Melanoma patient outcomes predicted by computational biology

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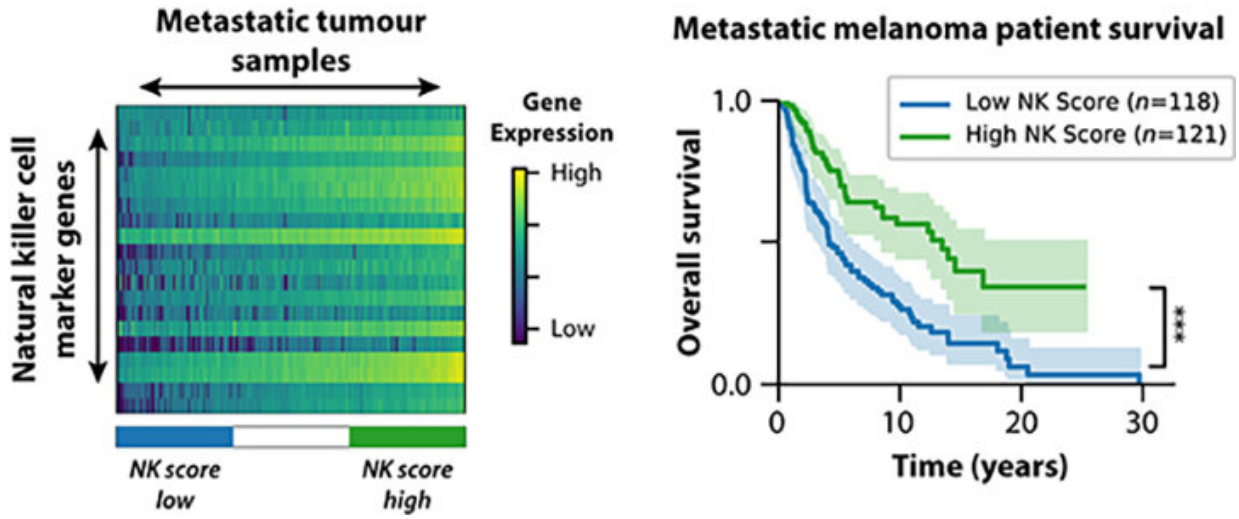

By measuring the levels of expression of natural killer (NK) cell genes in melanoma patient samples (left), the research team could distinguish patients with different levels of expression of the NK gene signature. The plot on the right shows that patients with a high level of the gene signature survived, on average, longer than those with a low level of the gene signature. Credit: Walter and Eliza Hall Institute of Medical Research

Walter and Eliza Hall Institute researchers have used computational biology to discover a "gene signature" that identifies a group of melanoma patients with improved rates of survival.

By looking at the genes expressed or "switched on" in a type of tumour-

fighting immune cell called natural killer (NK) cells, researchers were able to group patients with metastatic melanoma by whether they had high, moderate or low expression of these genes in the tumours. Those patients whose melanomas showed higher levels of NK cell gene expression survived, on average, for longer than those whose melanomas had a lower level of the NK cell genes.

The discovery, published in *Cancer Immunology Research*, suggests that the amount of NK cells in metastatic melanomas is a key factor in patient survival. The research has also suggested new approaches to selecting the best therapies for melanoma patients.

Predicting melanoma outcomes

Melanoma, a form of skin cancer, is the third most commonly diagnosed cancer in Australia, and causes more than 1000 deaths each year.

Melanoma often triggers immune responses, recruiting immune cells such as NK cells into the tumour, said Dr. Fernando Souza-Fonseca-Guimaraes, who jointly led the study with Dr. Joseph Cursons, Professor Nick Huntington and Dr. Melissa Davis.

"It has also been shown that patients whose melanomas have larger numbers of NK cells within them survive, on average, longer than those whose tumours have lower levels of NK cells," Dr. Souza-Fonseca-Guimaraes said. "In some patients, the anti-melanoma immune response can also be harnessed to treat the cancer, a form of treatment called immunotherapy that has recently shown great promise."

Natural killer cells could be detected in melanoma tumours by their unique patterns of gene expression, said Dr. Cursons. "Using a technique called RNA-sequencing, we could measure the relative proportions of different genes within a tumour—including genes that are switched on in

NK cells," he said.

Using computational biology, the team discovered a group of 20 NK cell genes that were expressed at different levels across samples of metastatic melanoma. "Excitingly, this "NK gene signature' correlated with the survival rate of these patients: patients with a high expression level of these NK genes survived, on average, longer than those patients with low levels of the gene signature," Dr. Cursons said.

"This reinforces the role of NK cells as key melanoma-fighting immune cells."

Improving melanoma therapies

The identification of a gene signature that predicts the survival rates of melanoma patients could open new opportunities for personalising melanoma therapies, Dr. Davis said.

"New classes of immunotherapy drugs are already in clinical use, and many of these act by enhancing the anti-tumour effects of immune cells," she said. "By quantifying the level of NK cell infiltration in a tumour, the NK gene signature we developed could help to decide how likely a patient is to benefit from immunotherapies."

The NK gene signature could also be combined with other gene signatures that predict patient outcomes, further refining the understanding of melanoma biology and patient outcomes.

"Another gene signature that we developed, looking at signalling via the protein TGF-β, identified cancer patients who had poor outcomes. When we assessed this TGF-β gene signature in younger melanoma patients, we found that those with low TGFβ and high NK gene signatures had the best survival outcomes," Dr. Davis said.

While the research is preclinical and is not currently available for predicting patient outcomes in a clinical setting, the team hope it could assist in the development and trialling of new approaches to treating metastatic melanoma.

"We hope our research provides a justification for future melanoma clinical trials to routinely include measures of gene expression—an area called transcriptomics—to differentiate groups of patients and how well they may respond to available therapies," Dr. Davis said. "This work really emphasises the importance of computational biology in furthering our understanding of cancer biology and patient outcomes."

More information: Joseph Cursons et al. A Gene Signature Predicting Natural Killer Cell Infiltration and Improved Survival in Melanoma Patients, *Cancer Immunology Research* (2019). DOI: 10.1158/2326-6066.CIR-18-0500

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