Arthritis drug could help treat advanced skin cancer

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Credit: University of East Anglia

Treatment for the most deadly form of skin cancer could be more effective if combined with a well-known drug for rheumatoid arthritis, new research has shown.

The study, by scientists at the University of East Anglia (UEA), found that in mice, using the two treatments together almost completely stopped the growth of a melanoma tumour.

Although only five per cent of skin cancer cases involve melanoma, it

causes the majority of deaths from the disease. If caught early, melanoma is very treatable, but once the cancer has metastasised or spread, then treatment becomes more difficult.

In recent years, a number of new treatments have been developed for metastatic melanoma, some targeting certain genetic mutations. However, the disease can quickly become resistant to most drugs, so research is focusing on combinations of treatments, as lead researcher, Dr. Grant Wheeler from UEA's School of Biological Sciences, explains.

"By combining therapies, it's possible to attack the disease from several angles, which makes it harder for the melanoma to develop resistance to any of the drugs," he said.

"Our research has shown that there could also be further benefits – by joining these two drugs together you may be able to enhance their effects, getting a treatment that is more than the sum of its parts."

Dr. Wheeler, working with colleagues from Norwich Medical School and UEA's School of Pharmacy, focused on leflunomide, an immunosuppressive drug approved for treatment of rheumatoid arthritis. Previous research by the team had shown it to be effective in use with drugs that target melanoma with a certain genetic mutation, known as BRAFV600E. Their latest research – published in the journal *Oncotarget* – has discovered more about how leflunomide works against melanoma and tested it in combination with another melanoma drug, selumetinib.

Selumetinib is one of a number of drugs that target the activity of a protein called MEK, to which melanoma is addicted for its survival. MEK inhibitors are already used in combination with BRAF inhibitors to combat resistance, but Dr. Wheeler's research – part-funded by the John Jarrold Trust – shows that adding leflunomide to the mix may make it even more effective.

When the team tested leflunomide in the lab, it was found to work on melanoma cells irrespective of the genetic signature of the cancer. This means that leflunomide has the potential to be used in all melanoma cases, not just for tumours harbouring BRAF mutations.

The team looked specifically at how leflunomide was acting on the melanoma cells and found that it was able to stop the cells in an early phase of their growth and then force them to kill themselves, a process known as apoptosis.

But when the scientists tested leflunomide on melanoma cells jointly with selumetinib, they found it was more effective than either drug on its own. This finding was replicated in tests on mice with melanoma tumours: using the two drugs together almost completely halted the growth of the tumour over a 12 day period, which far outstripped the effect of either drug used in isolation.

However, many questions remain to be answered before this combination could go into clinical trials, including testing whether melanoma can develop resistance to the treatment.

Dr. Wheeler said: "With melanoma treatments, the main problem has been the development of tumour resistance. One way this is being combatted is through immunotherapy treatments which harness the body's own defences. However, new combination therapies are always needed and we need to identify new drugs that can be added to the arsenal of anti-melanoma therapies available for patients. It's possible that leflunomide could play that role."

"The anti-rheumatic drug, leflunomide, synergizes with MEK inhibition to suppress melanoma growth" is published in the journal *Oncotarget* on December 19, 2017.

More information: The anti-rheumatic drug, leflunomide, synergizes with MEK inhibition to suppress melanoma growth. *Oncotarget*. DOI: 10.18632/oncotarget.23378

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