifty phenotype is induced when maternal nutrition is substantially inadequate. Refinements of this idea focus on the processes of developmental plasticity, which in normal situations provide the settings of homeostatic mechanisms to be tuned to allow the individual flexibility to modify their phenotype to match the anticipated future environment (5). However, there is a wealth of evidence from both epidemiological studies and experiments in animal models to show that when this prediction is wrong and the adult nutrient environment does not match that of the developmental period, mismatch confers a greater susceptibility to develop metabolic disease in later life (6). Although we resist the term developmental programming, which is better suited to genetic deterministic processes, it is becoming evident that risk of MetS can be developmentally induced. We propose “primed” may be a more suitable term than “programmed.”

The developmental origins of MetS
Early epidemiological data supporting the developmental origins of MetS concentrated on retrospective clinical studies that associated poor nutrition during development with a greater risk of adult cardiovascular disease, especially if the developmental and adult environments were dissimilar (7,8). More recently, the detrimental effects of this mismatch are seen in developing societies with increasing affluence and where human populations are undergoing socioeconomic change. In addition, much of the data that supports the role of maladaptive developmental plasticity, and priming of the MetS features, has been generated from experimental animal studies. For example, animals exposed to nutritional mismatch between the prenatal and postnatal environments develop obesity, adipocyte hypertrophy, reduced activity, leptin and IR, elevated blood pressure, endothelial cell dysfunction, and altered cardiovascular and renal function (9–13). There is also evidence to suggest that manipulation of the fetal protein provision can modify the process of pancreatic islet cell expansion, leading to small β-cell mass at birth and persistent detrimental effects on glucose homeostasis (14). Recent molecular evidence has shown that maternal protein restriction followed by catch-up growth of the offspring can alter adipocyte gene expression profiles and that physiological changes that persist into adulthood contribute to the onset of features of MetS (15).

It is pertinent that developmental plasticity can operate within a range of environments and not simply poor nutrition. For example, plasticity may also induce maladaptive phenotypic characteristics during excessive nutritional environments such as gestational diabetes or maternal obesity (16). These conditions are becoming very prevalent in western societies and may perpetuate transgenerational cycles of metabolic disease. Current estimates in the US state that one-third of women at childbearing age are obese (17). Consequently, experimental findings from models of overnutrition are beginning to attract much scientific interest. Preliminary studies have shown that overfeeding during the preweaning period permanently increases adipocyte hypertrophy (18). Recent findings from animal models of maternal obesity and high-fat feeding during early development show that adult offspring have impaired glucose tolerance, hypertension, hyperinsulinemia, dyslipidemia, hypothalamic leptin resistance, and NAFLD (19–22). It is likely that the high-fat diets used in these studies stretch metabolic plasticity during development further than its adaptive capacity, inducing overt disruption of development. As a result, even a “matched” exposure to a high-fat diet in the adult environment worsens an already maladapted phenotype. In support of this theory, recent studies have shown that high-fat–induced developmental priming of ectopic (gonadal and hepatic) fat accumulation is exacerbated when the dietary challenge continues in the postweaning phase (23). Thus, a transgenerational amplification of an obese phenotype ensues. Collectively, these data suggest that poor maternal diets may provide a common origin for the multifactorial disorder that is MetS. Currently, the mechanisms by which this dietary insult may prime susceptibility to MetS are under investigation.

Mitochondrial function
Mitochondria are central to metabolism and therefore unsurprisingly have been implicated in the development of MetS. Epidemiological studies have shown that low mitochondrial function (judged from reduced mitochondrial DNA) is observed in patients with type 2 diabetes, hypertension, and a greater waist:hip ratio (24). Mitochondrial dysfunction has also been extensively reported in patients with IR, particularly in the skeletal muscle and the liver. In addition, because mitochondria are inherited through the female line, they are a candidate vector for the inheritance of maternally derived nutritional/metabolic stress. This may account for the correlations observed between mitochondrial DNA and birth weight, suggesting that low mitochondrial status is somehow linked to the thrifty phenotype (24). Indeed, experiments using simple invertebrate model systems have demonstrated that very early stresses during the initial stages of development cause changes to mitochondrial activity that persist into adulthood (25). In support of this, maternal high-fat feeding in rodent models has been shown to affect renal mitochondrial copy number and glucose homeostasis (22). Human studies have also implicated mitochondrial dysfunction in the developmental origins of MetS. Specifically, inherited perturbations in mitochondrial oxidative phosphorylation have been linked to IR in the skeletal muscle of insulin-resistant offspring of patients with type 2 diabetes (26). More recently, we have shown that feeding a high-fat diet to pregnant rodents developmentally primes the hepatic expression of genes involved in lipogenesis and impairs hepatic mitochondrial function through reduced electron transport chain enzyme activity (23). These metabolic alterations then cause an increased flux of dietary fatty acids away from β-oxidation and toward lipogenesis and triglyceride synthesis (23). This results in an offspring phenotype that closely resembles human NAFLD. Furthermore, high-fat feeding in the adult environment in addition to the developmental environment exacerbates the fatty liver phenotype to a more severe form of liver fatty liver disease (nonalcoholic steatohepatitis) (23). Although these findings may provide important insights into the pathology of the developmental origins of MetS components, further investigations are required to elucidate the mechanisms leading to altered mitochondrial biogenesis and function.

