EPIGENETICS RESEARCH AT THE BABRAHAM INSTITUTE

Stem cells and differentiation

'Pluripotent' stem cells are unspecialised cells that can be coaxed to develop into any cell type in the body, during a process known as 'differentiation'. They have a specific set of epigenetic marks that help to switch on genes and these are required for keeping the cells unspecialised and temporarily switch off genes that are required for later differentiation. A similar process happens as tissues form during development of the embryo.

In the body, specialised cells, such as skin cells, do not naturally revert back to pluripotent stem cells. However, in the lab we can reprogram adult cells to generate pluripotent stem cells by erasing epigenetic marks, triggering the activation of genes that are needed to make stem cells. This process is known as 'induced pluripotent stem cell' (or iPSC) reprogramming.

Babraham Institute research into how epigenetic marks are established and erased is improving our understanding of normal development and also how pluripotent stem cells can be generated more efficiently, which is a requirement for their use in 'regenerative medicine'. This holds the promise of repairing damaged tissues and organs by stimulating the body's own mechanisms to heal previously irreparable tissues or organs.

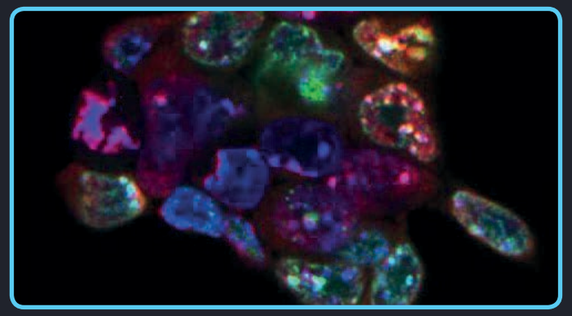
The Epigenetic Clock

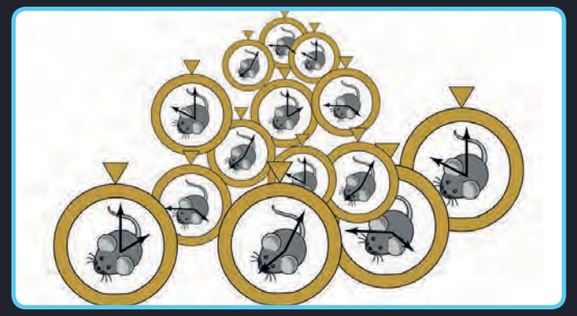
Changes in epigenetic information also underlie the process of ageing. During ageing in humans, DNA methylation at certain sites within our DNA changes in a predictable fashion, allowing us to estimate someone's age from their epigenetic information.

This 'epigenetic clock' predicts biological age rather than your actual (chronological) age, meaning that humans with certain diseases or unhealthy lifestyles may have an accelerated epigenetic clock.

Recent research from the Babraham Institute has shown that mice also have an epigenetic clock. A mathematical model was generated that can predict the age of a mouse with an accuracy of about +/-3 weeks. A high fat diet was also revealed to accelerate biological ageing in mice, according to this model.

This discovery provides us with a new way to study ageing in the lab, paving the way for novel research into ageing and ageing-related diseases.





Mouse embryonic stem cells (ESCs) stained for DNA (blue), DNA methylation (red) and DNA hydroxymethylation (green)

For more information on epigenetics please visit: www.babraham.ac.uk/our-research/epigenetics

