

4

Prof Mark Hanson
University of Southampton
Mailpoint 887
Princess Anne Hospital Coxford Road
SO16 5YA Southampton, UK
Email: m.hanson@soton.ac.uk

Developmental origins of health and disease – new insights

M.A. Hanson*(1), P.D. Gluckman (2) (1.Division of Developmental Origins of Health & Disease, University of Southampton, 2.Liggins Institute, University of Auckland)

Epidemiological and animal studies show that small changes in the environment during development, e.g. in nutrient provision or balance, induce phenotypic changes which affect an individual's responses to their later environment. These may in turn alter the risk of chronic disease resulting from inadequate responses, e.g. to a rich environment leading to metabolic syndrome or cardiovascular disease. Recent research shows that animals exposed to such a mismatch between pre- and postnatal environment develop obesity, reduced activity, leptin and insulin resistance, elevated blood pressure and vascular endothelial dysfunction. We have found an important role for molecular epigenetic processes in producing such effects, processes which are targeted to promoter regions of specific genes in specific tissues but which also include changes in histone structure and post-transcriptional processes involving miRNAs. Such fine control of gene expression endorses the view that the mechanisms have been retained through evolution as a result of the adaptive advantage which they confer, rather than representing extreme effects of developmental disruption akin to teratogenesis. Moreover there may be adaptive advantage in a developmental cue inducing a phenotypic change in generations beyond the immediately affected pregnancy, and there is now a range of human and animal data which support this concept. Such effects – which might be termed non-genomic inheritance – may be mediated by a range of effects including alterations in maternal adaptations to pregnancy in successive generations or behavioural influences. Recent data however also show that epigenetic effects such as DNA methylation can be passed to successive generations. This suggests that they might persist through meiosis. There is now evidence for transmission via the male lineage which may also involve miRNA-mediated effects. Environmental toxins, including endocrine disruptors, can play a role in inducing greater risk of chronic disease even at low exposure levels, especially if they act via the normal epigenetic processes involved in developmental plasticity. Current research in this area is important for mechanistic understanding and for developing novel prognostic markers of later disease risk. It also emphasizes the long-term multi-generational effects which appropriate interventions may confer to reduce the risk of chronic disease in subsequent generations.

MAH is supported by the British Heart Foundation and PDG by the National Research Centre of Growth and Development