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Keeping skin cancer in check—how the environment influences the tumor

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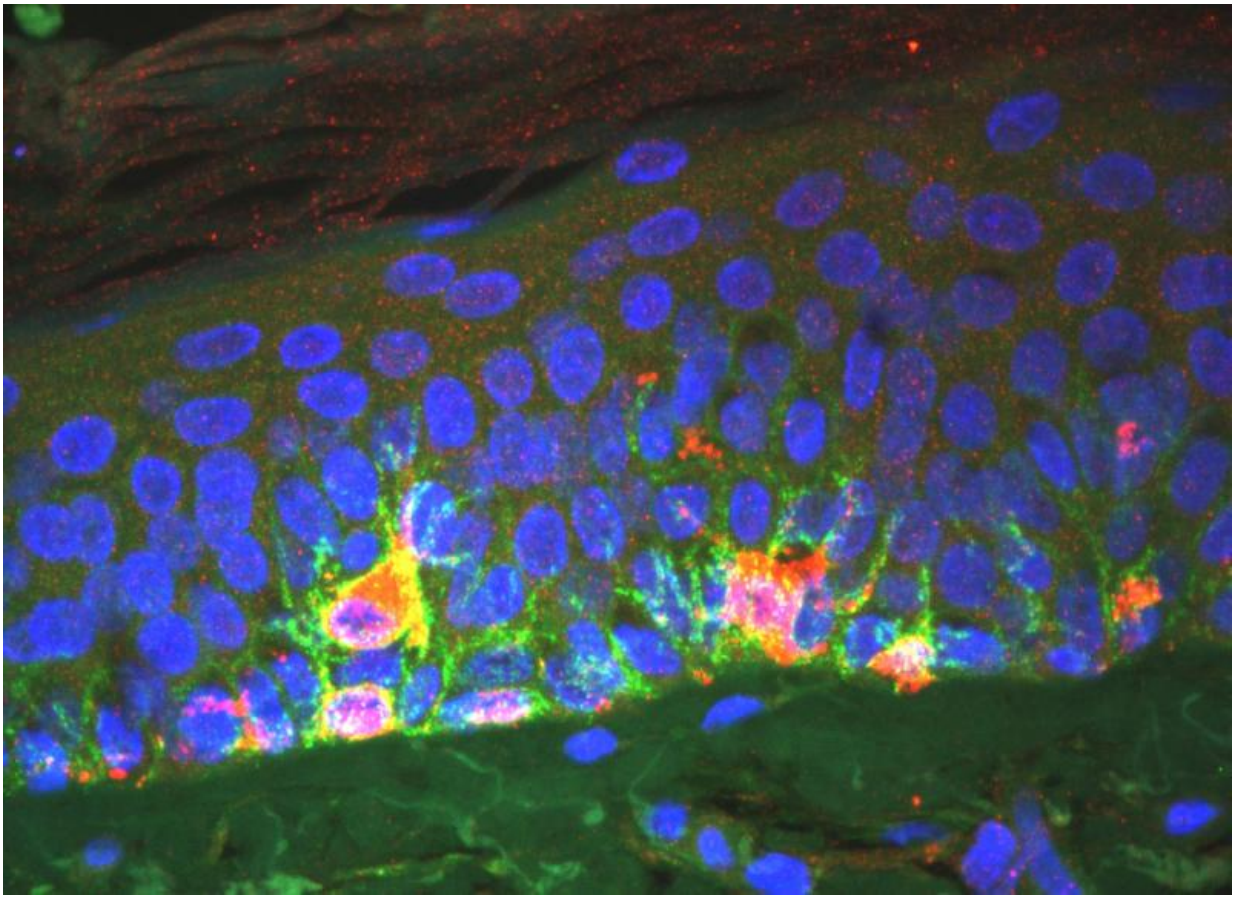

Human melanoma. Credit: University of Cologne - Universität zu Köln

Malignant melanoma is the fastest-growing type of cancer and the most fatal skin disease. Sandra Iden and her team at the Cluster of Excellence

on Aging Research (CECAD) at the University of Cologne investigated the influence of the surrounding tissue on the formation and growth of tumor cells. Their results are now published in the *Journal of Experimental Medicine*.

Our skin is our most important barrier to the surrounding environment. Every day, it has to fight threats like UV-light, mechanical stress or germs and viruses. Excessive exposure to sunlight is one of the biggest risk factors of skin cancers. While in the 1960s the lifetime risk to develop malignant melanoma was 1:600 today it is about 1:100. Therefore, research on this type of cancer, which only has a good chance of treatment if diagnosed early, is important.

The outer layer of the skin, the epidermis, consists of different cell types. Keratinocytes form the skin barrier and are fundamentally important for wound healing, whereas melanocytes play a crucial role in protecting us against UV-light. They produce the pigment melanin, which can absorb energy and transform it into heat to prevent DNA damage. Melanoma arises from transformed melanocytes. "So far, melanoma research has mostly concentrated on intrinsic changes of the tumor cell or on its recognition by the immune system. Meanwhile, many mutations are known that increase the growth of melanoma cells," explains Sandra Iden, senior author of the study. "We can now show that the surrounding epithelium has a strong impact on melanocyte fate and early stages of tumor formation. Keratinocytes keep the melanocytes in check and thereby decrease the risk of developing a melanoma."

The so-called polarity proteins, in particular Par3, play an important role in this process. Their task is to control cellular shape and function. For their investigations the scientists used mice with an increased risk of developing melanoma. This predisposition mimics the disease in humans. "We were able to specifically interfere with polarity protein signaling in epithelial cells surrounding the tumor. We found that this

disrupts the direct communication between keratinocytes and melanocytes, which resulted in increased tumor formation and metastasis." Further analyses showed that Par3 prevents the transformation of melanocytes by regulating an important molecule for cell-cell contacts, P-cadherin. "Loss of Par3 leads to increased P-cadherin-mediated binding between melanocytes and keratinocytes, thereby promoting tumor cell expansion and invasiveness," Sandra Iden adds.

In cooperation with researchers of the Dermatology Department at the University Hospital Cologne, Sandra Iden's team analyzed human tissue samples of skin cancer patients. "We collected samples of different stages of melanomas and analyzed how the expression of Par3 and P-cadherin correlated with tumor growth. Interestingly, we found that with further progression of the tumor, the expression of Par3 decreased, while the contacts between tumor cells and the neighboring epithelium showed P-cadherin accumulation. Moreover, melanoma patients with high expression of P-cadherin showed a decreased survival rate as compared with patients without P-cadherin alterations. The results from the mouse model and the human samples are thus very consistent. Collectively, we were able to show how the surrounding healthy tissue cells influence the cancer cells, change their architecture and control their susceptibility to tumor formation. For future preventive, diagnostic and therapeutic approaches against cancer, we should broaden our view and also consider changes in the healthy tissue surrounding the tumor."

More information: Melina Mescher et al. The epidermal polarity protein Par3 is a non–cell autonomous suppressor of malignant melanoma, *The Journal of Experimental Medicine* (2017). DOI: 10.1084/jem.20160596

Provided by University of Cologne