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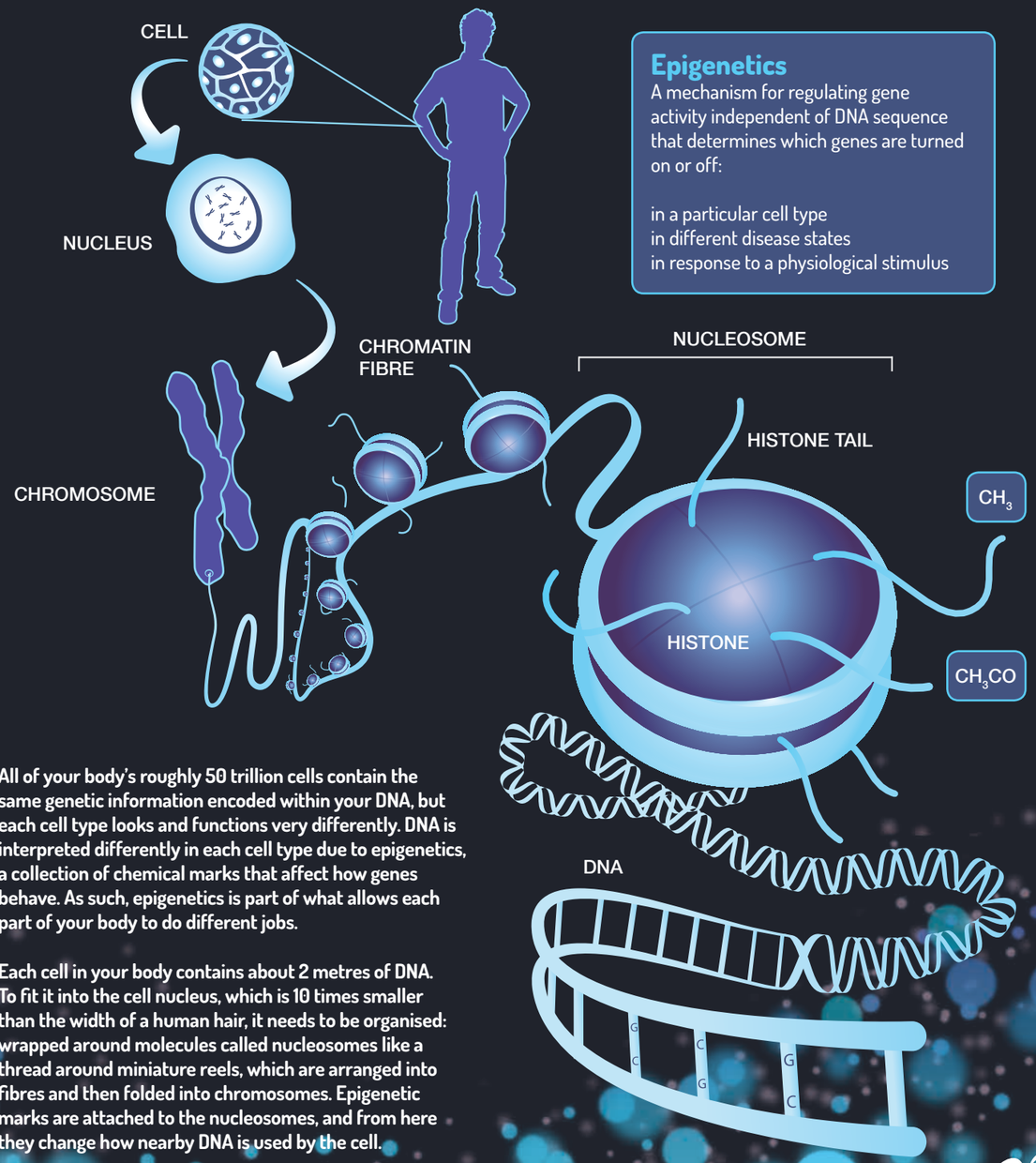
MAKING YOUR MARK

Exploring Epigenetics



Epigenetics
A mechanism for regulating gene activity independent of DNA sequence that determines which genes are turned on or off:

in a particular cell type
in different disease states
in response to a physiological stimulus

All of your body's roughly 50 trillion cells contain the same genetic information encoded within your DNA, but each cell type looks and functions very differently. DNA is interpreted differently in each cell type due to epigenetics, a collection of chemical marks that affect how genes behave. As such, epigenetics is part of what allows each part of your body to do different jobs.

Each cell in your body contains about 2 metres of DNA. To fit it into the cell nucleus, which is 10 times smaller than the width of a human hair, it needs to be organised: wrapped around molecules called nucleosomes like a thread around miniature reels, which are arranged into fibres and then folded into chromosomes. Epigenetic marks are attached to the nucleosomes, and from here they change how nearby DNA is used by the cell.

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EXPLORING EPIGENETICS

Each chromosome contains many genes which are sections of genetic instructions that contain the information that controls a cell's activity and that provides the blueprints to produce proteins. Each gene can produce RNA in a process called transcription. When the cell uses the information from the RNA this is called translation.

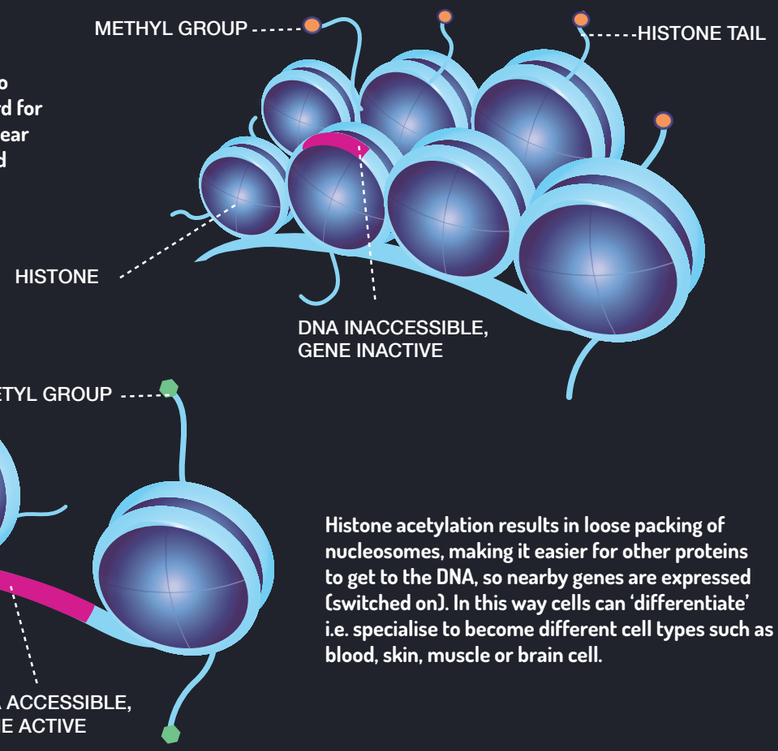
Epigenetic marks can be small chemical modifications (e.g. methylation) of the DNA or the histone proteins that make up the nucleosomes. They do not alter the DNA sequence, but affect how it is read to make RNA. Different histone marks affect how strongly DNA sticks to histones, making it more or less accessible. This in turn affects whether the gene is switched on or off. Each cell type has its own set of epigenetic marks, which act like a set of instructions to determine which genes are active and what the cell will do.

