

PROJECT LEADER

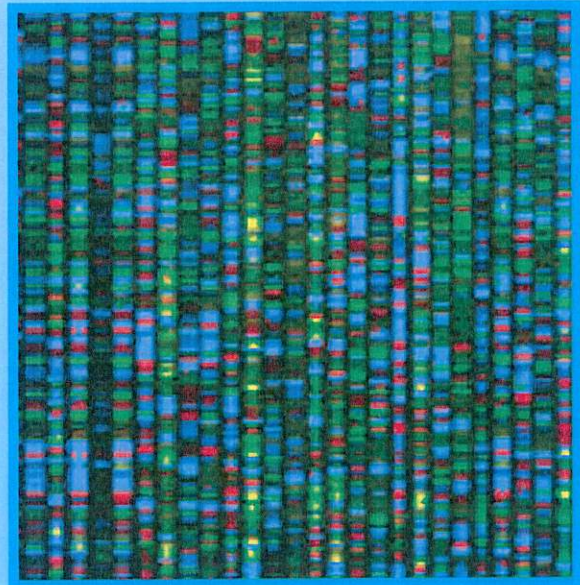
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HEALTHY DESPITE HIV

» In some people an effective protection against AIDS (Acquired Immune Deficiency Syndrome) is encoded in their genes. Even more than ten years after the infection with HIV (Human Immunodeficiency Virus), the disease does not break out in these patients. Only extremely small quantities of the virus can be found in their blood – a sign that it hardly replicates at all. "This knowledge should make us hope. We must find out what factors are holding the virus in check in these people. Perhaps that is an important step in the struggle against AIDS", says Dr. Matthias Platzer, head of the Explorative Project "Genomic Variability of Host Factors in the AIDS Macaque Model – Role in Resistance to and Disease Course of Viral Infections in Humans and Non Human Primates" at the Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI) in Jena.

An interdisciplinary team is now searching for the crucial genes in the rhesus monkey. The team's members include the immunologist and virologist Dr. Ulrike Saueremann and Professor Gerhard Hunsmann of the German Primate Center in Göttingen, the Kiel mathematician Professor Michael Krawczak, the genetics professor Peter Nürnberg of the University of Cologne and the microbiologist Dr. Roman A. Siddiqui, who also works at the FLI in Jena. In Rhesus monkeys the SI-Virus (Simian Immunodeficiency Virus) elicits an immune deficiency which is very similar to the human HIV infection. Since some of these animals do not develop an AIDS-like disease after infection, they are an ideal model for researching resistance mechanisms. "The monkey model gives us the advantage of having a great deal more data about the infection, for instance the kind and time of the transmission, the quantity and type of the infectious virus and the complete course of the disease. Above all, we know the personal and familial medical history of the infected primates. Such data are very valuable for systematic studies and are never available for humans," Matthias Platzer adds.



DNA sequencing

The NGFN researchers are searching through the entire genome of the infected primates. They are looking for genetic markers which only occur in resistant animals. Using these markers they can limit the areas in the genome that make survival possible after such an infection. Sequencing these DNA segments should then identify the particular factors in the genome, which protect resistant monkeys from falling ill. The results of the search will be entered into a database made available by the genome networks Infection and Inflammation and Environmental Diseases. The cooperation with the competence network HIV/AIDS in turn ensures that the results gained in the animal model are quickly incorporated into human AIDS research.



ALTERNATIVE mRNA SPLICING: MORE INFORMATION FROM FEW GENES

» How can a complex organism like the human being function with only about 30,000 genes? After all, even the simple nematode worm *Caenorhabditis elegans* has about 19,000 genes. One answer is alternative mRNA splicing. Probably more than half of all human proteins are produced via this mechanism. But what lies behind this?



Sample preparation

Alternative splicing can best be explained by stating what it is not: constitutive splicing. In constitutive splicing the coding segments (exons) – after removal of the non-coding sequences (introns) – are joined in the sequence in which they

also occur in the DNA. From a pre-mRNA always the same mRNA is produced. Due to alternative splicing the sequence of the mRNA is varied: individual exons can be shortened or lengthened, entire exons can be skipped. Through these processes many mRNA variants and thus also many different proteins are generated from one single gene. Often these processes are regulated in a tissue-specific and development-specific manner.

The Explorative Project "Analyzing Global Regulators of Alternative Splicing in the Human System: A Combined RNAi and Microarray Approach" deals with the underlying mechanisms of alternative splicing. "Until now little has been known about which proteins regulate these processes and what their target sequences look like in the RNA. Our goal is to systematically identify the complete networks of splicing regulator proteins and their target

genes in the human genome," says project leader Professor Albrecht Bindereif. A new methodical approach is to help with this: Via RNA interference putative splicing regulators will be targeted individually and switched off. By using microarrays it can then be analyzed what effects switching off the regulator has on the splicing pattern of certain target genes. For this purpose splicing-sensitive microarrays are to be used that simultaneously allow the tracking of the alternative splicing pattern of a great number of candidate genes.