Overview of Mechanisms of Early Programming During Pregnancy

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More than 20 years ago the first epidemiological studies revealed a relationship between patterns of early growth and subsequent risk of diseases such as type 2 diabetes, cardiovascular disease, and the metabolic syndrome. Extensive studies during this time have revealed that both low birth weight (especially when followed by accelerated postnatal growth) and high birth weight were associated with metabolic disease later in life.

Evidence also shows not just that metabolic conditions are associated with patterns of early growth but also that similar relationships exist between birth weight and nonmetabolic parameters such as mental health and immune function. Studies of identical twins, individuals who were in utero during periods of famine, discordant sib pairs, and animal models have provided strong evidence that the early environment, including nutrition during fetal life, plays an important role in mediating these relationships. The concept of early life programming therefore is widely accepted.

However, the mechanisms by which a phenomenon that occurs in early life can have long-term effects on the function of a cell and therefore metabolism of an organism many years later are only starting to emerge. Insight into these molecular mechanisms has primarily come from the study of animal models including those established in nonhuman primates, sheep, pigs, rats, and mice. A major strength of studying a range of diverse species is that it allows the identification of molecular mechanisms that are conserved between species and therefore likely to represent fundamental mechanisms that are likely to be important in humans. However, most studies have been carried out in rodents as these allow mechanisms to be addressed across the life course of an organism.

It has become increasingly apparent that a single mechanism cannot explain all the observed programming phenomena. Based on current knowledge, the potential mechanisms can be categorized into three groups. These three mechanistic categories clearly are not mutually exclusive, and there is likely to be interaction among them (Table).
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Table. Proposed Mechanisms of Early Programming

One of the earliest proposed mechanisms was related to effects mediated by permanent changes in the structure and consequently the function of critical organs. It was suggested that during a critical period of development of an organ, exposure to a suboptimal level of a nutrient or hormone that is essential for appropriate development of that organ would permanently alter the structure and function of that tissue. Examples are low levels of nutrients early in life leading to a permanent reduction in pancreatic beta cell mass and renal nephron numbers, which can influence risk of type 2 diabetes and hypertension respectively.\(^2,3\)

Suboptimal levels of the hormones insulin and leptin in early life also can permanently influence the structure and, consequently, function of the hypothalamus, which plays a key role in regulation of energy balance and thus can influence risk of obesity.\(^4,5\)

More recently focus has been directed toward the potential role of persistent alterations in epigenetic modifications (eg, DNA methylation and histone modifications) leading to programmed changes in gene expression that form the basis of cellular memory.\(^6\) Several transcription factors including hepatocyte nuclear factor 4 alpha (HNF4α), pancreatic and duodenal homeobox 1 (PDX-1), and peroxisome proliferators-activated receptor alpha are susceptible to programmed changes in gene expression through such mechanisms. Fig 1 illustrates the role of HNF4α in the beta cell and consequently type 2 diabetes.
Transcription factors are particularly attractive targets of developmental programming because a whole network of other genes can be modulated through modulation of their expression.

A permanent effect of early exposures on the regulation of cellular aging has been suggested as another mechanism that can link a suboptimal early environment and long-term health. Increases in oxidative stress leading to macromolecular damage, including that to DNA and specifically telomeres, can contribute to such effects by leading to premature cell senescence. Mitochondrial dysfunction resulting from either defects in mitochondrial copy number or defects in mitochondrial complex activities could provide the source of the oxidative stress.

The main goals now in the programming field are to build on these findings and to translate them into ways to improve human health through development of preventative and intervention strategies. However, there are still major challenges that need to be addressed to achieve such goals. It is clear, certainly from animal models, that maternal overnutrition and undernutrition during pregnancy can affect not only the health of the mother but also the long-term health of the baby. However, modulation of diet during human pregnancy is not straightforward and it...
should be noted that maternal diet does not equate to fetal diet. Therefore, in many instances an apparently well-nourished or overnourished mother can deliver an undernourished baby as a result of poor placental function. Furthermore, although initial focus in human studies was directed toward high or low birth weight as a proxy for exposure to a suboptimal in utero environment, it is now apparent that birth weight is a very crude index of in utero experiences and that not every suboptimal environment influences fetal growth. Therefore, a need exists to identify at-risk individuals through good molecular markers (see strategies in Fig 2). These could be genetic, protein, or epigenetic factors, which to be clinically useful would have to be present in clinically accessible material such as blood, urine, placenta, or umbilical cord. The latter two are particularly attractive because they are available very early in life, thus providing the maximum time for intervention.

Fig 2. Strategies for identifying individuals at risk for certain metabolic diseases.
The insight gained from mechanistic studies may enable the design of targeted intervention studies and ultimately personalized medicines. Most of the diseases associated with a suboptimal environment are heterogeneous conditions. For example, type 2 diabetes is a phenotype that can result from a wide variety of factors that influence pancreatic beta cell function and/or insulin action. Therefore, it may be naïve to assume that the same medication will be suitable for all causes of type 2 diabetes. Mechanistic insight into the pathways that mediate the effects of a suboptimal early environment on type 2 diabetes risk could help identify rational drug targets.

Understanding environmentally driven processes provides more tractable targets for intervention than those driven by genetic processes. Therefore, further progress on understanding the pathways and mechanisms underlying early life programming offers the potential to help combat the burden of many common diseases faced by modern society.

References


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Q & A

Q: You mentioned that 50% of diabetics had a low level of hepatocyte nuclear factor 4 alpha. Did this track with disease progression or treatment?

Dr Ozanne: These were all postmortem samples from an array analysis from individuals who, I think, died in traffic accidents. The array just compared what genes were differentially expressed. The criterion was the classification of diabetes, not taking into account stage or treatment.

Q: I am still trying to work through methylation. You showed there was no effect in the promoter region but you did see it in the enhancer region, correct?

Dr Ozanne: I saw a small difference in methylation in the promoter region, but there was not methylation in the enhancer region.

Q: How well do you think we understand methylation, and how does that translate to, for instance, interventions?

Dr Ozanne: I think we still understand very little about DNA methylation and its regulation, particularly how we get gene-specific effects. We get changes in methylation at one region genome and not another. We do not really understand normal development and normal differentiation. We do not understand how that arises. It is even more difficult to interpret how it happens from a programming perspective. We do start to see differences in the promoter region later, with aging.

Q: How far are we from a pharmacologic or other type of intervention?

Dr Ozanne: I would say we are in the very early stages. Even in the cancer field, where the epigenetic mechanism has been seen, the epigenetic changes that have been recognized were much longer. We are even not at the stage where we can target those well from a disease perspective.

Q: Do you have data and animal models in which you have demonstrated the effects in the mitochondrial dysfunction associated with outcomes? Also, are there any data on the effects of nutrition modification and modifying mitochondrial dysfunction as a consequence?
**Dr Ozanne:** That is a good question. The answer to the first question is that we have not shown cause and effect, but certainly we have shown associations. So in collaboration with Dr Poston at King’s College London, we have shown that there is a defect in complex two, three linked activities, in the low-protein offspring in the kidney. And we have shown that this happens before we see differences in telomere shortening. We see the defect but we cannot, at this stage, prove that it is causing the telomere shortening. We are looking at potential interventions to address that.