Background

What is epigenetics?

Epigenetics is the suite of processes that ensures that our cells, which all contain the same genetic material, behave appropriately, so that a liver cell, for example, behaves as a liver cell and not as a brain cell.

Epigenetic mechanisms do this by marking genes for activity or inactivity and by consigning some genes to a condensed, inactive state in which they are wrapped tightly with proteins called histones.

In a liver cell, genes for healthy liver function are active while other genes, not required to make a liver cell work, are inactivated. Because descendent liver cells inherit this epigenetic state, they also behave as liver cells.

Humans have hundreds of cell types, wide ranges of activity of each cell type and, not least, there are billions of us on earth, so it has been extremely difficult to describe what a 'normal' or healthy epigenetic profile might look like.

Researchers in the BLUEPRINT project have focused on one tissue — blood — to reduce this challenge and then standardised the ways in which they examine and report their results. The outcome is a growing body of descriptions of how the human genome can make blood cells, how they develop into different types and what epigenetic changes occur to cause disease such as cancer and autoimmune disease.

Our human genome is a stable, archival copy of instructions, present in all cells, that is required to build a person. The epigenome is part of the dynamic and plastic machinery to interpret those instructions so that each cell type — liver, lung, gut, brain and the other 200 or so cell types — behaves as it should. When this control fails, the rogue cell can cause disease.

The epigenome marks some genes for inactivity and lifts others from dormancy. It does this in several ways, including tagging precise regions of the DNA code with a chemical that can change activity, or by wrapping genes up with proteins called histones that, when tightly packed together, prevent gene activity.

Although only infrequently inherited from one generation to the next, the epigenetic state of a cell is inherited by its descendants, so that, say, a liver cell's descendants also behave as liver cells.

Researchers in the BLUEPRINT project have studied one tissue in detail: they looked at blood, which is readily obtained either from healthy volunteers or from diseased individuals and which underlies many human diseases. Blood also encapsulates an elaborate series of developmental decisions, as stem cells in bone marrow and other locations follow pathways to become red blood cells, immune system cells or components of the blood-clotting system.

From a fertilised egg to the one hundred million cells that comprise a human adult, the genomes we inherit from our parents remain unchanged[1]. Each cell contains an identical genome, yet gut cells and brain cells make different proteins, have different shapes and respond to different stimuli.

[1]There are a few exceptions: red blood cells contain no DNA, because the nucleus is expelled as they mature (hence their short lifespan and hollowed shape), and some cells of the immune system rearrange parts of their genome to produce antibodies more efficiently. Importantly, our cells also contain efficient repair mechanisms to protect the sequence of our inherited genomes.

These differences are founded in different activity of different genes in specific cell types, a property that is shared by similar cells and inherited by descendent cells. The stability of gene activity is imposed in part by epigenetic changes to the genome.

A number of mechanisms modify the epigenetic state of a cell. One of the bases in DNA — cytosine (C) — can be modified by addition of a methyl group: when this occurs in cytosines near the start of a gene, it commonly reduces the activity of that gene. Detailed examination of methylC bases is an important tool in epigenetics research and in clinical diagnosis and prognosis.

DNA is normally associated with structural proteins, some of which can also play a regulatory role. Four classes of histone proteins form a repeated, beaded structure called a nucleosome around which the DNA is wound. If histone proteins in a gene region are modified, then activity of the associated gene can be altered in a cell and in its descendants.

Until recently, it was extremely difficult to test epigenetic markers in a single genome. More important, it was more challenging to survey many genomes.

Yet, to understand the role of epigenetics fully, these were precisely the challenges faced by researchers in the BLUEPRINT project. DNA technologies, data systems and analysis tools of today have made the almost impossible achievable: BLUEPRINT researchers have made the data of more than 1000 experiments publicly available.

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About BLUEPRINT

The project *BLUEPRINT – A BLUEPRINT of Haematopoietic Epigenomes* is a large-scale research project receiving close to €30 million euro funding from the EU. 42 leading European universities, research institutes and industry entrepreneurs participate in what is one of the two first so-called high impact research initiatives to receive funding from the EU. For more information, please visit:
http://www.blueprint-epigenome.eu

Contact Information

Prof. Dr Hendrik Stunnenberg, Coordinator of BLUEPRINT
Radboud University, Department of Molecular Biology, Faculty of Science
h.stunnenberg@ncmls.ru.nl
Phone +31 24 3610524

Dr Marion Bussemakers, Project Manager of BLUEPRINT
Radboud University, Department of Molecular Biology, Faculty of Science
m.bussemakers@ncmls.ru.nl
Phone: +31 24 3615157