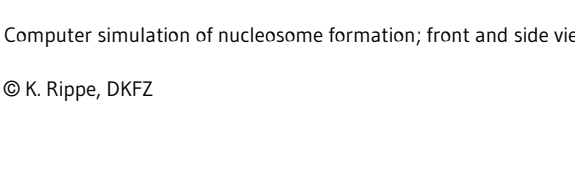
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Epigenetics – heritable traits without changing the DNA sequence

Epigenetics, i.e. the inheritance of traits that does not involve a change in the DNA sequence, was once a controversial subject that has since become a central focus of biological research. Epigenetic inheritance is now studied by numerous national and international research programmes. Many cellular regulatory and differentiation processes are controlled by epigenetic mechanisms that take place on different levels, including the DNA, histone, nucleosome and chromatin folding levels.



Computer simulation of nucleosome formation; front and side view.

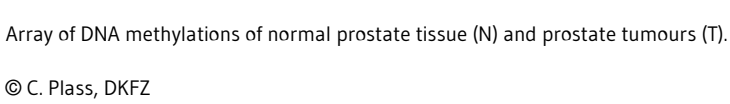
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Over the past decades, epigenetics has evolved from a highly controversial phenomenon – accepted at best as a bizarre anomaly – to a focal point of cellular and molecular biology research and there are now hundreds of scientific publications about it every year. Researchers have discovered epigenetic mechanisms in nearly all cells studied. These mechanisms play a key role in cellular regulatory mechanisms, control fundamental processes of cellular differentiation and contribute to natural diversity as well as playing a key role in the development of individual organisms from embryogenesis to ageing processes and death.

Epigenetics is the passing on of modified gene functions to subsequent generations without changing the underlying DNA sequence. Epigenetic modifications can be triggered by environmental factors. The bitter scientific disputes that previously raged about epigenetic inheritance were primarily due to the fact that epigenetic traits are not only passed on to daughter cells by normal cell division (mitosis), but also to germ cells by way of meiosis, and hence to subsequent generations.

This means that the hard-won victory of Darwin's Natural Selection Theory over Lamarck's Theory of Inheritance of Acquired Characteristics in the 20th century has to be put in perspective, and the supposedly insurmountable barrier between germline inheritance (egg cells and sperms) and soma (body cells) is broken down. It would appear that highly developed organisms such as mammals have a particularly complex range of epigenetic mechanisms.

The different levels of the epigenome



Array of DNA methylations of normal prostate tissue (N) and prostate tumours (T).

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Epigenetic modifications take place at different organisational levels that overlay the DNA base sequence, the level of classic genetic code and gene modifications caused by mutations. All epigenetic changes together constitute the epigenome. One of the most important epigenetic regulatory mechanisms is the transfer of a methyl group to the DNA base cytosine by enzymes called methyltransferases. The methylation prevents the DNA sequence from being transcribed. Such methylations are only possible – at least in humans and other mammals – when a guanine (G) follows a cytosine (C). Such CG sites occur in the human genome around 30 million times; a large part of the CG sites is methylated. Cancer cells usually have a vastly different methylation pattern from that of normal cells. In some cases, cancer may be due to the silencing of tumour suppressor genes (such as p53) through methylation, in others, cancer develops as a result of missing methyl groups.

Histone proteins are the second level at which epigenetic modifications can take place. Eight histone proteins form the core of nucleosome, around which a DNA segment (147 base pairs) is wrapped. Chemical groups such as acetyl, methyl, phosphate or ubiquitin moieties can be attached or removed from the amino acid tails that extend from the nucleosomes, resulting in a change of packing density of the DNA and modulation of the activity of genes affected by these changes. The modification pattern of the histones is passed on to daughter cells during mitosis and is one of the fundamental mechanisms that governs the differentiation of body cells. All epigenetic histone modifications taken together and their function are referred to as histone code.

The nucleosomes and the DNA-protein complexes are folded through a number of higher-order structures into the chromatin fibres of the chromosomes, DNA sequence regions far from one another can end up side by side, enabling them to interact.

