Epigenetics, lifestyle and ageing

Can we slow a ticking clock?

Holly Kerr

We now know that there is more to genetic variation than just the DNA base sequence itself. Our epigenetic landscape is subject to modification by our environment and lifestyle, as well as that of our parents and grandparents. Geneticist Holly Kerr explores the interplay between lifestyle, epigenetics and ageing

EXAM LINKS

AQA Regulation of transcription and translation
OCR A Control of gene expression
OCR B Epigenetics
Pearson Edexcel A Epigenetics
Pearson Edexcel B Factors affecting gene expression
WJEC Eduqas Epigenetics

Long before the discovery of the structure of DNA, scientists knew about genes. Genes are the heritable, coding units of DNA that encode the proteins that underlie the physical traits witnessed by Mendel in his famous pea plant experiments. But the complexity of DNA, its structure and organisation are still active fields of research, presenting many unanswered questions. Until recently, it was thought that genetic variation was brought about solely by differences in base sequences of DNA. However, there is more to consider than just the DNA sequence itself. Throughout our lives, heritable changes in gene expression can occur *without* changes to the DNA base sequence. This discovery has revolutionised our ideas about genes, the environment and inheritance.

The **epigenome** acts as an interface between the environment and our genome and can be altered by our lifestyle and as we age. Ageing in humans is complex, and studying it is a major challenge. However, with an unprecedented growth in the worldwide population of over 65s, understanding ageing is an urgent and global need.

Many lifestyle-related diseases, such as cardiovascular disease, type 2 diabetes and chronic kidney disease, are threatening healthcare systems. Despite advances in modern medicine and increased average lifespan, the so-called 'health span' of individuals (chronic-disease-free, healthy years) has failed to keep up. So how do we age, what are the molecular changes that occur with our lifestyle choices and can these be passed down to future generations? Epigenetics may hold some of the answers.

Box 1 The Dutch hunger famine – epigenetic memory

In certain areas of the Netherlands during Nazi occupation, there was a period of limited food supply. People affected, including pregnant women, ate a reduced diet providing less than 1000 kilocalories per day. The outcomes of the pregnancies were studied, comparing women who were affected at different times of their pregnancy. Children from affected pregnancies showed marked differences in disease prevalence later in life. In particular, famine affecting the mother during the first trimester of pregnancy resulted in increased incidence of cardiovascular disease and obesity in her children decades later. Evidence suggests the children's bodies were responding to the environmental condition, limited food supply, that their *mother* faced when pregnant.

Epigenetic changes were responsible. Genes involved in energy metabolism in the children from the Dutch hunger famine showed increased DNA methylation. This DNA methylation represses gene expression by preventing transcription of certain genes associated with metabolism. In starved conditions, this is clearly advantageous, since the body is preserving the little energy it has. When their diet had returned to normal, the epigenetic landscape of the children of the famine still reflected that of starved conditions and led to increased risk of obesity and disease.

This was one of the first pieces of evidence that we not only inherit the variation in our genes from our parents, but at least some of their epigenetic modifications also.

What is epigenetics?

Epigenetics is heritable modification to our DNA that does not alter the DNA sequence itself. DNA is packed into different forms – heterochromatin and euchromatin (see Figure 1). The genes in heterochromatin are less accessible, and therefore expressed at a lower rate than those in euchromatin. Which regions of the genome are in which type of chromatin can change, and is variable between cells of the same organism. Thus, the packing of DNA into chromatin allows eukaryotic genomes to regulate gene expression. The right genes are expressed at the right time, in the right cell and can be quickly switched off when necessary.

