New insight into drug resistance in metastatic melanoma

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(Medical Xpress)—A study by scientists in Manchester has shown how melanoma drugs can cause the cancer to progress once a patient has stopped responding to treatment.

Their findings suggest that using a combination of targeted therapies may be a more effective approach in the clinic.

Melanoma is a form of cancer that develops from melanocytes – the pigment-producing cells in skin. Advanced metastatic melanoma – where the cancer has spread throughout the body – is associated with poor survival, so new treatments are urgently needed.

In about 50% of melanoma cases, the tumour contains a mutation in a gene known as BRAF. Drugs that target BRAF – such as vemurafenib – have increased survival in patients with this mutation. However, many of these patients go on to develop resistance to treatment and their disease returns.

Now researchers from the Cancer Research UK Manchester Institute at The University of Manchester – part of the Manchester Cancer Research Centre – have explored what happens in melanoma cells following inhibition of BRAF.

Professor Richard Marais, who led the research, said: "BRAF inhibitors have improved survival for patients with metastatic melanoma. Unfortunately, eventual drug resistance is preventing long-term cure in most of these patients. We wanted to understand how these drugs might induce unwanted effects in melanoma cells – particularly in cells which also have a mutation in the RAS gene."

The group found that blocking BRAF activity, either using drugs or by altering a cell's genes, led to the RAS-mutated melanoma cells changing shape and becoming more invasive. These changes in behaviour would lead to metastatic spread of the disease throughout the body. Their study, published recently in the journal *Science Signaling*, showed that the BRAF inhibitors re-activated certain pathways within cells leading to melanoma cells becoming resistant to therapy.

"We found that we could counteract this behaviour by adding a second drug to the BRAF inhibitor – one that targets MEK. It looks like our study further supports the combined use of both BRAF and MEK inhibitors in melanoma patients," added Professor Marais.

Provided by University of Manchester