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Epigenetics and Health

Epigenetics refers to a range of factors that regulate the activity of genes. Such factors can contribute to a host of human diseases from cancer to mental illness and knowledge of epigenetics may help to reduce disease risk in ageing populations. This POSTnote examines how recent advances in this field can be used to develop new treatments, inform public health policy, and contribute to the UK economy.

Overview

- Epigenetics controls how genes function.
- The global market for epigenetic therapies and technologies is predicted to reach $2.5 billion (£1.6 billion) in 2013.[1]
- Abnormal epigenetics has been linked with diseases such as cancer and diabetes.
- Environmental factors such as maternal diet and smoking can lead to epigenetic change.
- Some epigenetic changes can last throughout a person's lifetime. Others are temporary and reversible. Knowledge of epigenetics has the potential to improve health through diet and behaviour change.
- In some species, epigenetic changes are passed from one generation to another; there is currently no direct evidence that this happens in humans.

Background

Genes contain instructions written in the DNA code that allow cells to make the complex molecules they need in order to function. Epigenetics – literally meaning 'above genetics' – is the study of the factors that regulate the activity of genes and that can control them from being fully off to fully on. Such factors exert control over gene function without altering the DNA code. For instance, even though identical twins share the same genes, epigenetic variations may mean that their genetic codes are used differently, leading to non-identical physical traits.

Abnormal epigenetics has been linked with diseases as diverse as cancer, diabetes, Alzheimer's and heart disease. Exposure to environmental factors such as cigarette smoke or dietary stress can affect epigenetic controls and predispose to disease. There is increasing evidence that early exposure to such factors – for instance in the womb – can increase the risk of diseases such as obesity in later life. Obesity is a public health priority with the Department of Health publishing its action plan to reduce obesity levels in 2011.[2] It is likely that the increasing focus on epigenetics – the number of epigenetics research papers increased 11-fold between 2002 and 2012 – will improve diagnosis, risk assessment and treatment of such diseases.

While the potential impact of epigenetics on health is self-evident, there are many gaps in knowledge. Large initiatives that are helping to establish sufficient evidence to support public health interventions include the US National Institutes of Health's $190 million Epigenomics Roadmap project and the International Human Epigenome Consortium partly funded (€30 million) by the European Commission.

How Does It Work?

Virtually all of the hundreds of different types of cell in the human body contain the complete set of more than 20,000 genes. In any given cell, some genes will be active and some not (silent genes). It is differences in combinations of active and silent genes that make a liver cell (say) different from a nerve cell; these patterns of gene expression are under epigenetic control. Epigenetics therefore plays a key role in cell development (Box 1). Retention of epigenetic instructions during cell division also ensures that a cell of a specific type always gives rise to daughter cells of the same type. Epigenetic control operates via many mechanisms but these include (see Box 1): chemical modification of DNA; modification of the proteins associated with DNA that pack it into the cell nucleus; and interactions between DNA and closely related molecules such as RNAs.

Box 1. Epigenetics in Action

Early Development

In order for a newly developing embryo to set its own epigenetic patterns, two waves of epigenetic 'reprogramming' take place where parental epigenetic information is largely erased. Firstly, when new sperm and egg cells are made, and secondly, immediately after fertilisation. When a newly fertilised egg divides, it gives rise to embryonic stem cells. Each of these is a 'blank canvas', capable of giving rise to all the specialised (but genetically identical) cells of the body. The developmental fate of each stem cell is highly responsive to environmental cues in the womb, and this may operate through epigenetics. Such cues tweak the natural course of development into childhood and beyond to give rise to a unique individual.

Epigenetic Mechanisms

Cells contain proteins that read, write and erase epigenetic marks and patterns (multiple epigenetic marks). This may occur through:

- **DNA methylation**. Adding methyl (CH_3-) groups to DNA is known as DNA methylation and has long-lasting effects. Depending on its position relative to the gene it may switch the gene off or on.
- **Histone modification**. Modifying the histone proteins associated with DNA can turn gene activity up or down (usually with shorter-lived effects than DNA methylation).
- **RNA interactions**. Interactions between DNA and small RNA molecules can also temporarily alter how active a gene is.

