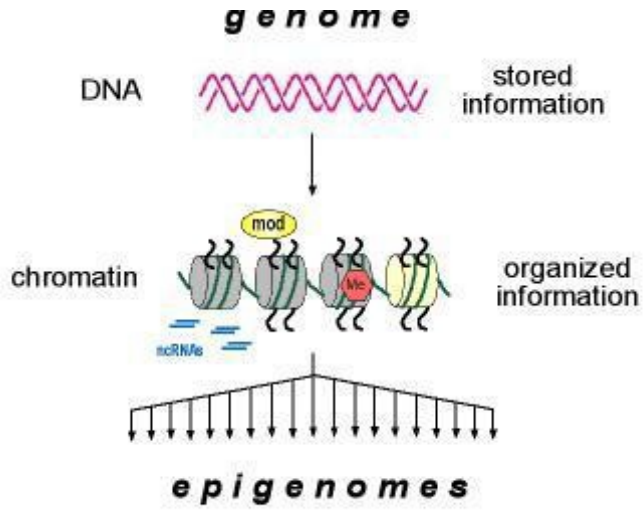
Healthcare industry BW

Genes and epigenetic mechanisms

The different cell types in a multicellular organism contain the same genome but differ from each other dramatically in both function and structure (nerve cells, kidney cells, etc.). The differentiation of the cells is linked to the identity of their precursors. This then raises the question: If the cells' destiny is not encoded in the DNA, how do they know what to become? The new director of the Max Planck Institute of Immunobiology in Freiburg, Professor Dr. Thomas Jenuwein, and his colleagues from the Department of Epigenetics are investigating the molecular mechanisms of epigenetic cell memory.

You are what you eat. Well, almost, but not quite. A mother's diet can affect the development of her children. For example, if mice of a certain mouse strain are given a diet that is rich in methyl-bearing compounds such as folic acid or vitamin B12, their offspring's coat will be brown rather than yellowish. Is it therefore safe to assume that the diet of the parents leads to changes in the DNA sequence of genes, which are then inherited by the next generation? In fact, it isn't. The cells of the mouse embryos need to have received the information about the dietary history of their progenitors through something else. This "something else" is referred to as epigenetic information.

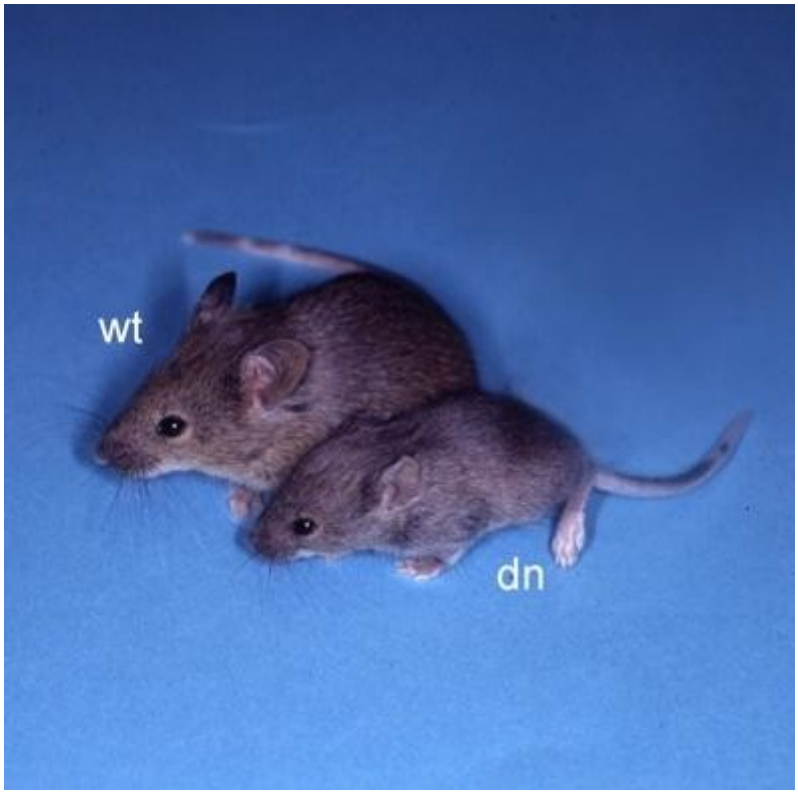
"The idea of epigenetics is actually very simple," said Thomas Jenuwein, director of the Max Planck Institute of Immunobiology in Freiburg and head of the emerging Department of Epigenetics since autumn 2008. "In addition to the DNA sequence, there is some kind of information that mediates the way the genetic code is transcribed and subsequently translated. This additional level of information comes from the chromatin, and not the naked DNA." The human genome is a thread about two metres long which has to be squeezed into a nucleus of only a few micrometres in diameter. And this can only be achieved when the DNA is tightly packed. The chromosomal DNA is wrapped around the nucleosomes, which consist of so-called histone proteins. The combination of long DNA molecules and proteins in the cell nucleus is what scientists call chromatin. The packaging of chromatin is regulated by the cell in order to control which genes are accessible to transcription enzymes that produce mRNAs for subsequent protein biosynthesis. Loosely packed chromatin enables the transcription of the genes whilst tightly packed chromatin prevents transcription.



