BRAF mutation confirmed as a strong target for cancer drugs

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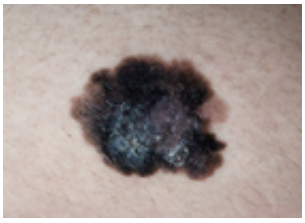

Malignant melanoma. Credit: Wellcome Images

(PhysOrg.com) -- Research has added to the evidence that a genetic mutation found in over 60 per cent of malignant melanomas is an important target for drugs to treat the disease.

A mutation in the gene BRAF is known to be present in over 60 per cent of malignant melanomas, a type of skin cancer that can spread rapidly and is difficult to treat.

To date, several drugs that target this mutation have shown promise in clinical trials in people with melanoma. However, researchers weren't sure whether this effectiveness was a result of the drugs blocking the activity of BRAF, as designed, or from some other effect of the drugs.

Doubts around the effectiveness of BRAF inhibitors have also been raised by the failure of a drug called sorafenib to improve the survival of people with melanoma in late-stage clinical testing last year.

Now, in research published in the journal 'Science Translational Medicine', Professor Richard Marais and colleagues at the Institute of Cancer Research have shown how these drugs work, confirming that BRAF is still a valid target for melanoma drugs.

The researchers constructed models using drug-resistant forms of the protein. They then tested whether the drugs retained their anti-cancer activity on tumour cells with mutated forms of the BRAF protein.

They found that sorafenib does not work in melanoma because it does not target the mutated form of BRAF in tumours. A second-generation drug called PLX4720 works in melanoma because it does target damaged BRAF.

"We have absolutely confirmed that BRAF is an important drug target for malignant melanoma, and that the clinical benefit from these second-generation drugs is due to their ability to target the damaged BRAF protein," says Professor Marais.

"It is crucial that we understand the mechanism behind these drugs' effects to ensure they are only given to patients with the specific genetic defects - in this case, a mutated BRAF gene - that will allow them to benefit. This knowledge may also help us combat resistance and develop new-generation drugs."

Drugs that target BRAF may also be important in treating other tumours in which BRAF mutations are common. These include thyroid cancer (in which BRAF is mutated in 45 per cent of cases), ovarian cancer (10 per cent) and colorectal cancers (13 per cent).

More information: Whittaker S et al. Gatekeeper mutations mediate resistance to BRAF targeted therapies. Sci Transl Med 2010.

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