Heritability

Epigenetic information is retained as cells divide. This means that epigenetic changes are often referred to as being 'heritable'. But this can be a confusing description because the word has two meanings:

- The passing on of epigenetic information to new cells during normal cell division within an individual. This is well established in humans.
- The passing on of epigenetic information from one generation to another. There is evidence for this type of 'trans-generational inheritance' (see below) in other species, but no direct evidence for it as yet in humans.

Disease

Epigenetics is critical to maintaining normal development and cell function. However, when epigenetic changes are made at the wrong time or in the wrong place, disease may arise as a result of abnormal gene function. For instance, there is some evidence from studies of twins that epigenetic factors may be involved in schizophrenia (Box 2). By linking specific epigenetic changes to different diseases, scientists are learning about the role of epigenetics in human health and the interplay between environmental factors and genetics that may predispose to disease.

Early Life Influences and Adult Disease Risk

Recent years have seen various preventive strategies to reduce the NHS disease burden by promoting healthier adult lifestyles. However, there is a growing body of evidence which suggests that epigenetic patterns set early in life and possibly even before birth create lifelong 'echoes' that influence adult health. These patterns may be protective, benign or harmful. For instance, there is some evidence linking a mother's diet during pregnancy to her child's risk of obesity at a later age, and that this may operate through epigenetic mechanisms (Box 2).

Box 2. Epigenetics and Disease

Identical Twins

If one of a pair of identical twins with the same upbringing develops schizophrenia, the chance of the other twin developing the disease is 48%, considerably higher than the corresponding figure in non-identical twins (17%).[3] The increased disease risk for identical twins suggests that the disease has a genetic component. However, the fact that the value is not 100% shows that genetics is not the sole factor that determines the disease. Divergent epigenetic patterns between identical twins may play a part in influencing the overall disease risk.

Maternal Diet and Childhood Obesity

Around 60% of the UK adult population is obese or overweight. The Government has noted that "obesity is probably the most widespread threat to health and wellbeing in this country"[2] because excess weight is a major risk factor for diseases such as type 2 diabetes, cancer and heart disease. Research in animals has shown that the maternal diet during pregnancy affects the epigenetic patterns of certain metabolic genes in the offspring, and that these patterns are associated with adiposity (fatness).

To explore whether this occurs in humans, researchers in Southampton followed a cohort of healthy pregnant women and their children from birth for nine years. They examined the methylation patterns of umbilical cord DNA at birth and compared it to the mother's diet during pregnancy and the child's adiposity at age nine.[4] They found that a low carbohydrate, high protein maternal diet was associated with greater fatness in the children. Furthermore, this was linked to epigenetic patterns at a specific gene that controls how fat is used in the body. Importantly, the epigenetic marks that switched this gene off already existed at birth. The finding was confirmed in a second group of six year old children. It supports the idea that the maternal diet during pregnancy may establish epigenetic marks in early life that affect the child's risk of obesity at a later age.

Cancer

In the UK, almost 900 people are diagnosed with cancer each day; annual NHS costs for cancer services are £5 billion.[5] Cancer is the uncontrolled growth of cells that occurs when cells lose the checks and balances that keep gene expression normal, and cells healthy. For instance, genes that normally suppress tumour growth can be turned off by too much DNA methylation (Box 1), while genes that promote cancer growth can be activated by removing DNA methylation marks. Both effects have been found in cancer cells. Epigenetic changes in gene expression have been linked to many cancers including bowel, breast, prostate, pancreatic, ovarian and lung cancers. Links have also been made between DNA methylation levels and modulators of cancer risk such as age, obesity and smoking.

Autoimmune Diseases

Conditions such as rheumatoid arthritis and type 1 diabetes arise when a person's own immune system attacks the body (so-called autoimmunity). Abnormal DNA methylation and histone modifications (Box 1) have been linked to increased levels of inflammatory proteins in bone joints, as well as over-activation of enzymes that destroy cartilage tissue in rheumatoid arthritis. Increased understanding of such diseases is a significant public health priority. For instance, rheumatoid athritis affects around 400,000 adults in the UK, and arthritis (all types) is the most common condition for which people receive Disability Living Allowance.[6]

Congenital Diseases

Human cells contain two copies of each gene: one from each parent. Research suggests that 99% of genes are expressed from both copies. But in the case of around 100 genes, epigenetic marks silence the gene from one parent. Errors in this normal process of 'genomic imprinting' can lead to rare but disabling illnesses. Eight such syndromes are currently recognised. The most common are Prader-Willi syndrome (characterised by extreme hunger, floppy muscles and reduced fertility) and Angelman syndrome (severe mental retardation, speech impairment and unsteadiness). Such imprinting disorders arise when the regulation of the imprinted genes goes wrong, which can be due to genetic and epigenetic causes.