In the cell nucleus, DNA (top) is arranged as chromatin (bottom), an assembly of nucleosomes (grey) and proteins. The organisation of the DNA can be influenced by histone modifications (yellow), methylation (methyl groups attached to the DNA; red) or non-coding RNAs (blue).

Agonists and antagonists

The packaging of the chromatin is therefore an important transcription control mechanism. Every cell in the human body has about 25,000 genes, of which only 8,000 to 9,000 are active. Neurones do not need certain proteins required by the liver and, vice versa, liver cells do not need the constituents required for producing synapses. A cell-specific programme determines which genes will or will not be transcribed. This programme is epigenetic in nature and remains effective even when the molecules that have switched it on have long since disappeared.



Mice lacking both histone methyltransferase genes (dn=double nil) are smaller than wild-type mice (wt) and have reduced survival rates.

But which molecular mechanisms determine whether the chromatin is tightly or loosely packed? In 2000, Jenuwein with his then colleagues at the Institute of Molecular Pathology in Vienna, Austria, discovered an enzyme that is able to add a methyl group to one of the histones (H3). The researchers called this enzyme histone methyltransferase (HMTase). Jenuwein's former doctoral student who is now his scientific coordinator, Monika Lachner, went on to discover that the methylated histone becomes a binding site for heterochromatin protein 1 (HP1). If HP1 binds to this binding site, then the specific chromatin region around this particular histone condenses and becomes inaccessible to transcription enzymes.

