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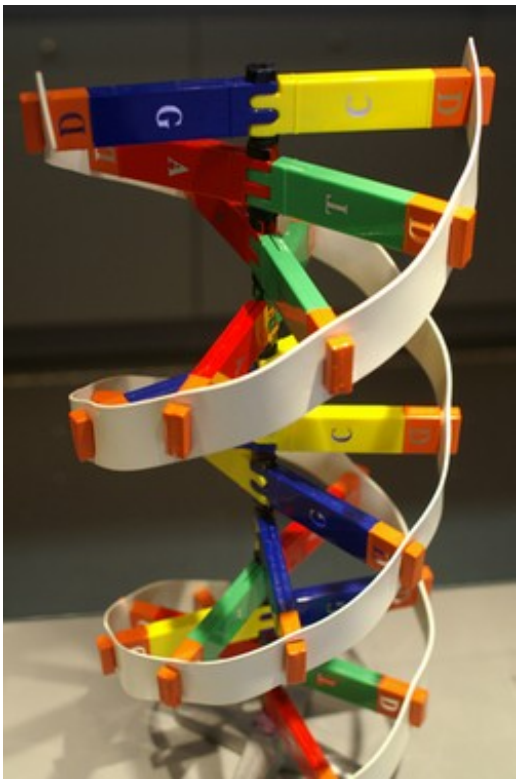
DNA – from Watson and Crick to modern molecular biology

Watson and Crick deciphered the structure of DNA around 60 years ago and thus provided the key to understanding how genetic information is passed on. Since this discovery, which laid the foundation for molecular biology, new insights and developments have significantly changed many research areas and have also found their way into our everyday lives. DNA sequencing, genetic fingerprinting or personalised medicine – Watson and Crick's heritage is omnipresent.



Thanks to Watson and Crick, we are aware of the structure of the DNA double helix as shown in the simplified model. © Bächtle/BIOPRO

In simple terms, deoxyribonucleic acid (DNA) is the stuff that genes are made of. The highly specialised biomolecule is impressive with its simple but powerful structure that winds around itself and which was discovered by James Watson and Francis Crick in 1953. The scientists were later awarded the Nobel Prize in Physiology or Medicine. Their model enabled them to explain the molecular structure of nucleic acids, and also pinpoint DNA as the carrier of genetic information.

Although many researchers around the world had focused on DNA before, Watson and Crick were the discoverers of the famous DNA double helix. In the years subsequent to their path-breaking discovery, numerous Nobel prizes were awarded for the discovery of restriction enzymes and for the development of DNA sequencing or PCR, techniques without which modern molecular biology would be inconceivable.

Today, the range of possibilities for the analysis and manipulation of DNA seems limitless. The basic features of the mechanisms of replication and translation are widely known and can be specifically manipulated in the laboratory to produce genetically modified organisms, to name but one example. The analysis and manipulation of DNA have thus become standard tools for biologists.

Deciphering the genetic code

The ability to sequence DNA represents another milestone in DNA research. The Sanger sequencing method, also known as dideoxy sequencing, was originally developed by Frederick Sanger for the sequencing of RNA, but soon became the most widely used DNA sequencing method. Sanger's classical enzymatic chain-termination method was awarded the Nobel Prize in Chemistry in 1980 and remains in wide use, albeit in a slightly modified form. Cutting-edge sequencing methods, which are known as "next-generation sequencing", allow a greater throughput by parallelising the sequencing process and producing millions of sequences concurrently. Pyrosequencing is one of the "next-gen methods". It relies on the indirect detection of the activity of the enzyme DNA polymerase, which enables the highly parallel analysis of DNA samples. Another next-gen method is sequencing by hybridisation which involves the determination of the DNA sequence by hybridising DNA fragments to a nucleotide matrix on a glass carrier.

The Human Genome Project, which set out to determine the sequence of base pairs that make up the human genome in 1990, took 13 years to complete. Human genomes can now be sequenced in as little as six weeks. So-called 3rd generation sequencing methods have since supplanted the 2nd generation sequencing methods, and enable an even greater throughput and help reduce the time to result and costs. 3rd generation sequencing involves the real-time sequencing of single DNA molecules without needing to amplify the DNA using PCR.

Despite the huge impact of the Human Genome Project, it did not provide insights into the function of the entire set of human genes, as the interaction of genes and their regulation is much more complex than initially anticipated. Nevertheless, the new sequencing methods have opened up unforeseen possibilities, especially in the field of medicine. Some human diseases can already be diagnosed on the basis of their DNA sequence and therapies can be tailored to the specific genetic characteristics of the person being treated. In the field of medicine, the diagnosis and personalised treatment of tumours play a major role because the underlying cancer-causing mutations can vary greatly between tumours of different tissue and cell types and between individuals with the same tumour. These genetic characteristics may have a huge impact on the efficacy of anti-cancer drugs. Scientists around the world are therefore focused on identifying predictive biomarkers that help in selecting the right drug for an individual patient.

Genetic fingerprinting – genetic information as forensic evidence

DNA has not only become an integral part of science and medicine, courts of law have also long admitted DNA test results as evidence. A genetic fingerprint is produced from a sample of DNA that

can for example come from blood or hair. PCR has the advantage that even tiny samples are sufficient and is used to detect the length of short tandem repeats. This is done by amplifying specific non-coding, short tandem repeats like TATATA… or TACTAC… that are repeated numerous times. The number of copies of the repeat element, and hence the length of the DNA fragment under investigation, varies greatly between individuals. Forensic science normally looks at the profile of 8 to 15 loci, which gives a nearly unique band pattern (ed. note: following the electrophoretic separation of the PCR fragments) that statistically occurs in only one out of several billion people. Although genetic fingerprinting is unable to provide a 100% accurate statement as to whether a suspect is the actual offender, it still achieves a very high likelihood of discrimination. PCR-based genetic fingerprinting is also used for parental testing to determine whether a man is the biological father or a woman the biological mother of a child. The test determines whether there is at least one match between the child's and the alleged father's/mother's alleles under examination, as the child receives one allele from the father and one from the mother.

DNA nanotechnology: DNA as molecular construction material

Schematic representation of a synthetic DNA-based lipid membrane channel that is the result of specifically designed DNA nanostructures. © Hendrik Dietz, Friedrich Simmel/Technical University of Munich

Over the last few years, DNA has been emerging as a building material for the assembly of nanostructures rather than as a carrier of genetic information. The new DNA nanotechnology research discipline takes advantage of the strict base pairing rules underlying the formation of DNA double helix structures, which means that only complementary nucleotide sequences bind to each other. This enables the design of nucleotide sequences that will selectively assemble to form defined structures such as DNA tubes or grids or even functional units, so-called molecular machines that can exert movement.

All this is possible due to the base-pairing properties of DNA that ensure that so-called sticky ends – protruding single-stranded regions – have nucleotide sequences that form base pairs with complementary single-stranded regions. This opens up numerous applications in the field of nanotechnology. Using sticky ends enables DNA grids to bind specifically to a specific target molecule and be used as sensors. Another vision is the development of biological computers and the use of DNA as digital data storage device. This would appear to be a good idea as DNA storage systems can be more densely packed with data and are hence more compact than any hard drive storage systems. Our genetic information is so densely stored in the four bases that it fits into all our body cells. Researchers have already encoded a selection of books in artificially produced DNA segments and thus provided evidence that it is possible to store huge volumes of data in DNA. However, the method is still far too expensive for broad application.

Article

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Bettina Baumann
BioLAGO

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DNA and RNA replication