Research Perspective

Maternal diet , aging and diabetes meet at a chromatin loop

Susan E. Ozanne[1,2], Ionel Sandovici[2,3,4] and Miguel Constância[2,3,4]

[1] *Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Cambridge CB2 OQQ, United Kingdom*
[2] *National Institute for Health Research Cambridge Biomedical Research Centre, Cambridge, United Kingdom*
[3] *Metabolic Research Laboratories, Department of Obstetrics and Gynaecology University of Cambridge, Cambridge CB2 0SW, United Kingdom*
[4] *Centre for Trophoblast Research, University of Cambridge, Cambridge CB2 3EG, United Kingdom*

Key words: *nutrition, aging, epigenetic, Hnf4a, type 2 diabetes*
Received: *520/11; Accepted: 5/25/11; Published: 5/25/11*
Corresponding authors: *Miguel Constância, PhD; Susan E. Ozanne, PhD;* ***E-mail:*** *jmasmc2@cam.ac.uk; seo10@mole.bio.cam.ac.uk*

Copyright: *© Ozanne et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited*

Abstract: We have recently demonstrated that exposure to a suboptimal diet during early development leads to abnormal epigenetic regulation of a promoter-enhancer interaction at the gene encoding HNF-4α, a key transcription factor required for pancreatic β-cell differentiation and glucose homeostasis. In addition, our studies revealed that the suboptimal maternal diet amplifies the age-associated epigenetic silencing of this locus. In this research perspective we discuss these novel findings in the context of the growing list of epigenetic mechanisms by which the environment can affect gene activity and emphasize their implications for the understanding of the mechanistic basis of the development of type 2 diabetes with age.

Maternal diet and the developmental origins of type 2 diabetes

It is well established that what we eat has a major impact on our health. However, there is growing evidence to suggest that diet during pregnancy and lactation may be particularly important as not only does it influence the health of the mother, it may have a permanent effect on the health of her children and even her grandchildren. The concept that environmental factors, such as nutrition during early development, influence both our health span and lifespan has been termed the developmental origins of health and disease hypothesis [1]. Focus on this possibility was prompted by the results of a series of epidemiological studies that revealed relationships between patterns of early growth and long-term risk of metabolic conditions such as type 2 diabetes (T2D) and cardiovascular disease [1]. Initial studies demonstrated that there was a linear relationship between birth weight and prevalence of these conditions in later life, with individuals with the lowest birth weight being around six times more likely to have T2D than those with the highest birth weight [2]. These associations have been replicated in numerous populations worldwide representing multiple ethnic groups, though those in some of the more contemporary cohorts where there was a high prevalence of maternal obesity also revealed an increased risk of metabolic disease in the very high birth weight offspring [3]. Subsequent studies demonstrated that the detrimental effects of being born small for gestational age were exaggerated if an individual grew rapidly in early postnatal life [4]. It was also demonstrated that accelerated postnatal growth, independently of growth *in utero*, increased the risk of metabolic conditions such as obesity [5].

Observational studies linking patterns of early growth with long-term health don't provide proof that suboptimal nutrition mediates these relationships. However studies in human cohorts and in animal models have provided strong evidence that environmental factors, including nutrition, play an important role. The strongest evidence from human

studies supporting the role of the environment in mediating the relationships between birth weight and long-term health has come from the study of monozygotic (identical) twins. These studies revealed that in monozygotic twin pairs discordant for T2D, the diabetic twin has a lower birth weight than their non-diabetic co-twin [6, 7] Assessing the role of maternal diet in mediating the relationships between fetal growth and long-term health in a human context is complex. However, studies of individuals *in utero* during periods of famine have shown direct relationships between severe maternal nutrient deficiency and increased risk of T2D in the offspring [8, 9]. The importance of neonatal nutrition for long-term health has been demonstrated very clearly in human studies. Initial observational studies demonstrated the protective effects of breast-feeding on future risk of metabolic disease [10] and subsequent randomized intervention studies revealed causal relationships between nutrition during early postnatal life and long-term metabolic health [11]. Animal models have provided compelling evidence that maternal diet during pregnancy and lactation influence long-term health including risk of T2D, obesity, hypertension and cardiovascular disease. The developmental origins of health and metabolic disease is therefore widely accepted.

Interaction between maternal diet and aging in T2D risk

Most conditions associated with patterns of early growth and nutrition are diseases associated with aging. Therefore, perhaps not too surprisingly, the small size at birth has been associated with increased mortality in humans. In a large Finnish study a low birth weight was associated with increased mortality at all ages in women and with premature death (< age 55) in men [12]. Studies in rodent models have also shown direct associations between maternal diet and lifespan of the offspring [13, 14]. Maternal protein restriction during pregnancy resulting in low birth weight, followed by postnatal catch-up growth through suckling by normally fed dams (recuperated offspring) led to a reduction in lifespan. In contrast, maternal protein restriction and slow growth during the lactation period resulted in increased life span and conferred protection from the detrimental effects of an obesogenic diet. In addition to differences in aging at the whole body level, these same rodent models have revealed effects of maternal diet on aging at the cellular level, as demonstrated by differences in rates of telomere shortening and in markers of cellular senescence [15].

The islets of Langerhans in the endocrine pancreas, the only cells in the body that can produce insulin, appear to be particular vulnerable to the detrimental effects of maternal diet on their aging trajectory. This is consistent with the early environment having a major influence on regulation of glucose homeostasis and consequently diabetes risk. Some of the earliest effects on telomere shortening resulting from maternal protein restriction are observed in pancreatic islets and this is accompanied by premature induction of p16, one of the most robust biomarkers of aging [15]. In addition, maternal protein restriction during pregnancy and lactation results in increased age-associated oxidative stress and development of fibrosis [16].

The molecular bases of the interaction between maternal diet, aging and the risk for T2D are currently poorly understood. However, the hypothesis that this interaction could be mediated by epigenetic mechanisms offers an attractive explanation for the link between nutrition, regulation of gene expression, and the risk for disease (Figure 1).

Epigenetic dynamics during early development and aging

Gene transcription is the result of the interactions between transcription factors and chromatin at a number of genomic regulatory elements including promoters, enhancers, insulators and silencers. Accessibility to these sites is mediated by epigenetic modifications of histones and DNA. It is widely accepted, for example, that upon histone acetylation, genes become actively transcribed, whereas deacetylation leads to repression. Modifications of the DNA itself, such as methylation and most recently hydroxymethylation, are also important indicators of the transcriptional regulatory activity of many genomic loci.

Epigenetic marks are responsive to environmental and developmental cues, as there is a need to modify the transcriptional outputs of genes throughout the life of an organism [17, 18]. It is clear that chromatin structure changes in response to the cell's many stimuli. Certain epigenetic marks can be added and removed before a cell divides or within few cell divisions. Such short-term flexibility is particularly important to allow appropriate responses to acute environmental cues. Other epigenetic marks can be maintained for many cell divisions. Long-term stability is required for epigenetic programming of the early embryo, a process that refers to the acquisition and stable propagation of marks that define cell types and maintain cellular memory [18].

Deregulation of epigenetic processes with age is a common feature in mammals [19]. Widespread and tissue-specific age-related DNA methylation changes