Scientists at the Babraham Institute are investigating how epigenetics can control our DNA to switch genes on and off at the right time in response to the right signals. This can have important consequences for our development, growth and long-term health. We can study epigenetic marks using a technique called Chromatin Immuno Precipitation sequencing (ChIP-seq)

What is a nucleosome?

Each nucleosome is constructed from eight histone proteins. Each histone has a globular 'blobby' shape with a 'tail' extending away from it. These tails can be modified with epigenetic marks - methyl (CH_3) or acetyl (CH_3CO) groups. The DNA is wrapped around the nucleosomes.

Methylation attaches methyl groups to histones, this can cause nucleosomes to pack tightly together. This makes it hard for the cell to read the DNA and so genes near methylated nucleosomes are repressed (switched off).



Histone acetylation results in loose packing of nucleosomes, making it easier for other proteins to get to the DNA, so nearby genes are expressed (switched on). In this way cells can 'differentiate' i.e. specialise to become different cell types such as blood, skin, muscle or brain cell.

To further understand the role that methylation and acetylation may play in controlling the transcription of genes, we want to know which marks are found near which genes in different cells.

How can we study epigenetic marks?

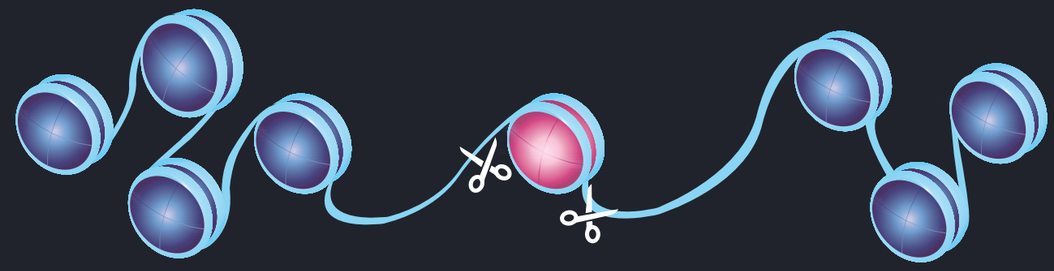
We use a technique called Chromatin Immuno Precipitation Sequencing (ChIP-Seq) in which the DNA is broken apart and specialised proteins called antibodies are used to filter out particular epigenetic marks. The DNA wrapped around the marked histones is collected and we can then analyse these sections of DNA on a sequencing machine.

The machine reads the genetic code of A's, T's, G's and C's that each piece contains. We use the code to identify where each piece of DNA came from and the gene it is part of.

RUN YOUR OWN ChIP-SEQ EXPERIMENT

Take a 2-metre paper strip – which represents the entire DNA sequence in each cell – and wrap it twice around each of the nucleosomes on the activity board in turn, working from left to right.

The part of the sequence wrapped around the pink nucleosome is the 'accessible' DNA.



Carefully cut the strip on each side of the nucleosome.

This represents the section of DNA associated with the particular epigenetic marks we are investigating, which in this example is H3K27ac, an acetylation mark. In the lab, the sections of accessible DNA would be separated from the whole sample using antibodies attached to magnetic beads.

Unwind your section of accessible DNA and compare it with the two sequences at the bottom of the board to discover which gene is being transcribed.

How do we find out what the results mean?

We have to break DNA into pieces so that we can sequence it and find out where epigenetic marks are. When we get the sequencing results back, we have to compare the sequences of these DNA fragments to how we know the DNA of a mouse or human (for example) looks. We then work out where our DNA fragments came from in the DNA, a bit like using the picture on a puzzle box to help us complete a jigsaw.

With applications such as Seqmonk, developed by the Babraham Institute's Bioinformatics Facility, we can visualise and analyse the data, which enables us to study gene activity and its relevance to development, ageing and ageing-related diseases.

Each dot in the diagram represents one sequence and indicates the position it came from originally. The first results or 'reads' are placed in the middle of the plot and as more reads come from the same place in the DNA, the stack of reads increases in height towards the top and bottom of the plot.

In this image the reads are selected based on the presence of a specific epigenetic mark, so we will get more reads where the mark is present in the genome, and fewer where it is absent. The larger stacks of reads show us the places in the genome where the mark was found most often. By studying where these are and how they change we can learn how the epigenetic mark is being used by the cell.