Investigating treatment resistance in cancer

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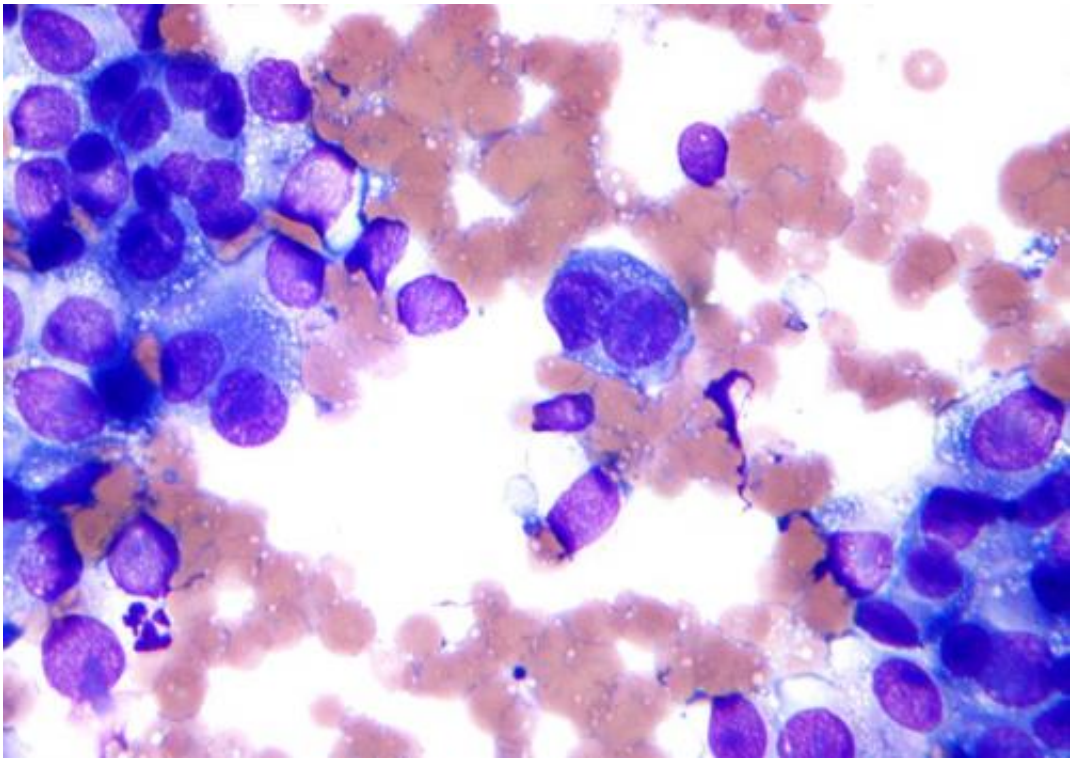

Micrograph of malignant melanoma. Cytology specimen. Field stain. Credit: Nephron/Wikipedia

Melanoma and liver cancer are becoming more widespread in Europe and the U.S. While both diseases progress very differently, they are among the types of cancer most likely to be fatal in the Western world. Three groups of researchers from the Institute of Biochemistry at Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) led by Prof. Dr. Anja Bosserhoff, Dr. Peter Dietrich and Prof. Dr. Claus Hellerbrand

have jointly discovered a mechanism to steer the growth of the cancer cells in both types of cancer, a discovery that is highly significant for future treatment strategies.

At first glance, there are not many similarities between two such different types of cancer as black skin cancer (malignant melanoma) and liver cancer (hepatocellular carcinoma). The main risk factors for melanoma are too much exposure to the sun, sunburn and genetic predisposition. Liver cancer, on the other hand, very often occurs in a liver that has been damaged by alcohol or obesity or as a result of chronic viral hepatitis. However, what both types of cancer have in common is an uncontrolled growth of malignant cells. These end up destroying vital tissues and organs within the body, leading eventually to the death of the patient.

Similar chemotherapy treatments are used to treat both types of cancer. "Although these tumours are found in very different locations, the drugs used to treat them focus on the same signal pathway, inhibiting the growth and splitting of cancer cells," explains Dr. Peter Dietrich. "These treatments are very effective in the first few weeks, but unfortunately, after a few months, the cancer cells nearly always become resistant to them." Groups of researchers at the Institute of Biochemistry at FAU have now discovered a mechanism which steers the growth of the cancer cells and their resistance to chemotherapy in both types of cancer.

New approaches opening up new treatment options

The scientists at FAU took a new approach, with experts on two very different types of cancer, melanoma and liver cancer, carrying out joint research. They cooperated in an attempt to discover more general mechanisms that cause cancer and resistance to treatment. Their research was successful—the teams led by Prof. Dr. Anja Bosserhoff, Dr. Peter Dietrich and Prof. Dr. Claus Hellerbrand discovered that both skin

cancer and liver cancer cells produce more of a certain protein—KRAS—and increase production even more during treatment, making them dependent on this protein.

"While these may at first glance appear to be such different types of cancer, they are both able to create more of this protein due to the lack of an extremely small RNA molecule, referred to as a microRNA," explains Prof. Dr. Anja Bosserhoff. "Levels of the KRAS protein, which is responsible for increased growth and resistance, are usually kept at a low level by this microRNA, which acts as a stop sign and integrated safety switch in healthy cells. We noticed much lower levels than normal of this microRNA in both types of cancer, and even a complete absence in some cases. As a result, the cancer gene KRAS is released, which can in turn lead to an unchecked growth of the cancer and resistance to treatment."

This mechanism could be used to treat cancer effectively in future. Based on their new findings, the researchers want to inhibit tumour growth and prevent resistance to treatment. "Several approaches were successful in our studies," says Dr. Peter Dietrich. "The lost microRNA can be returned to the cancer cells using genetic engineering, allowing the uninhibited KRAS protein to be regulated again. Another option is to switch off KRAS directly in the cells, which could also lead to a breakthrough in treatment resistance. Finally, new substances were used successfully to inhibit KRAS. These substances, used alone or in combination with previous drugs, could form the basis for new, effective treatments." Prof. Dr. Claus Hellerbrand is also convinced by the concept. "The approach has a lot of potential and we working on developing it. FAU has now filed an application to have this discovery patented as a treatment option for skin and liver cancer."

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