Modifications to chromatin and addition of chemical groups to DNA or to histones are all part of an individual's epigenetic landscape. This landscape is flexible and can respond to changes in the environment. Epigenetic modifications may then be passed down from parent to offspring, which means that future generations have some degree of 'epigenetic memory' of the previous generation's environment. An example of this was the Dutch hunger famine (see Box 1). The many factors that individuals experience throughout

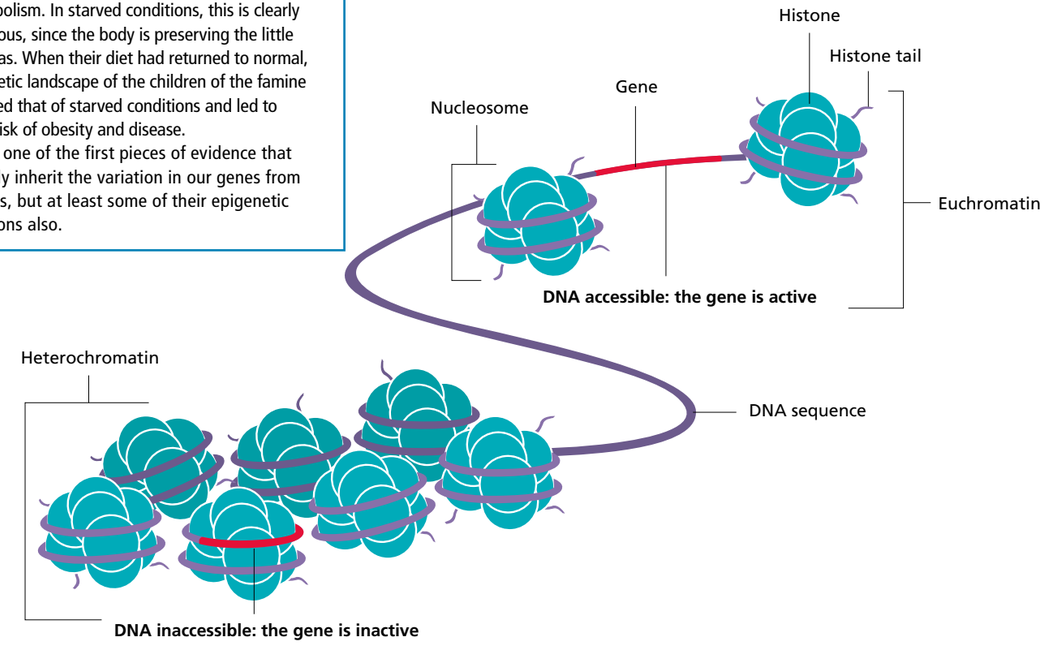

Figure 1 Eukaryotic genome showing DNA wrapped around small proteins called histones, arranged in units of eight with DNA spiralled around them to form nucleosomes. Nucleosomes form along the DNA sequence with small linking sections between, like beads on a string. Heterochromatin is tightly packed, condensed DNA; euchromatin is more loosely packed DNA. This means that some genes are less accessible to proteins such as transcription factors, whereas others are more open and accessible

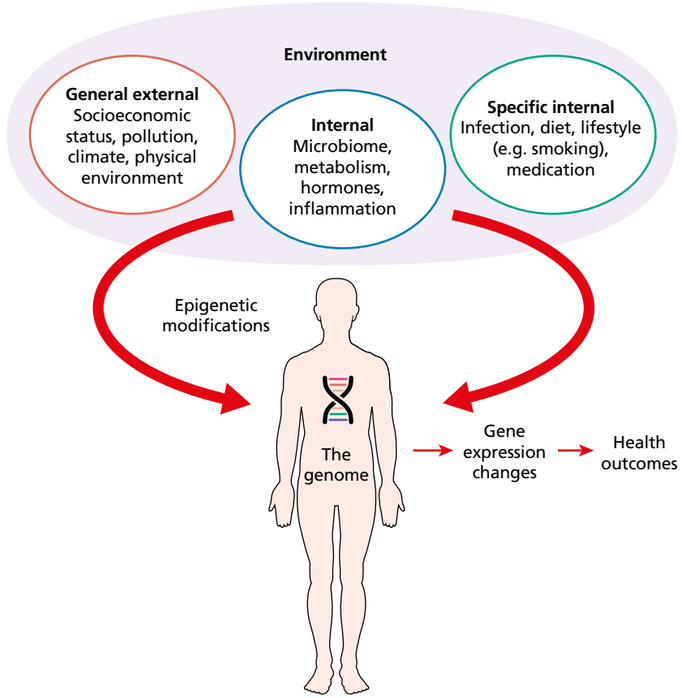

Figure 2 Interaction between the environment, the epigenome and the genome. Environmental factors such as diet, socioeconomic status, medication and lifestyle can be translated to the genome through epigenetic modifications

