Tumour mutations harnessed to build cancer vaccine

Preliminary attempt in humans generates robust immune response.

- Heidi Ledford

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Personalized vaccines could provide new options to treat cancers driven by multiple genetic mutations.

Vaccines made from mutated proteins found in tumours have bolstered immune responses to cancer in a small clinical trial.

The results, published on 2 April in *Science*[1], are the latest from mounting efforts to generate personalized cancer therapies. In this case, three people with melanoma received vaccines designed to alert the immune system to mutated proteins found in their tumours.

It is too soon to say whether the resulting immune response will be enough to rein in tumour growth, but the trial is a crucial proof of concept, says Ton Schumacher, a cancer researcher at the Netherlands Cancer Institute in Amsterdam.

“We don’t really know how strong an immune response has to be to be clinically meaningful,” he says. “Nevertheless, it’s an important step.”

Cancer is a genetic disease, driven by mutations that lift the brakes on cell proliferation. But the mutated proteins produced by cancerous cells can serve as a siren call to immune cells, signalling the presence of a cell that has become, in a sense, ‘foreign’.

Unfortunately, many of these calls are never heard. Some tumours suppress nearby immune responses, and mutated tumour proteins may not be expressed at high enough levels to rally immune cells. Researchers have long dreamed of using those mutated proteins to generate a vaccine, says immunologist Beatriz Carreno of Washington University in St. Louis, Missouri, but lacked the technological wherewithal to do so.

Clinical success

The advent of cancer-genome sequencing and an improved understanding of the immune system have converged to make that approach possible. Last year, two groups[2]’ [3] showed that such vaccines can work in mice. Carreno and her colleagues have now taken the approach into humans.

The researchers sequenced the tumour genomes in samples taken from three people with melanoma and catalogued the mutated proteins in each sample. They then chose seven protein fragments per patient for use in the vaccine.

White blood cells were taken from each patient and cultured in the laboratory to generate immune cells called dendritic cells. These cells were then exposed to the protein fragments, allowed to mature in the laboratory and then infused into the patients. By then, the dendritic cells had taken up the protein fragments, and were able to present them to immune cells in the body. The result: immune cells trained to target the mutated proteins produced by the tumour[1]. Such immune cells were evident in the patients' blood two weeks after vaccination.

Researchers have tried to develop cancer vaccines for decades, but early signs of success have tended to give way to disappointment in larger clinical trials. The same could hold true in this case, but there is cause to be optimistic, says Schumacher. Past vaccines were made with proteins that are also found in normal cells, but were simply more abundant in tumours. The immune system is trained to tolerate such proteins, so responses to the proteins remained weak even after vaccination.

In this case, the proteins are not found in normal cells, and therefore should elicit a stronger response, he notes. Carreno adds that previous vaccines also generally involved only a single cancer-associated protein. Her vaccines are based on seven.

Carreno thinks that the approach could also work in other cancers that contain a lot of mutations, such as lung, colon and bladder tumours. And although the procedure is complicated, pharmaceutical companies have shown that they are willing to take on complex, personalized cancer therapies. “The pipeline for identifying mutated proteins will get more efficient with time,” Carreno says. “This therapy is no more complicated than the other therapies that are now being considered.”

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References

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