Cora Mund and Verena Beier

THE INTERPRETATION OF GENETIC INFORMATION

We inherit our genetic make-up from our parents in the form of the DNA sequence. But not all information regarding which genes are to be transcribed and which are not is passed on from one generation to the next. Epigenetics is concerned with such mechanisms "outside" of the DNA sequence. Epigenetic information is acquired in the course of a lifetime. A central epigenetic mechanism is DNA methylation. This process usually occurs on a cytosine (C) which is immediately followed by a nucleotide with the base guanine (G). Although the sequence CG does not occur very often in the human genome, there are certain regions where there is more frequent incidence. They are defined as CpG islands. If such islands are methylated in the promoter region of a gene, it can no longer be transcribed. The CpG islands thus work like a switch. "The DNA methylation pattern represents the epigenetic program of the genome and determines the interpretation of genetic information. Differences in methylation generate differences in the expression pattern," explains Dr. Jörg Hoheisel, coordinator of the Systematic-Methodological Platform (SMP) Epigenetics of the German Cancer Research Center (DKFZ).

DECIPHERING THE METHYLATION CODE

Certain methylation patterns are associated with the appearance of different illnesses. With cancer, for example, a strong methylation of tumor suppressor genes can frequently be observed. "We know that changes in the DNA methylation patterns belong to the earliest and most frequent events in the development of cancer. Nevertheless, still very little is known how these changes arise and exactly what role they play in the degeneration of a cell," says Professor Hermann-Josef Gröne, who oversees the tumor database at the DKFZ in Heidelberg and who also works in the SMP Epigenetics. Furthermore, often there is not any information about how the methylation pattern differs in healthy and diseased tissue. "And this knowledge could be useful for the diagnosis and prognosis of diseases or for the development of new therapies," he says. One reason for the knowledge gap is the lacking methodology: Until now the scientists have not had any tools at their disposal for a genome-wide epigenetic analysis. The researchers at the SMP Epigenetics intend to change this.

MICROARRAYS FOR METHYLATION PATTERNS

Jörg Hoheisel explains the selected approach: "Using a trick, the methylation status of a nucleotide can be represented as single nucleotide polymorphism (SNP). That is why we plan, analogous to the microarrays that search the genome for SNPs, to use microarrays also for a genome-wide and gene-specific analysis of the methylation pattern." The genome researchers then want to correlate the gained information to clinical data and the results of the transcription analyses.

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Using this method, fundamental insights into the role of DNA methylation during tumor development should be possible. In addition, Jörg Hoheisel and his colleagues want to identify methylation patterns that allow diseases to be diagnosed and their prognosis to be assessed. Likewise, the scientists hope that the methylation pattern will also give an indication how effective a medication is.

COMPETENT PARTNERS

The SMP Epigenetics includes both research institutes and private companies. All participants can already look back on several years' experience in the field of epigenetics. One example for the cooperation of research institutions and industry is located at the University of Bonn. Here Dr. Andreas Waha has developed a microarray that contains 7,680 CpG islands of the human genome and which can be used to study epigenetic changes of the genomic DNA. One objective of his project is to extend the microarray so that all CpG islands of the human genome can be analyzed. In particular, he plans to identify all tumor-relevant CpG islands. To accomplish this, he is supported by the Berlin company Epigenomics, which is the leader worldwide in the commercial use of epigenetics. Researchers of the DKFZ, together with the company febit biotech are developing microarrays which are suitable for routine analyses of the methylation pattern. They, too, are focusing on sites that are typical for cancer diseases. DNA methylation analysis has several characteristics which make it an ideal candidate for routine applications. DNA is a relatively stable molecule and thus easier to handle than for example RNA, which is analyzed in transcription studies. Moreover, the regulation mechanisms act much more slowly with reference to the methylation status than regulation mechanisms on the transcription level. The moment the sample is taken is therefore less critical. Another advantage is that the methylation signals "on" or "off" can be digitalized from the very beginning and thus are excellently suited for evaluation at the computer. Within the framework of the SMP, scientists not only undertake a targeted search for significant patterns, but also gather fundamental information about the methylation status of a chromosome, quasi as standard for later studies. This takes place in a coordinated approach between Professor Jörn Walter (University of Saarbrücken), Professor Albert Jeltsch (International University Bremen), Dr. Richard Reinhard (Max Planck Institute for Molecular Genetics, Berlin) and Dr. Matthias Platzer (Leibniz Institute for Age Research – Fritz Lipmann Institute, Jena).

FIRST SUCCESSES

Jörg Hoheisel's team has already taken a first step in establishing genome-wide microarrays in collaboration with the Epigenetics Division of the DKFZ headed by Dr. Frank Lyko. In the scope of a project carried out to prepare their joint work in the Systematic-Methodological Platform, the scientists designed an oligonucleotide microarray with which they can also determine parallel the methylation status of 53 cytosines in the promoter region of a gene. Project team member

Cora Mund

Cora Mund is delighted: "While investigating the methylation status it is possible for the first time to combine a high-throughput with a high resolution." With the previous methods, only the methylation status of merely a few cytosines of a gene could be determined. Next, the Heidelberg scientists want to expand their method: Currently they are working on a chip to ascertain the methylation status of 250 genes which play a role in prostate cancer. "We are convinced that with epigenetic analyses we can provide reliable results that are suitable for routine applications," Jörg Hoheisel explains. "We expect a lot from epigenetics especially for cancer research."

References

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