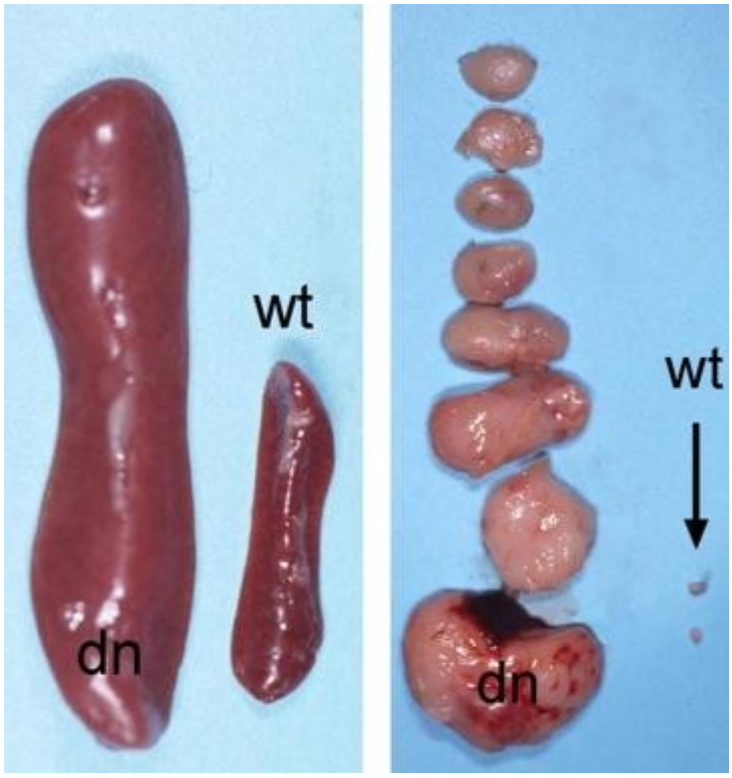
"We had discovered a mechanism that led to the tightening and hence inaccessibility of chromatin," said Jenuwein. The antagonist of the HMTase enzyme, the enzyme histone acetyltransferase (HAT) which adds acetyl groups to histones, had been known since 1996. HATs lead to the loosening of the chromatin structure and make the genes accessible to the transcription machinery. Nowadays, epigeneticists know of several more mechanisms that control transcription. For example, non-coding RNAs can prevent the expression of genes, and methyl groups can be added to the DNA. This mechanism leads to the brown coats of mice whose mothers live on a methyl-rich diet. The degree of methylation of the agouti gene affects the coat colour in mice. If the mother takes up a large quantity of methyl molecules, then the agouti gene becomes highly methylated and switches off.

An area with a promising future

The Max Planck Institute in Freiburg is the first institute in Germany to establish a department that is entirely devoted to epigenetic mechanisms. Alongside Jenuwein's work, the epigeneticist Asifa Akhtar will also coordinate a research project, starting in summer 2009. Akhtar is an expert in dosage compensation in Drosophila, a genetic regulatory mechanism that doubles the transcription rate of genes on the X chromosome in males so that they are equally expressed in males and females, who have two X chromosomes. Following her post-doctoral period, Akhtar successfully established a research group at the EMBL in Heidelberg. In addition to Jenuwein's and Akhtar's groups, there will be five other junior researcher groups working on epigenetic mechanisms.

Jenuwein's team is part of the European Epigenome Network of Excellence (Epigenome NoE) which was established by Jenuwein himself along with Geneviève Almouzni from the CNRS Institut Curie in Paris and Phil Avner from the CNRS Institut Pasteur in Paris. The consortium brings together another 24 groups, 26 associated members and 12 newly established teams from a number of European countries. The network is based on the idea that well known researchers apply for third-party funds and then pass on a part of these funds to young researchers, thereby giving creative young scientists access to scientific careers. All the groups work closely together. The NoE also has an online presence, where it maintains the www.epigenome.eu website for the general public and the www.epigenome-noe.net for the scientific community.

Jenuwein is trying to find out whether there is an epigenetic code. How many histone modifications are required to induce the tightening or loosening of the chromatin? And where do these modifications need to be made? He also wants to find out how epigenetic memory works. Which proteins are involved? When do they remain permanently bound to gene segments? The answers to



Mice lacking the two histone methyltransferase genes often develop lymph cancer. Their spleen (picture on the left, dn) is larger than that of wild-type mice (picture on the left; wt). Their lymph nodes (picture on the right) are also larger that those of wild-type mice.

these questions could be significant for the field of human medicine. If the researchers were able to understand how cells determine their identity, i.e. how they choose whether they become muscle or liver cells, then it may be possible for the scientists to reverse the process and turn the cells into stem cells. "Epigenetic transcription regulation also plays an important role in the development of cancer where the transcription rate of certain genes has become out of control," said Jenuwein.

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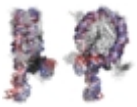

Epigenetics – heritable traits without changing the DNA sequence