Placental transport
Maternal obesity during pregnancy can often result in fetal overgrowth, increasing MetS susceptibility later in life. Although preliminary, there is recent evidence to suggest that high-fat maternal diets can cause upregulation of placental nutrient transport, resulting in fetal overgrowth (27). In a rodent model, placentas of high-fat–fed animals exhibited a 5-fold increase in glucose transporter 1 protein expression and a 9-fold increase in sodium-coupled neutral amino acid transporter protein expres-
Epigenetic processes

Clearly, MetS susceptibility has an inherited or familial component; however, even though some fixed genomic variations have been associated with high risk, the overall risk in the population attributable to such single nucleotide polymorphisms is small (28). Instead, subtle alterations in gene expression, such as those involved in placental nutrient transport, are responsible for an increased risk of disease outcome in many members of the population to a variable extent, rather than genomic alterations. In recent years, epigenetic regulation leading to such subtle modulations in gene expression (therefore not including genetic imprinting) of key metabolic genes has emerged as a contributing factor to increased MetS susceptibility. Epigenetics may provide a mechanism by which developmental plasticity mediates developmental priming. Therefore, epigenetics may be the interface between nutritional stimuli during development and resulting phenotype, thus being central to the developmental origins of the MetS.

Epigenetics has been defined as the study of heritable changes in gene expression that occur in the absence of a change in the DNA sequence itself. In mammals, these changes are mediated through DNA methylation, covalent histone modifications, microRNA, and poly-comb group complex recruitment (29,30). The epigenetic marks act alone or in combination (histone code) to alter chromatin structure and function and ultimately promote or inhibit gene transcription (Table 1). Therefore, chromatin is the ideal substrate for nutrient-sensitive transcriptional instructions, existing in multiple permutations leading to multiple phenotypes. In addition, the epigenetic state of chromatin can undergo transgenerational epigenetic inheritance, a process facilitated by the incomplete erasure of epigenetic modifications during gametogenesis and embryogenesis, resulting in a maintained epigenetic state in future generations. It is suggested that epigenetic mechanisms underlie the increased incidence of MetS in adults prenatally exposed to the Dutch famine and the transgenerational effects of prenatal exposure to the Dutch famine in the grandchildren of women exposed (31). Recent rodent studies have confirmed this hypothesis and shown that maternal nutritional constraint can reduce DNA methylation of the promoter regions of transcriptional regulators such as PPARα even in liver tissue of the F2 progeny (32).

Epigenetics and nutrition

Recent evidence has clearly demonstrated alterations in epigenetic status following manipulation of the nutrient environment during the developmental period. This research has chiefly focused on the DNA methylation of key metabolic genes, which in general correlates with transcriptional repression. DNA methylation presents the most probable candidate, because only methylated CpG are considered stable and heritable in somatic cells, whereas other chromatin modifications and epigenetic processes appear to be principally associated with the act of transcription. Thus, maternal calorie restriction has been associated with hypermethylation of the oncogene Hras in adult offspring (33). Maternal protein restriction, on the other hand, has been shown to cause hypomethylation of key metabolic transcriptional regulators such as the glucocorticoid receptor and PPARα, which can at least in part be attributed to the reduction of the enzyme responsible for maintaining DNA methylation patterns, DNA methyltransferase 1, a feature that is also observed in the protein-restricted offspring (34,35). Because folate acts as a methyl donor, the authors postulated that supplementing the protein-restricted dams with folate could restore reduced methylation levels (and subsequently decrease transcription of genes of interest) back to wild-type levels. Although the hypomethylation of glucocorticoid receptor and PPARα was rescued, the hypomethylation of other gene promoters, such as the insulin receptor, was maintained, signifying the specificity of epigenetic changes during development (36).

Although models investigating the effects of protein restriction and an unbalanced nutrition on the epigenotype and phenotype of offspring are applicable to mismatched populations in developing countries, another important problem is the transgenerational amplification of obesity and other features of MetS occurring commonly in Western society. Consequently, there are a number of recent studies reporting the increased incidence of type 1 and 2 diabetes and features of MetS in offspring of mothers with gestational diabetes or type 1 diabetes (37). Once again, epigenetic processes have the potential to be at the core of inherited and exacerbated metabolic disease. Studies using the obese Agouti [A(vy)] mouse have shown that the genetic tendency for obesity was progressively exacerbated when the A(vy) allele was passed along successive generations (38). Moreover, methyl supplementation appeared to reduce this effect but was independent for the A(vy) locus, again demonstrating of complex epigenetic specificity (38). Collectively, these data suggest that epigenetic mechanisms are enhanced or impaired following maternal nutrition, which, in turn, amplifies the risk to develop MetS features later in life.

