

**Epigenetic correlations with adult phenotype: Implications for nutritional interventions. Dr Steve Hodgkinson, Liggins Institute, University of Auckland, Auckland, New Zealand**

It is a well-established principle in biology that an organism's genotype provides only the framework for its eventual adult phenotype, and that environmental cues during development fine-tune the phenotype to match the individual organism to its particular environment. The science of how the genome interacts with the environment has been termed epigenetics and the research area of developmental epigenetics is rapidly gaining momentum globally.

Epidemiological research has suggested a link between early life events and later mortality in humans. An initial explanation was provided by the "thrifty phenotype" hypothesis - a model of disease causation more recently extended by the realisation it represents an example of the broader phenomenon of developmental plasticity or programming. The intent of developmental programming is to match the growing fetus to its predicted post natal environment but it can become maladaptive when the 'fit' between the predicted and later environments is mismatched. Where adverse programming occurs a "metabolic phenotype" may result characterised by aberrant glucose and insulin responses and gross phenotypic changes such as obesity providing a model for the developmental origins of the "metabolic syndrome" in humans.

Increasing evidence suggests at least three developmental pathways to the metabolic phenotype - including obesity and type 2 diabetes - which is fast becoming a major human health challenge of the 21<sup>st</sup> Century. The pathways include maternal under nutrition during pregnancy, maternal over nutrition and post natal nutritional excess.

We have focussed on the molecular basis of developmental programming. The mechanism of epigenetic regulation is now known to involve stable changes to the methylation status of CpG islands in the promoter regions of key metabolic genes. There is increasing evidence that metabolic plasticity is affected by epigenetic regulation of key metabolic genes and that measurement of epigenetic status of such genes early in life correlates with gene expression levels and phenotypic outcomes in adulthood. Validation of such correlations in a large population will allow prediction of individual growth trajectories, with wide implications for preventive medicine.

A major current focus is to determine the validity of making perinatal epigenetic measures to identify whether the newborn has been exposed to an adverse intrauterine environment and to assess the potential use of this information as a predictive measure of biological outcome. A second focus is to develop strategies for intervention to allow us to manage or reverse undesirable epigenetic programming / growth trajectories and maximise biological potential. In recent work we have found that epigenetic change is potentially reversible by specific factors. Intervention may potentially be achieved by pharmaceutical or nutritional means and proof of concept for the approach has been demonstrated using the adipokine – leptin and folate.

In our view nutritional foods (in the broadest sense) have considerable potential in meeting the health burden of the metabolic phenotype and therefore present a major opportunity for the industry both in terms of pregnancy and post natal nutrition. While therapeutic intervention will certainly have its place, in context, the developmentally programmed neonate is not actually 'pathological' but, rather, is on a developmental trajectory to later on set disease. For this reason we believe targeted nutritional interventions based on formulations containing validated bioactive food ingredients may have a particular advantage.