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Sunburns strike twice: Skin inflammation following UV irradiation promotes cancer cell spread along blood vessels

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Melanoma is particularly dangerous because it can form metastases in vital organs such as the lungs, liver or brain. UV radiation is considered to be the most significant triggering factor. An interdisciplinary team of researchers from the University Hospital and the LIMES Institute of the University of Bonn has now discovered that sunburns contribute to the development of this malignant disease not only through direct alteration of pigment cell genomes but also indirectly through inflammatory processes in the surrounding tissue. The results are now being published online in the renowned journal "*Nature*".

According to predictions from the Robert Koch Institute, approximately 20,000 people in Germany will develop malignant melanoma in 2014. More than 2500 of those affected will die from metastases to internal organs. "The inflammatory reaction of the skin after severe sun exposure promotes the early migration of melanoma cells along vessels within the body," says Prof. Dr. Thomas Tüting, professor of Experimental Dermatology at the University of Bonn Hospital and leader of the study team.

Melanoma cells migrate along blood vessels

To understand the development and early metastasis of malignant melanoma, the researchers developed experimental models in mice which allowed them to investigate the effect of inflammatory responses

following UV exposure. "We repeatedly observed increased melanoma metastases in the lungs of UV-irradiated mice," reports the dermatologist Dr. Evelyn Gaffal. Analyses of melanoma tissue sections revealed the spread of tumor cells along blood vessel surfaces in inflamed skin. Using modern methods of fluorescence and electron microscopy, the researchers observed a close association between melanoma cells, inner blood vessel walls and immune cells, especially neutrophils.

Activated neutrophils pave the way for melanoma cells

Further experiments showed that neutrophils play an important role in metastasis. They are attracted by alarm signals emitted by UV-damaged keratinocytes in the epidermis. The use of special mouse strains which lack important molecules required for the activation of innate immune defense shed light on the underlying signaling pathways.

Inflammatory mediators promote melanoma cell motility

Researchers in the LIMES Institute of the University of Bonn developed new experimental methods to investigate the interaction between melanoma cells and cells of the inner blood vessel walls, known as endothelial cells. In doing so, they observed that melanoma cells can migrate particularly effectively on blood vessel surfaces. "Melanoma cells increase their motility in an inflammatory environment," says Prof. Dr. Waldemar Kolanus.

Further investigations with human melanoma cells and modern genomic methods provided insights how inflammatory mediators stimulate melanoma cells migration. "During embryonic development pigment cell precursors travel long distances along blood vessels in the body in order

to reach their final destination in the skin. These migratory programs are erroneously reactivated in melanoma cells by inflammation," says Prof. Dr. Michael Hölzel from the Institute of Clinical Chemistry and Clinical Pharmacology in Bonn.

Important insights for new treatment strategies

"Our findings may explain why patients with superficially ulcerated melanomas and neutrophil infiltration frequently develop organ metastases" says Prof. Tüting. The researchers hope to develop new forms of targeted therapy in the future which specifically interfere with inflammatory signaling cascades and inhibit the migration of melanoma cells on the surfaces of blood vessels. The interdisciplinary cooperation between different research groups in Bonn within the Collaborative Research Center 704 and the Excellence Cluster ImmunoSensation provide an excellent basis for such ambitious projects.

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