their lifetime from their conception, such as nutrition, pollution, hormones, medication and more, can be transmitted through epigenetic modifications. These can result in changes in gene expression and, ultimately, change an individual's health outcomes (see Figure 2).

Let's look at two of the main epigenetic modifications on a molecular level – DNA methylation and histone modifications.

DNA methylation and the epigenetic clock

DNA can be **methylated** at cytosine bases. This epigenetic modification typically results in **transcriptional repression**. A gene with methylated DNA bases is less accessible to transcription factors than a gene with no methylated bases, thus preventing it from being transcribed. Inactive (untranscribed) genes therefore tend to have more DNA methylation than actively transcribed genes.

In humans, patterns of DNA methylation are established early in development. Large regions of our genomes contain potentially harmful **transposons** that are kept inactive by methylation. As we age, our DNA methylation patterns change. Generally, ageing is associated with broad loss of DNA methylation. This means that those harmful transposons may become active and become a threat to genomic stability, increasing the risk of mutations and diseases, including cancer.

By looking at the DNA methylation of only 353 positions in the human genome, researchers can accurately predict the age of an individual and their life expectancy. Those with a DNA methylation age higher than their true chronological age have an increased risk of mortality, independent of lifestyle and pre-existing conditions.

We can think of our DNA methylation patterns as the defining point of our 'epigenetic clock'. The clock starts ticking when we are conceived, with a certain proportion of DNA demethylation across our genome. External factors can slow or speed up the loss of methylation. Researchers have shown that some lifestyle factors, including aspects of diet, can slow the epigenetic clock (maintain DNA methylation and a youthful biological age). Conversely, risk factors such as smoking can result in accelerated ageing, where our DNA methylation patterns indicate a biological age higher than that of our chronological age (see Figure 3).

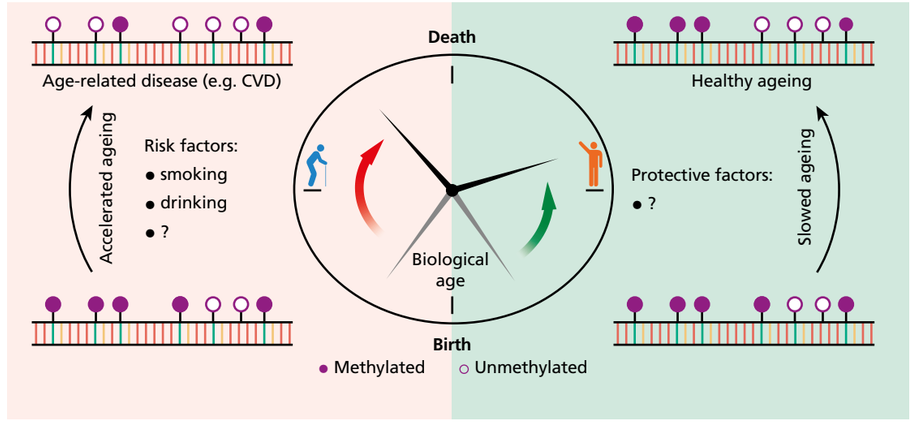

Figure 3 The epigenetic clock. Protective factors such as a healthy diet are thought to slow the epigenetic clock. Risk factors such as smoking and drinking are found to accelerate the loss of DNA methylation and result in increased risk of age-related diseases such as cardiovascular disease (CVD)


Leading a healthy lifestyle can help to prevent accelerated ageing

TERMS EXPLAINED

DNA methylation The addition of a methyl group (CH_3) to cytosine bases of DNA.

