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Melanoma—mechanisms of BRAF-inhibitor resistance deciphered

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BRAF mutation occurs in between 40% and 50% of metastasising melanomas (skin cancers), boosting tumour growth. Patients with metastasising melanomas and who display BRAF mutation can be treated with an inhibitor that acts specifically against BRAF mutation (BRAF inhibitor in combination with MEK inhibitor). Initially the treatment is extremely effective but, after a maximum of 11 months, the patient becomes resistant to it. Verena Paulitschke from MedUni Vienna's Department of Dermatology has now identified some of the mechanisms that might cause this resistance. This could well lead to new treatment concepts and predictive biomarkers, as well as an improved general understanding of the pathomechanisms leading to the disease.

The human BRAF gene produces a protein (B-Raf) that is an important component of the RAS-RAF signalling pathway, thereby playing a role in normal cell growth and survival. However, mutated forms can cause this signalling pathway to become overactive. This in turn leads to uncontrolled cell growth and cancer.

The aim of the researchers from MedUni Vienna's Department of Dermatology is to understand these resistance mechanisms and, in a next step, to delay or even prevent the development of resistance. With the aid of proteomics technology, it has now been possible to obtain the first insights into the underlying mechanisms. The key technology of mass spectrometry ("shotgun proteomics"), in particular, enables to identify and characterise proteins from human cells. The proteins are enzymatically digested and the arising peptides separated.

"We were able to show that resistance to the BRAF inhibitor is associated with elevated expression of the lyosomal compartment (Note: spherical vesicular cell organelles), with increased cell binding and with morphological changes in the cells, from spherical to spindle-shaped," explains Paulitschke. Based on this resistance profile, it was then possible to demonstrate the effectiveness of the reservatrol derivative M8, a naturally occurring polyphenol found primarily in grapes. "As cell models, we used cells with induced resistance and primary cell systems, in which similar signatures were identified. It was then possible to correlate the expression of proteins (which were upregulated in the resistant cells) with poor progression free survival using tissue sections or sera of melanoma patients," says the MedUni Vienna researcher.

"New technologies such as 'shotgun proteomics' have enabled us to make a mechanistic analysis of innovative therapeutic approaches. Using these strategies, it has been possible to obtain new insights into the underlying mechanism of resistance to BRAF inhibition and, based on that, we might be able to develop new rational therapeutic concepts and predictive and pharmacodynamic biomarkers," says Paulitschke.

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