Website address:
https://www.gesundheitsindustrie-bw.de/en/article/news/enhancers-promote-the-activation-of-cancer-causing-genes

Enhancers promote the activation of cancer-causing genes

Scientists from the EMBL and the DKFZ in Heidelberg have made an important discovery about a highly aggressive childhood brain tumour: the oncogenes are activated as a result of comprehensive DNA rearrangements that had moved them into the vicinity of DNA sequences called enhancers. This activation mechanism might play a role in many types of tumours and therefore has the potential for being used in the targeted development of new, more effective drugs.

Medulloblastoma, which is the most common type of malignant brain tumour in children, is classified into four distinct subgroups that vary greatly in terms of aggressiveness of the disease. Group 3 and 4 tumours are particularly common and are among the most aggressive. "For these two tumour groups, hardly any characteristic genomic changes that drive tumour growth and would make potential targets for drug development have been identified," said Prof. Dr. Peter Lichter, head of the Department of Molecular Genetics at the German Cancer Research Center (DKFZ) in Heidelberg. Lichter is also the coordinator of the PedBrain Tumour network which is part of the International Cancer Genome Consortium (ICGC). This consortium systematically analyses all genomic alterations in paediatric brain cancer in order to discover new targets for the development of gentler modes of treatment.
In collaboration with an international team of colleagues, scientists from the DKFZ and the EMBL have published the sensational results of their analyses in the renowned scientific journal Nature. The researchers made the important discovery that a previously unknown regulatory mechanism promoted the development of cancer and it is most likely that this mechanism also plays a crucial role in the development of other types of cancer.

The benefit of being able to think outside the box

The researchers in Heidelberg sequenced the genomes of 137 of the more aggressive group 3 and group 4 medulloblastomas which are characterised by the rapid growth of the cancer cells and high metastasis rates. The sequence data were analysed in detail by a group of EMBL researchers led by Dr. Jan Korbel. Instead of looking for alterations in the genes, the team, unusually, focused on areas in the DNA sections between the genes. "Our work shows that it is worth thinking outside the box, particularly where cancer genomes are concerned," says Korbel. The researchers had already shown previously that such thinking is highly important. In 2013, they discovered a mechanism known as chromothripsis – also in medulloblastomas - in which chromosomes are cut into countless fragments and stitched back together in a haphazard way (see article entitled "Genomic structural variations can cause cancer" published on BIOPRO on 4th March 2013, see link in the top right-hand corner).

Dr. Jan O. Korbel, head of the Genome Biology Unit, European Molecular Biology Laboratory

The PedBrain researchers found comprehensive structural changes in the 137 genomes analysed and also discovered that these changes differed between the individual patients. Large regions of DNA had been deleted, duplicated, or changed their orientation; some genomes contained mutations that seem to have arisen at different points in time and had undergone comprehensive rearrangement. However, despite their different nature, these structural changes had identical consequences in all tumours under investigation, namely that one of two oncogenes (either GFI1 or GFI1B), which are not active in healthy tissue, was moved from a usually inactive environment to a position close to DNA sequences called enhancers. Enhancers are short DNA fragments that can, sometimes quite dramatically, increase the activation of genes.

GFI1B and GFI1 are located on different chromosomes, but have similar functions: they code for DNA-binding proteins that act as transcription factors. They are usually not active in the brain. However, in medulloblastomas, the movement of the genes to a position close to an enhancer leads to their

Cover of J. Korbel's Cancer Lectures.
© EMBL

activation. The researchers concluded that the activation of these genes contributes to the development of cancer.

The only gene that had been known to play a key role in group 3 and 4 medulloblastomas was MYC, a gene that is permanently expressed in many cancer cells. However, this gene could not explain the tumour's high metastasis rate and the bad prognosis for the patients. "We were surprised to find two genes, i.e. GFI1B and GFI1, in addition to MYC. Moreover, these genes were activated in a way that cancer researchers would not normally look for," says Korbel.

Animal experiments carried out with a research group led by Robert Wechsler-Reya from the Stanford Burnham Institute in La Jolla, California, confirmed the role of GFI1B and GFI1 as oncogenes involved in the development of medulloblastomas. In the laboratory, neuronal stem cells were genetically modified so that either GFI1B or GFI1 was switched on at the same time as MYC. The modified stem cells were subsequently implanted into the brains of healthy mice. The mice developed aggressive, metastasing brain tumours that were very similar to group 3 medulloblastomas. This is the first animal model that enables researchers to study the genetics of medulloblastomas and the activation of oncogenes resulting from 'hijacked' gene enhancers. In mice, brain tumours only develop when MYC is also activated. The connection between this gene and the GFI1B and GFI1 oncogenes still needs to be clarified.

Developing drugs that inhibit the growth of tumours

Thomas Zichner (left) and Jan Korbel analysing the activation of genes in tumours.

Dr. Paul A. Northcott, Department of Paediatric Neurooncology, German Cancer Research Center.

"The mechanism of how oncogenes can be activated by hijacked enhancers had previously been overlooked. The reason for this is down to the fact that this mechanism can only be discovered with an extremely careful analysis of the genome," explains Prof. Dr. Stefan Pfister, molecular geneticist at the DKFZ and paediatrician at the Heidelberg University Hospital. His colleague, Dr. Paul Northcott, explains further: "No one has previously been able to discover such a process in a solid tumour despite the fact that it is similar to a phenomenon that was discovered in leukaemia in the 1980s."

Northcott is the lead author of a comprehensive multi-author study that showed that DNA rearrangements in medulloblastomas enhance the effect of oncogenes. This phenomenon is due to the Philadelphia chromosome. This abnormal chromosome was discovered in patients with chronic myeloid leukaemia (CML) by Peter C. Nowell at the University of Pennsylvania in Philadelphia in 1960, which is why the genetic abnormality is referred to as Philadelphia chromosome. It later turned out that the Philadelphia chromosome is due to a translocation that results in the oncogenic BCR-ABL fusion gene where the BCR region leads to the continuous activation of ABL, which results in unregulated cell division, i.e. cancer. The development of a groundbreaking drug for chronic myeloid leukaemia (imatinib, marketed as Glivec or Gleevec) has prolonged the survival of many CML patients by specifically inhibiting the cancer-causing BCR-ABL protein.

The researchers from Heidelberg now hope that the discovery of the fact that the oncogenes GFI1 and GFI1B are activated as a result of chromosomal rearrangement will also lead to the development of drugs that make the treatment of children with such aggressive brain tumours a lot gentler and more effective. Substances that inhibit these two oncogenes are already undergoing preclinical testing. In addition, tests that assess the activity state of GFI1 and GFI1B (which, as stated above, are not normally active in the brain) are new possibilities for diagnosis of the two particularly challenging group 3 and 4 medulloblastomas.

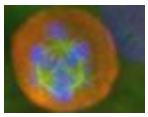
Publication:

Northcott PA, Lee C, Zichner T …(+ additional 72 co-authors)… Lichter P, Korbel JO, Wechsler-Reya RJ, Pfister SM: Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. Nature (2014) doi:10.1038/nature13379;
www.embl.org/press/2014/140622_Heidelberg

Article

14-Jul-2014
EJ
BioRN

The article is part of the following dossiers



Cancer – basic research, successes and trends

EMBL