These effects can also be passed on to the next generation. It has turned out that the position of the centromeres, DNA regions to which spindle fibres attach during mitosis, is controlled by epigenetic mechanisms rather than by the DNA sequence. The spindle fibres attach to a histone variant called CenH3, which is only found in the nucleosomes of centromeres. The overproduction of CenH3 leads to abnormalities in the spindle apparatus and faulty cell divisions. This leads to severe developmental disorders and is often also characteristic of cancer cells.

Environmental effects and their inheritance

Position of histone CenH3 (red) in the chromosome centromeres (blue).

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It is nowadays basically undisputed, and has been shown in animal experiments, that the pattern of epigenetic change in genes can be induced by the environment and passed on to the offspring, although, for obvious reasons, watertight direct evidence cannot be provided for humans. However, plenty of convincing indirect evidence is available. Long-term observations have shown that severe famine experienced by pregnant women not only affects the health of the unborn baby, but also that of the grandchildren. A similar transfer of experiences from fathers to sons and grandsons has also been shown.

The epigenetic programming of organisms already occurs during early embryonic development. It has been shown in mice that unborn embryos are particularly sensitive to environmental stimuli. This is certainly also true for humans. Children of mothers who have experienced massive domestic violence during pregnancy often reveal epigenetic changes in the gene coding for the glucocorticoid receptor that controls the signalling pathway of the stress hormone cortisol.

The heat shock protein Hsp90 is also assumed to play a crucial role in linking environmental factors with the epigenome. Hsp90 is important for the functional integrity of signalling proteins that enable communication between cells. Hsp90 is a so-called chaperone that helps proteins assume and retain their correct conformation. It is present in virtually all organisms and is increasingly formed in cells in stress situations (e.g., elevated temperature). Other intensively researched candidates of epigenetic regulation are microRNAs, which play a key role in genetic regulation, particularly gene silencing. Regulatory inactive methylated microRNAs have been identified in cancer cells.

The mechanism that underlies the inheritance of epigenetic factors to the offspring following meiosis is still unknown. It appears that the relevant information is at least partially passed on by way of egg cell fertilisation through the sperm cell. After several fertilisation processes and meiotic divisions, epigenetic information seems to be progressively lost. However, there are known examples from the animal and particularly the plant kingdom that are induced by chemicals, food, bacterial infections, high temperatures, radiation and other environmental stimuli and that are stably passed down through many generations.

Epigenetics - a major research priority

The importance of epigenetics in the modern life sciences is reflected in the large number of university, national and international research programmes. There are very few researchers not involved in at least one research programme that touches on epigenetic research. One of the major programmes focusing on epigenetic phenomena is the multinational Human Epigenome Project, which is the sequel to the Human Genome Project. It is led by the International Human Epigenome Consortium (IHEC) and German scientists contribute collectively through the German Epigenome Programme (DEEP), involving numerous institutions including the German Cancer Research Center (DKFZ) in Heidelberg and the Freiburg-based Max Planck Institute of Immunobiology and Epigenetics (MPI). Prof. Dr. Thomas Jenuwein, who established epigenetics at the Freiburg-based Max Planck Institute, which has since changed its name to reflect its work, previously also headed up the European Epigenome network of excellence. Its successor, the EpiGeneSys network of excellence is funded under the EU's 7th Research Framework Programme and focuses primarily on the connection between epigenetics and systems biology. The MPI, Freiburg University and the Freiburg University Medical Centre have established a collaborative research centre on medical epigenetics that covers basic research as well as clinical application projects. The CancerEpiSys consortium is funded by the BMBF and is specifically focused on research into cancer-related epigenetic modifications. This consortium also involves researchers from Heidelberg and Ulm. The molecular analysis of tumours at the DKFZ not only involves the complete genome sequence, but increasingly also the epigenome.

Dossier

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Dr. Ernst-Dieter Jarasch
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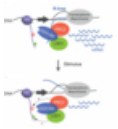
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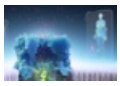
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