Better approach to treating deadly melanoma identified by scientists

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(Medical Xpress)—Researchers funded by Cancer Research UK have been looking at why new drugs called "MEK inhibitors", which are currently being tested in clinical trials, aren't as effective at killing cancer cells as they should be.

They discovered that MITF - a protein that helps cells to produce pigment but also helps melanoma cells to grow and survive - is able to provide cancer cells with a resistance to MEK inhibitors.

Dr Claudia Wellbrock and her team at the Wellcome Trust Centre for Cell-Matrix Research compared human melanoma cells that respond to the drug to cells that don't. They discovered that the cells that didn't respond to the drug contained higher levels of the protein SMURF2.

The researchers reduced the level of SMURF2 in the melanoma cancer cells and then treated the tumour with the MEK inhibitor. They found a 100 fold increase in the sensitivity of the cells to the drug. It appears that removing SMURF2 radically decreases the level of MITF in melanoma cells, making the MEK inhibitor a lot more powerful.

Using mice with tumours the team found that over a three week period there was a substantial decrease in tumour growth when the removal of SMURF2 was used in combination with MEK inhibitors.

Dr Wellbrock says: "Much of cancer research is now focussed on finding new drug combinations. It's recognised that cancers frequently

find new ways to combat even the most novel and highly efficient drug treatments, so we are now focussing on targeting the mechanisms that allow the cancer cells to overcome the drug effects. We're very excited about the potential for this new approach that has proved to be so effective in our experiments."

One of the drawbacks of the MEK inhibitor drug is that it targets all cells. MEK (MAP/ERK kinase protein) is present in all cells but cancer cells have overactive MEK. This means the drug must be used in small doses and for a lengthy period to avoid harming healthy cells. By reducing SMURF2 to increase the drug's effectiveness smaller doses could be given over a shorter time period, reducing the level of toxicity in healthy cells.

Dr Wellbrock says: "If we can reduce the toxicity to all cells it will mean cancer treatments are less harmful to patients. It's vital that we improve the treatments for melanoma which is the fifth most common cancer in the UK. By the time many people are diagnosed with melanoma the cancer has already started to spread and advanced tumours can be highly resistant to conventional cancer treatments. The development of resistance to new drugs has also been a major drawback. If we can identify more potent and less toxic drug combinations to tackle melanoma then we could save thousands of lives."

This study was funded in part by Cancer Research UK and the results have been published in the *Journal of the National Cancer Institute*.

Talking about the research Dr Julie Sharp from the charity said: "Recently there have been some really exciting developments in treating melanoma – but new approaches that tackle the problem of resistance are still needed. This type of research will be a key focus of the planned new Manchester Cancer Research Centre which will bring together a wide range of research expertise to revolutionise cancer treatment."

The next step for Dr Wellbrock will be to find a drug that can reduce the activity of SMURF2 in cancer cells. The Manchester research team are now screening drug libraries for an existing drug that may already be approved for use for a different illness.

It's hoped that identifying a drug to use in combination with MEK inhibitors will provide a much more powerful and ultimately more successful approach to treating melanoma.

More information: The paper "Effect of SMURF2 Targeting on Susceptibility to MEK Inhibitors in Melanoma" can be viewed here.

Provided by University of Manchester