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CLINICAL GENETICS

Sequencing for tailored melanoma immunotherapy

Missense mutations that cause amino acid substitutions in tumours can be recognized as foreign by the immune system, thereby initiating a tumour-specific T cell response. In a new approach to melanoma treatment, sequencing has been used to identify specific antigens that are expressed in patients' tumours, and the unique sequences of these peptides were then used to develop a personalized vaccine, according to the paper published in *Science*.

The study builds on previous work investigating the possibility of conditioning patient-derived dendritic cells to present cancer-expressed antigens on their own human leukocyte antigen (HLA) proteins and using these cells as a vaccine in patients with melanoma to enhance the antitumour immune response and to elicit T cell memory. In this previous work, the researchers reported that a vaccine with the melanoma antigen GP100 had therapeutic benefits in some patients with melanoma despite the fact that this antigen is also expressed on normal cells. "Given this shared pattern of expression, T cell responses elicited by these antigens may not be sufficiently robust to promote effective tumour destruction," explains Beatriz Carreno, lead author of the paper. "We were interested in identifying additional cancer antigens, and we teamed up with Elaine Mardis and her group to incorporate next-generation sequencing in a pipeline for identification of antigens that were uniquely expressed by each patient's melanoma tumour".

Three patients with advanced cutaneous melanoma were enrolled into the Phase I clinical trial. "The novel approach we used in this study was to first evaluate the mutated genes in each patient's tumour, using next-generation sequencing of DNA and RNA," explains Mardis. By comparing the tumour DNA to the

patient-matched normal genome, the team were able to identify mutations that change the amino acid sequence of the resulting antigens, and an algorithm was then used to predict HLA binding affinity. RNA data were used to examine which of the predicted 'neoantigens' were expressed in the melanomas. "The final list of neoantigens with evidence of high expression were then tested using specimens from the patient to refine the list to those mutated peptides most likely to elicit an immune response," says Mardis. A set of seven mutated peptides unique to each patient were incorporated into a vaccine formulation by co-culturing the peptides with dendritic cells to develop the personalized vaccine for each patient.

To assess T cell immunity to the mutated peptides, the patients' peripheral blood mononuclear cells were monitored weekly. Notably, the team showed that in each patient at least three of the seven peptides had a corresponding T cell population in the blood. "T cell immunity to neoantigens can be pre-existing" says Carreno, "but, more importantly, vaccination with amino acid substituted peptides expands the antigenic breadth of the antitumour responses". In addition, the increased diversity of the T cell populations after vaccination might lead to more efficient tumour destruction.

Importantly, no adverse events were reported in the patients, showing promise for this approach in future studies and possibly with other types of malignancies.

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ORIGINAL RESEARCH PAPER Carreno, B. M. et al. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. *Science* <http://www.dx.doi.org/10.1126/science.1238288> (2015)