Surprising role of gene regulator protein in development of skin tumors

November 18 2013

Findings by scientists from the Max F. Perutz Laboratories (MFPL) of the University of Vienna and the Medical University of Vienna reveal a surprising role for histone deacetylase 1 (HDAC1) – a member of a family of chromatin modifying proteins – in the development of skin tumors. The results from Christian Seiser and his team also emphasize that care must be taken when using HDAC inhibitors as anti-cancer drugs.

Skin tumors – when healing of scratches and cuts goes

wrong

The skin is the largest organ of the human body, protecting us from dehydration and external impacts. It's a self-renewing tissue, meaning that if we hurt ourselves for example by scraping or cutting our skin, new skin cells will replace the old damaged ones and our wound will heal. On a molecular level this process is controlled by a wide range of factors, ensuring that the right number of undifferentiated progenitor cells differentiate into skin cells and make their way to replace the old damaged ones. If something goes wrong during this process, pathologies, including skin tumors, can be the consequence. And with non-melanoma skin cancers being the most frequent human tumors, there is clearly a tremendous need to understand the underlying molecular mechanisms, to allow the development of drugs to treat these types of cancer.

Chromatin or how to fit the genomic DNA in a cell's nucleus

One regulatory mechanism known to be involved in skin development and renewal is chromatin modification. Basically, chromatin is the DNA of a cell wrapped around a barrel shaped structure of proteins – so-called histones – condensing the DNA so that it can actually fit within a cell's nucleus. The histones that form the barrels can be reversibly modified via the attachment of small chemical groups, which in turn regulates how tightly the DNA can be wrapped around them and therefore how condensed the chromatin is. This process controls which proteins are made in a cell at a given moment, also determining in the early stages of life which cells develop into muscle cells, brain cells or skin cells for example. In self-renewing tissues, such as the skin, chromatin modification is also involved in regulating the replacement of old or damaged cells in later stages in life.

Targeting HDACs to treat cancer

One type of chromatin modifiers is called histone deacetylase (HDAC), of which 18 variants are known in humans. HDAC inhibitors are already approved for cancer treatment but most of these drugs are not specific and act on several HDAC variants. This is a problem, as inhibiting the wrong variant can actually accelerate cancer progression as the team of Christian Seiser at the MFPL and the Medical University of Vienna has now shown. In a project supported by the Austrian Genome research program GEN-AU they looked at the two variants, HDAC1 and HDAC2, which based on previous results were promising targets for tumor therapy and are known to have redundant functions. "When we ablated the function of either of these proteins in the skin of a mouse model system it had no obvious effect.

However, when we ablated HDAC1 function completely and HDAC2 function partly we saw severe developmental defects and the spontaneous development of skin tumors," explains Christian Seiser. They further investigated this phenotype in a skin tumor model system, provided by Maria Sibilia from the Institute for Cancer Research of the Medical University of Vienna, and found that deactivating HDAC1 actually accelerates tumor development, while HDAC2 deactivation has no effect.

These results came as a big surprise for the researchers, who had initially thought that deactivating or inhibiting HDAC1 would halt cancer progression, but found that in skin cancer the opposite is true. Christian Seiser says: "Our results highlight that it is crucial to understand the individual role the various HDAC variants in different cell types and hence different types of cancer, before HDAC inhibitors can be used safely as therapeutics."

More information: Mircea Winter, Mirjam A Moser, Dominique