

Epigenetic modifications in the early life programming of disease

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Background

Epidemiological studies have shown that early life events influence susceptibility to later cardiometabolic disease ⁽¹⁾. This process, termed fetal ‘programming’, is thought to reflect the action of a factor during a sensitive developmental period to alter tissue development and function, producing lifelong effects. The potential role of epigenetic changes in mediating the early life origins of disease is being increasingly recognised ⁽²⁾. In animal models, altered maternal diet during pregnancy or postnatal behavioural programming is associated with altered gene methylation and expression, notably at the glucocorticoid receptor (GR) gene ⁽³⁻⁵⁾. We have previously studied a group of men and women born in Motherwell, Scotland in 1967-1968, whose mothers had been advised to eat a high meat, low carbohydrate diet in pregnancy to prevent pre-eclampsia. In these individuals, higher maternal intake of meat and fish and lower intake of green vegetables during pregnancy was associated with higher adult blood pressure, impaired glucose tolerance and HPA axis activation in the offspring ⁽⁶⁾. Green vegetables are an important source of folate, and in rodents, manipulation of dietary folate alters gene methylation and expression. The documented changes in metabolic status and HPA axis activity in response to the unbalanced maternal diet in these individuals indicate that this is a uniquely valuable cohort to study.

Aims

The aim of this study was to study changes in DNA methylation at key candidate genes and to identify new targets of epigenetic dysregulation in this unique cohort and to relate these findings to both early life factors (maternal diet, neonatal anthropometry) and to measures in adult life including blood pressure and anthropometry. We performed these analyses in a group of individuals born in Motherwell between 1967 and 1968 who were re-recruited for a further study in 2008.

Methods

The participants included 34 individuals aged 40 years from the Motherwell cohort study whose mothers had eaten an unbalanced diet in pregnancy, previously linked with elevated blood pressure and cortisol in adult offspring. DNA methylation status at key candidate genes was analysed by pyrosequencing performed on bisulphite converted DNA extracted from buffy coat. DNA was also hybridised to Illumina Infinium HumanMethylation27 beadchip arrays.

Results

Methylation at specific CpG residues at the promoter region and differentially methylated regions of candidate genes correlated with neonatal anthropometric variables and with increased adiposity and systolic blood pressure in adulthood. Methylation was significantly altered in offspring of mothers with the most unbalanced diets in pregnancy. A number of new candidate genes have been identified on microarray and are currently undergoing validation.

Conclusions

Alterations in DNA methylation at candidate genes are present in adulthood in association with both early life parameters and with cardiometabolic risk factors. The data indicate a persisting epigenetic link between early life maternal diet and/or fetal growth and

cardiovascular disease risk in humans. This data has been submitted for publication (Drake AJ et al). Our further studies are focussed on identifying to what extent these epigenetic modifications are established in early life and maintained into adulthood or are substantially altered by postnatal lifestyle. In addition we have identified a number of new genes which may be targets of epigenetic dysregulation in early life. Finally, data generated in this study has formed the basis for a number of grant applications.

References

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