Brain Disorders

Neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's have all been linked to molecular epigenetic changes. There is also emerging evidence for an epigenetic contribution to neuropsychiatric conditions including bipolar disease, schizophrenia (Box 2) and depression. Epigenetic faults can also lead to neuro-developmental disease. For instance, Rett syndrome is an autism spectrum disorder that affects over 1,000 girls in the UK who have a faulty protein involved in the epigenetic regulation of many genes. By targeting this protein, scientists found a promising way to reverse Rett symptoms in mice. Further research is now needed in humans (Box 3).

A particular challenge with investigating the role of epigenetics in brain disease is that research usually relies on post-mortem samples. A network of ten 'brain banks' co-funded by the Medical Research Council, is available to researchers;[7] housing over 7,000 brain tissue samples across the UK.

Transgenerational Inheritance of Disease Risk

Recent years have seen much debate over whether epigenetic changes can be inherited over multiple generations in human populations. Links between ancestral environmental exposures and observed traits in descendants have been found in studies involving hundreds to thousands of people. For example, fathers who started smoking before puberty tend to have sons who carry an extra 5-10kg of fat mass on average compared with sons of all other fathers. Paternal grandfathers who experience childhood famine tend to have longer-lived grandsons.[8] Epigenetic transgenerational inheritance might explain these sorts of observations.

However, there is not yet any direct molecular evidence in humans that specifically implicates an environmental exposure with an observed trait across generations. One possible mechanism for transgenerational epigenetic inheritance would be for some epigenetic marks to escape the epigenetic reprogramming process (Box 1). Researchers recently discovered that a small number of DNA methylation sites evade erasure in mouse studies,[9] but evidence in humans is lacking.

Box 3. Rett Syndrome and Hopes for Epigenetic Interventions

Rett develops in girls at 6-18 months and leads to walking, speech and breathing difficulties, seizures, and unusual eye movements. Patients need 24 hour care, although improved disease management means that many now live into adulthood. The disease is caused by loss of the $MeCP_2$ protein. $MeCP_2$ is an important part of the epigenetic control system because it reads DNA methylation marks. Restoring $MeCP_2$ using genetic engineering techniques in Rett affected mice reversed Rett symptoms.[10] This suggests that curing Rett is biologically possible, but extensive further research is required before clinical treatments can be developed. Nevertheless, the hope for a 'cure' has compelled affected families to invest into research-focused charities that fundraise exclusively for research into Rett cures, alarming the established charitable groups that offer more traditional support and guidance.

Potential Policy Impact

Medicine and Technology

Epigenetic controls are attractive therapeutic targets because they appear to contribute to many human diseases and are reversible. Some of the main approaches being pursued are outlined below.

- **Sequencing epigenetic patterns.** This has the potential to improve understanding of disease; large databases of epigenetic information are already being compiled. Cheaper, faster and more sensitive technologies for detecting epigenetic marks are under development (Box 4). The Government recently pledged £100 million to sequence 100,000 genomes within the NHS;[11] similar approaches may be needed for epigenetic sequencing.
- **Epigenetic reprogramming of cells.** Mature cells can be reprogrammed back into stem cells in a laboratory. Such 'induced pluripotent stem cells' (iPSCs) have great potential as disease models and for screening potential new treatments. The Human Induced Pluripotent Stem Cells Initiative (HipSci), jointly funded by the Medical Research Council and The Wellcome Trust, is building an iPSC bank from 1,000 people to study diseases. In theory, it may be possible to use iPSCs as therapies in humans, much like embryonic stem cells. However, generating iPSCs is currently expensive and inefficient and the subtle differences observed between iPSCs and stem cells derived from embryos mean that there are safety concerns about therapeutic use.

Box 4. Epigenome Banks and Sequencing Technologies

International consortia are sequencing epigenomes of healthy and diseased people. With the data often being made freely accessible, researchers can more easily look for links between genes, epigenetics and disease. These efforts rely on robust and reliable sequencing technologies. A widely used technology is the Illumina array (US), which interrogates 480,000 (out of 30 million) DNA methylation sites at once and costs around £100 per sample. New technologies are being developed by companies such as Oxford Nanopore (UK) and PacBio (US) that may allow the simultaneous sequencing of DNA and epigenetic marks. The Wellcome Trust recently provided £200 million to launch Syncona Partners, an investment company with a view to creating sustainable healthcare businesses. An epigenetics sequencing start-up company, Cambridge Epigenetix, is the first to benefit from Syncona funding.

