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Epigenetics and Primary Care

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Epigenetics is the study of how changes to chromosome structure record and/or transmit changes in the expression of genes. Epigenetic mechanisms act during development to control mechanisms such as cell proliferation and differentiation, tissue formation, organogenesis and the emergence of physiological function. They also act throughout life to regulate gene expression over the long-term. Epigenetic mechanisms respond to a wide range of biological signals, including stimuli from the external and social environments. So, why should this matter to General Practice?

We know that poverty and socio-economic deprivation are directly linked to premature mortality and morbidity(1). We also know that despite universal access to free healthcare, inequitable health care outcomes persist in socioeconomically deprived populations.(2) While some of the disease-causing effects of poverty and deprivation are biologically direct, such as inadequate diet or exposure to alcohol, tobacco and other toxins, there may also be later-emerging effects, in which epigenetic mechanisms play a part.

Epigenetics across the lifecourse.

While scientific understanding of the mechanisms by which adversity and social inequality lead to health consequences is still developing, it seems likely that processes are involved which regulate the production of inflammatory cytokines and stress hormones such as noradrenaline and cortisol. Together the accumulated effect of these stress-related biological signals is known as allostatic load(3). It refers to allostasis, the process of restoring physiological set-points after exposure to stressors (which may be environmental or social). Repeated or chronic exposure to stressors appears to erode the capacity of allostatic mechanisms to restore physiological set-points, and so promote survival under duress. Thus, over time, the consequences of prolonged exposure to stressors become more pronounced. By helping us to understand how these processes change, epigenetics provides an explanatory model through which the biological embedding of low socio-economic status (SES) affects the functioning of a person’s genome. In turn this model has begun to stimulate new ways of thinking about how environmental factors such as social inequality generate or perpetuate health inequalities.

Evidence of long-lasting epigenetic effects has been clearly observed in the consequences of the Dutch Winter Famine during 1944-45. For several months, the daily rations in Amsterdam were between 400 and 800 calories. The survivors were a well-defined group of individuals, all of whom suffered just this single period of malnutrition, at exactly the same time. Epidemiologists followed up not just the adult survivors but also the offspring of women who were pregnant during the famine. Early gestation-exposed individuals showed a three-fold increase in coronary heart disease, a more atherogenic lipid profile, increased levels of obesity, increased risk of Type II diabetes and an increased risk of breast cancer (4–6). Other studies of famine have shown similar results (5), and these effects are now being seen in the grandchildren of the women who were malnourished during the first three months of their pregnancy(4,7). Starvation is not the only trigger for long lasting impacts: other population studies have demonstrated associations between maternal mental wellbeing, child abuse and low SES with regard to poor long term mental health and chronic disease(8,9). Furthermore, it seems likely that the increase in type 2 diabetes worldwide – while to some extent heritable – is developing too quickly to be due to genetic differences, but appears to be more long-lasting than the direct exposures to adversity.(10)

How do environmental exposures become biologically embedded, and can they be reversed?

Epigenetic mechanisms influence the structure of chromatin, which is the complex formed of DNA and chromosomal histone proteins. Chromatin structure influences the accessibility of DNA to the gene transcription machinery, which drives differentiation of every cell type, all of which have the same DNA, by regulating the expression of different genes. A cell, organ or person’s phenotype is thus determined not only by genome but also by the epigenome. At present, there are three well-understood mechanisms by which epigenetic factors affect gene expression: DNA methylation, histone modification, and non-coding RNA-mediated pathways. DNA methylation usually results in gene silencing or reduced gene expression. A wide range of histone modifications are known that either increase or decrease the amount of gene transcription, depending on the modification. Finally, microRNAs (miRNAs) are a class of non-coding single stranded RNAs of 19-25 nucleotides in length, which regulate gene expression by binding to complementary sequences within messenger RNAs (mRNAs), blocking mRNA translation and/or promoting mRNA degradation.

While there is abundant information about how these epigenetic mechanisms are deployed extensively in somatic tissues, their roles in the transgenerational transmission of chronic disease risks, via the germ line, are less well understood. One likely explanation of how epigenetic changes may be passed from one generation to another is that during pregnancy, the foetal germ cells that will give rise to the mother's grandchildren are exposed to the same environmental factors as both the mother and the somatic tissues of the foetus. Epigenetic modifications could thus be acquired by foetal germ cells during gestation, the functional impacts of which may not emerge until later life (11).

As epigenetic mechanisms are regulators of gene expression, it is important to ask whether once applied, they are reversible. This appears to be the case: for instance there is accumulating evidence that mind-body therapies designed to reduce stress-related arousal and promote coping are associated with reductions in expression of genes for pro-inflammatory cytokines(12).

What are the implications of Epigenetics for Primary Care?

The GP core curriculum emphasises the need to understand the physical health of our patients in combination with the psychological, socioeconomic and cultural dimensions of health. If the epigenome is modifying gene expression, as a direct - but sustained or delayed - response to environmental stressors, then the need to move from the primacy of a biomedical model to an integrative holistic approach becomes particularly important. An epigenetic explanatory model allows us to see how many of our patients from socioeconomically deprived backgrounds are disadvantaged not only by the immediate lack of access to material, nutritional and educational support that are conducive to the development and expression of capabilities for flourishing, but also by the cumulative biological embedding of their ongoing social deprivation, which perpetuates and indeed further widens health and societal inequity (13). In the case of symptoms such as chronic widespread pain(14), where epidemiology shows strong associations with social adversity, but immediate causal links between stress and symptoms are rare(15), epigenetic mechanisms provide potentially useful material for GPs to construct "rational" explanations (16) about the complex links between adversity and illness. Recent progress in epigenetics research raises many questions about how the social and environmental determinants of health influence disease risk, and there is a growing awareness of the potential ethical, social and legal implications of these findings.(17) Future progress in this field will benefit from the development of collaborative communities of laboratory, behavioural and social scientists, clinicians and policy makers, working with patients and the wider public, in the conduct of pioneering research that will help to improve health outcomes for all.

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