Epigenome The heritable network of chemical changes to DNA in the genome that do not affect the DNA base sequence itself.

Transcriptional repression Blocking the transcription of DNA to RNA and thus decreasing gene expression.

Transposon A DNA element, sometimes called a jumping gene, that can move around in the genome via a cut-and-paste mechanism.

Histone modifications

Histones are the small proteins around which DNA wraps to form nucleosomes (see Figure 1). Sticking out from each nucleosome are histone tails. These long, flexible ends of the histone protein can be chemically modified. Tagging histones with different chemical groups can upregulate or downregulate gene expression. For example, a histone tail tagged with an acetyl group (CH_3CO) blocks transcription and decreases gene expression.

A single histone tail can have multiple different modifications with different chemical groups. The combined effect of many histone modifications in a region of DNA works to regulate transcription. Some modifications open up the DNA, recruit transcription factors and turn genes on. Others may close the DNA off and turn genes off. This is known as the 'histone code' and, like DNA methylation, it changes as we age. Research on yeast showed that acetylation of different histones regulates age at replication. Some histone acetylation can be decreased by caloric restriction, which then turns on stress response genes including those involved in ageing and replication. Epigenetic signalling can therefore link diet and lifespan.

Lifestyle, ageing and disease

Ageing is an inevitable process. However, accelerated ageing has largely been associated with lifestyle and could perhaps be prevented and, to some extent, reversed. How environmental factors result in cellular changes associated with ageing and disease, and how these are inherited, is not clear. What is increasingly understood is that lifestyle factors of an individual in their early years have profound effects later in life. Childhood home conditions and father's occupation, for example, have been found to correlate with risk of disease in adulthood. Socioeconomic factors including nutrition, lifestyle and physical environment are at play.

In addition to the Dutch human famine study described earlier (see Box 1), studies in rodents reveal that communication between the environment and the epigenetic landscape begins from the point of conception. Maternal stress affects the intra-uterine environment and results in long-term effects on behavioural and health outcomes in adult rats. This is mediated through changes in lengths of the ends of chromosomes (telomeres) and DNA methylation in the developing brain where the relevant genes are expressed. Our epigenetic landscape is being shaped before birth, and can have consequences for health later in life.

Diet can modify our epigenetic landscape and affect the levels of microbes in our gut. In extremely long-lived humans who have aged healthily, there is an increase in diversity of gut bacteria with age. These can be sourced from our foods. One metabolite, trimethylamine N-oxide (TMAO), derived from animal-protein-rich foods such as red meat, is found in high concentrations in the blood of patients with age-related diseases. Low fruit and vegetable intake can also have detrimental effects on our gut and, as a result, our epigenetic landscape.

Since epigenetic changes are reversible, researchers hope to develop therapeutics to restore DNA methylation and types of histone modifications. These therapeutics may then pave the way to increasing a disease-free health span in humans. But there is no youthfulness pill on the market yet. The best way we can prevent accelerated ageing and promote a longer health span is through our lifestyle. An apple a day might really keep the doctor away!

FURTHER READING

'Epigenetics: why inheritance is weirder than we thought': www.youtube.com/watch?v=AvB0q3mg4sQ

'Lick your rats': https://tinyurl.com/y8dwxo8u

'Race against the ageing clock', Babraham Institute: https://tinyurl.com/y6pzxotz

KEY POINTS

- There are heritable changes in gene expression that can occur without changes to the base sequence of DNA – epigenetics.
- Changes in the environment can cause changes to our epigenome.
- As we age, our epigenetic clock is ticking and can be slowed through protective factors, or accelerated through risk factors.
- Epigenetics is important in the development of disease, and therapies targeting dysregulation of the epigenome are increasing.

Holly Kerr recently graduated in genetics from the University of Glasgow. After working at the Lighthouse Laboratory in Glasgow testing for COVID-19 in the summer of 2020, she started her PhD at the University of Edinburgh studying models of infectious disease.