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Study suggests patients should be screened before receiving vemurafenib

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Different genetic mistakes driving skin cancer may affect how patients respond to the drug vemurafenib, providing grounds to screen people with melanoma skin cancer before treatment, a new study by Cancer Research UK scientists suggests

The findings, published in the journal Genes and Development, show that certain rare gene faults in the tumours of patients receiving vemurafenib may also explain why some patients develop secondary non-melanoma skin cancers.

Vemurafenib works by targeting a common fault in the gene BRAF, called V600E, which is present in at least half of melanomas. The drug stops BRAF from activating a key pathway that drives cancer growth.

But this common fault is not present in all people who develop melanoma and around 18 per cent of patients given the drug go on to develop other, less serious, forms of non-melanoma skin cancer, called squamous cell carcinoma, which need to be surgically removed.

To try and find out why, the University of Leicester-based researchers have been using mice to study a group of rare inherited developmental disorders called RASopathies, which are also caused by faults in the gene BRAF, but not the common fault that causes melanoma.

They studied a specific rare fault in BRAF called L597V, which is found both in melanoma patients and in people with RASopathies.

The rare fault was not found to cause cancer on its own. But when a second gene, called RAS, was faulty too the mice developed cancers similar to those caused by the common fault. However, although the tumours were similar the biology driving the cancers was subtly different.

Crucially this meant that the drug vemurafenib had the opposite effect on cells with the rare fault in BRAF, meaning it actually boosted cancer growth.

Lead author Dr Catrin Pritchard, from the University of Leicester, said: "This study shows that the L597V fault only leads to cancer when it happens alongside other faults in the cell, explaining why people with RASopathies don't usually develop the disease. But because this rare fault works in a different way from the common one, vemurafenib has the opposite effect and actually causes secondary tumours, albeit less serious non-melanoma ones. This suggests that people should be screened to see what faults they have before they are given vemurafenib."

Dr Julie Sharp, senior science information manager at Cancer Research UK, said: "Cancer Research UK scientists were among the first to discover the link between melanoma and faulty BRAF, and since then drugs like vemurafenib, which block this pathway, have proved to be a major leap forward in the treatment of advanced melanoma. These results, however, could explain why vemurafenib is less effective in some patients who go on to develop secondary cancers. We now need clinical trials to see whether analysing BRAF faults can help predict response to vemurafenib in people, as well as mice."

More information: doi: 10.1101/gad.193458.112

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