TABLE 1 A summary of selected epigenetic mechanisms and their role in transcription

<table>
<thead>
<tr>
<th>Epigenetic mark</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>CpG methylation</td>
<td>Inactive transcription</td>
</tr>
<tr>
<td>Histone methylation</td>
<td>Both active and inactive chromatin/transcription depending on amino acid methylated, and number of methyl groups present</td>
</tr>
<tr>
<td>Histone acetylation</td>
<td>Active transcription</td>
</tr>
<tr>
<td>Histone phosphorylation</td>
<td>Both active (Histone 3) and inactive (Histone 1) transcription, and chromatin condensation (Histone 1, Histone 2B)</td>
</tr>
<tr>
<td>Histone ubiquitination</td>
<td>Prerequisite of Histone 3 methylation, and transcriptional activation</td>
</tr>
<tr>
<td>Polycomb group proteins</td>
<td>Inactive transcription</td>
</tr>
<tr>
<td>Micro RNA</td>
<td>Inactive transcription</td>
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</tbody>
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Implications and interventions
Because the epigenetic control of key genes is central to the developmental priming of the MetS phenotype, epigenetics provides a likely target for pharmacological therapies. Several compounds have been identified that are able to regulate DNA methyltransferase or histone deacetylase activity. For example, the plant-derived isoflavone genistein can reactivate methyl-silenced genes. However, this effect is genomic. Animal studies inducing global demethylation have indicated that whereas the risk of colorectal cancers is reduced, the risk of lymphoma and sarcoma is simultaneously increased (39). Therefore, the lack of specificity of such compounds makes them less attractive as therapeutic agents than previously considered. However, it may be useful to shift the research focus to consider epigenetic mechanisms such as DNA methylation as not the driving force behind the developmental priming of disease but instead as a conduit mechanism that transfers information regarding the transcriptional patterns required in a particular environment. Therefore, epigenetic processes facilitate a transcriptional state, which may be inherited and may impart an increased risk of MetS development in the context of a mismatched environment. In other words, it is not the epigenetic landscape that is ultimately causal to the phenotype but the stimulus (albeit on a cellular level) that it receives. This in part explains tissue-specific epigenetic modulations, because each particular tissue will receive specific stimuli and resides within a unique milieu. In support, Waddington’s (40) descriptions of the epigenetic landscape state that the complex relief features of the epigenetic surface are themselves largely the expression of a prodigiously complex network of interactions underlying it. The current biological importance of this can be extrapolated; the transcriptional hub, a network of regulatory proteins, which exists in different combinations depending on environmental conditions, controls the epigenetic regulation of genes. Therefore, elucidation of these hubs at key genes would allow the generation of more targeted and specific therapies.

Currently, successful disease interventions target the physiological mechanisms involved in MetS onset, such as metformin and statins. However, in practice these are used once the disease has already become manifest or is in its early stages. Recent evidence has shown that statin administration to animals consuming a high-fat diet during pregnancy, or in their young offspring, can reduce the risk of obesity, hypertension, hypercholesterolemia, and inflammation in adult offspring (41). In addition, high-fat diet–induced transgenerational reduction in endothelial progenitor cells, a marker of predicted cardiovascular function, can also be rescued by giving statins at critical periods in development (41). Similarly, administration of leptin to neonates of undernourished dams has been shown to reverse epigenetic changes and several other primed metabolic sequelae, including weight gain, hyperinsulinemia, and increased total body adiposity (42). Although more work is needed to characterize these effects and the mechanisms involved, these findings emphasize that intervention at critical periods during development is an area of potential pharmacological therapeutic benefit.

Conclusions
The growing prevalence of metabolic disease challenges biological researchers to elucidate the mechanisms involved in the etiology and the pathogenesis of MetS and its associated features. Evidently, the disease itself and the mechanisms leading to its onset are multi-factorial. However, exposure to an inappropriate diet during the developmental period clearly plays a role in exacerbating the risk of disease onset. It is also emerging that a continuation of poor nutrition in adult life may cause transgenerational amplification of this disease risk. The mechanisms priming increased risk heritability are beginning to be understood, such as inheritance of biochemically altered mitochondria and epigenetic modulation of key metabolic genes. However, further investigation is required before these processes can be manipulated to provide beneficial therapeutic strategies. In the meantime, the strategy most likely to be successful involves educating women of child bearing age and their partners about the true impact of diet during pregnancy and early development, enabling them to make positive nutritional choices and ultimately to reduce disease risk in their potential offspring.

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Literature Cited