Scientists find new way to combat drug resistance in skin cancer

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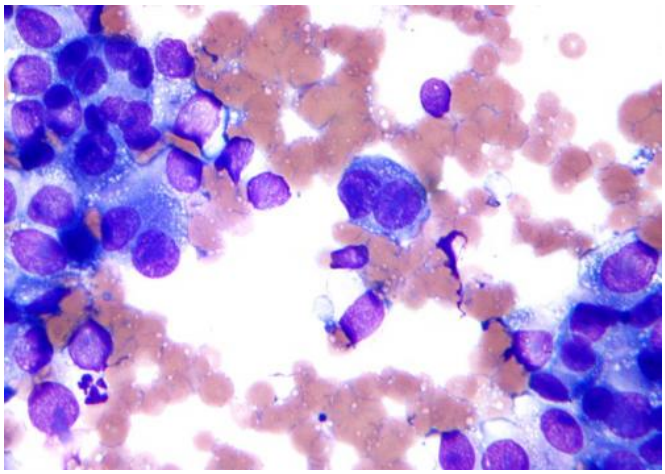

Micrograph of malignant melanoma. Cytology specimen. Field stain. Credit: Nephron/Wikipeida

Rapid resistance to vemurafenib – a treatment for a type of advanced melanoma, the deadliest form of skin cancer – could be prevented by blocking a druggable family of proteins, according to research published in *Nature Communications* today.

Scientists at the Cancer Research UK Manchester Institute, based at the University of Manchester, have revealed the MLK family of four enzymes 'undoes' the tumour-shrinking effects of vemurafenib.

Around half of metastatic melanomas – aggressive skin cancer that has spread to other parts of the body – are caused by a fault in the cell-growth gene BRAF, causing the signal telling cells to multiply to be permanently switched on.

Vemurafenib blocks BRAF and stops the cancerous cells from growing. But cancer cells usually find a different way to turn the pathway back on – cancelling out the drug's effects. Most metastatic melanoma patients stop responding to the drug within about six months, leading to a relapse of the disease.

This new research has found MLK enzymes can be responsible for reactivating the BRAF pathway, even in the presence of vemurafenib. By blocking these enzymes, which previous studies have shown is already possible, the researchers hope they can stop resistance to vemurafenib so the cancer cells are still vulnerable to the drug.

The findings also show that some melanoma patients have additional gene mutations that switch MLK genes on, causing patients to develop resistance to vemurafenib more quickly.

Lead author, Dr John Brognard, at Cancer Research UK Manchester Institute, said: "This exciting research reveals that melanoma cells have enzymes acting like a manual override switch to regenerate growth signals – even after vemurafenib has switched them off.

"Additionally, this family of enzymes are turned on in metastatic melanomas that are not caused by BRAF, suggesting they may serve as a new target in metastatic melanomas for which there are limited treatment options.

"The good news is there are already experimental drugs that can block these enzymes in the laboratory. And this research paves the way for the development of drugs to overcome vemurafenib resistance in melanoma patients."

Professor Nic Jones, Cancer Research UK's chief scientist and director of the Manchester Cancer Research Centre, a partnership between CRUK, The University of Manchester and The Christie NHS Foundation Trust, said: "This exciting research opens new routes to treat this difficult disease. Thanks to people's generosity we've funded research that revealed that the BRAF gene is behind around half of all melanomas. And

several drugs that target BRAF are now showing promise in clinical trials.

"Rates of melanoma in Britain are now five times higher than in the mid-1970s, but survival rates have also improved, with more than eight in 10 surviving for more than 10 years.

"We hope this latest research will lead to new treatments enabling even more people to beat this disease. Melanoma research is a key priority for the Manchester Cancer Research Centre."

More information: Marusiak, A., et al Mixed-lineage kinases activate MEK independently of RAF to mediate resistance to RAF inhibitors, *Nature Communications*, 2014.

Provided by Cancer Research UK