Box 5. Epigenetic Diagnostics

Stratified Cancer Therapy

The protein made from the MGMT gene helps to repair damaged DNA. In some cancer patients, the MGMT gene is turned off by DNA methylation. Such patients show little response to the chemotherapy drug temozolomide. However the drug is effective in patients where the MGMT gene is still active. A commercial diagnostic test that measures DNA methylation levels in the MGMT gene and allows those patients who will benefit from temozolomide to be identified is in the final stage of clinical approval. This pre-screening step could avoid wasted treatment time and undesirable side-effects for patients who are not likely to benefit from the drug.

Potential Blood Test for Predicting Breast Cancer Risk

Breast cancer is the most common cancer in the UK, accounting for 31% of all new cancers in women. Breast cancer risk is currently assessed by genetic testing and by profiling risk factors such as family history, ethnicity and age. Inherited mutations only account for an estimated 5-10% of breast cancers; testing for epigenetic changes could catch some of the remaining cases. Tests on blood samples collected from women before their breast cancer diagnosis showed that women with the highest levels of DNA methylation at a specific gene involved in DNA repair were twice as likely to go on to develop breast cancer.[12] The blood was taken on average three years before diagnosis and in some cases, up to eleven years earlier.

- **Epigenetics as the basis for new cancer treatments.** Some blood cancer treatments stop proteins from making epigenetic changes that encourage cancer. However, these have severe side effects because they affect all cells, not just cancer cells. Researchers are investigating new ways to exploit epigenetics for developing more targeted treatments.
- **Epigenetic changes as diagnostics.** Molecular changes such as epigenetic patterns can signify the presence or future development of disease. This is useful for diagnosis, for stratification of patients into groups according to whether they will respond to a particular treatment, and may also allow the early detection of patients at increased risk of a disease (Box 5). The Government recently pledged £130 million for stratified medicine in its 'Strategy for UK Life Sciences'.[13]

Health Policy

Maternal and Infant Nutrition

Evidence that epigenetic patterns acquired early in life can influence later health is likely to reinforce messages about the importance of adequate nutrition for pregnant women, their partners and their babies. The Change4Life programme in England, part of the DH's Public Health Responsibility Deal,[14] already includes nutrition and physical activity guidance for pregnant women and babies. Families may access support and advice from SureStart Children's Centres across the UK, although future funding for these centres is uncertain. Epigenetics evidence may also shape the National Institute for health and Care Excellence's (NICE) guidelines for supporting low income pregnant women, who are more likely to have poor diets.[15]

Guthrie Cards

Blood collected from newborn babies by a heel prick is routinely soaked onto pre-printed ('Guthrie') cards for disease screening at birth. Research has shown that archived Guthrie cards can be used as a source of DNA for sequencing and epigenetic analysis.[16] This allows researchers to compare a patient's epigenetic and genetic features at birth with their current profiles, a process that may provide insights into the various causes behind disease progression. These cards can be archived by centres holding a licence issued by the Human Tissue Authority. However, a survey conducted by the NHS Newborn Blood Spot Screening Programme showed that the storage of Guthrie cards throughout the UK is highly variable (average five years, longest 35 years).

Use of blood samples from Guthrie cards for anonymised research is permissible within research projects that have ethical consent. Any form of testing that is traceable to an individual requires consent. In Ireland, Government plans to destroy to one million Guthrie cards in order to comply with EU data protection laws was met with public disapproval; the decision was eventually overturned by the Health Minister.

Behaviour Change

NICE public health guidance has already highlighted the need to equip practitioners with the competencies and skills needed to support behaviour change.[17] Evidence from epigenetics research is highly relevant to behaviour change guidance and advice because epigenetic changes are potentially modifiable through lifestyle and diet. Advice to pregnant women on behaviour change to avoid exposure to potentially harmful factors during early embryonic development is likely to be particularly important. Any emerging evidence of transgenerational epigenetic inheritance of disease risk in humans would also be highly relevant.

Endnotes

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