include NK cell recruitment and activation factors.

When NK cells were co-cultured with KP lung tumour cells, T + P induced their association and NK cell-mediated killing of senescent cancer cells. KP lung tumour cells with reduced SASP factor expression based on short hairpin RNA (shRNA)-mediated decrease of p65, required for SASP induction, failed to activate NK cells, and T + P was not effective in mice bearing KP lung tumour cells expressing p65 shRNA. The authors confirmed their findings in an autochthonous model of *Kras*-mutant lung cancer and found that tumour necrosis factor and ICAM1 were critical SASP factors to facilitate NK cell surveillance.

Here, it was shown that NK cells, in response to cytostatic drug therapy, act as a natural senolytic to clear out senescent cancer cells in *Kras*-mutant tumours.

Ulrike Harjes

ORIGINAL ARTICLE Ruscetti, M. et al. NK cell-mediated cytotoxicity contributes to tumor control by a cytostatic drug combination. *Science* **362**, 1416–1422 (2018)

which encodes a transcription factor in the Notch pathway, significantly reduced the number of EVP cells and restricted metastasis compared with wild-type mice.

The authors therefore suggest that EVP cells might be an important therapeutic target in regulating cancer, and they are set to translate this research into patients. "We have obtained funding for a small mechanistic trial in which SOX18 inhibition will be initiated upon diagnosis of melanoma, and sentinel lymph nodes collected 3 weeks later will be examined for changes in vascularization," says Khosrotehrani. The hope now is to investigate potential novel anti-vascular cancer treatments that target EVP cells to restrict tumour growth and metastasis, and future studies could determine whether vasculature derived from EVPs occurs in tumour types other than melanoma.

Jordan Hindson

ORIGINAL ARTICLE Donovan, P. et al. Endovascular progenitors infiltrate melanomas and differentiate towards a variety of vascular beds promoting tumor metastasis. *Nat. Commun.* **10**, 18 (2019)

IMMUNOTHERAPY

Glioblastoma is 'hot' for personalized vaccines

Some tumours, such as glioblastoma, are poorly infiltrated by immune cells and are defined as 'cold'. Two phase I studies, recently published in *Nature*, show that the administration of personalized vaccines to newly diagnosed glioblastoma patients generates tumour-reactive T cells that infiltrate glioblastomas, turning them into 'hot' tumours potentially susceptible to further immunotherapy approaches.

Glioblastomas are characterized by a low mutational load and are estimated to contain few non-synonymous mutations, of which only a minority are processed to human leukocyte antigen (HLA)-presented neoepitopes that have the potential to induce a T cell response. The lack of antigenic epitopes is thought to be a major factor limiting glioblastoma immunogenicity. Therefore, vaccines targeting tumour-specific epitopes could unleash an immune response.

Keskin et al. designed a personalized vaccine strategy based on the identification of neoantigens in individual patients by comparing whole-exome sequencing data from the surgically resected tumour with the data from matched normal cells. They identified the coding mutations and, for each patient vaccine, selected a pool of 7–20 peptides representing actionable neoepitopes predicted to bind with high affinity to the HLA class I molecules of each patient.

A similar multi-epitope-based personalized vaccine was engineered by Hilf et al. in their study, although they targeted both neoantigens and unmutated tumour-specific antigens to increase the number of actionable epitopes. Neoantigens were selected using a protocol similar to that described by Keskin et al. The unmutated antigens were selected from a common pool of glioblastoma-specific HLA-bound peptides. For each patient, the unmutated peptides were ranked based on individual HLA immunopeptidome data and pre-vaccine T cell reactivity. Patients were vaccinated with a pool of 9 unmutated peptides (APVAC1) followed by a 20-peptide pool preferentially targeting neoantigens (APVAC2).

In the Keskin et al. study, eight patients with glioblastoma were vaccinated and five patients received both a priming and a booster vaccination. The two patients who did not receive the corticosteroid dexamethasone to treat side effects generated robust circulating T cell responses against multiple immunizing peptides. The response included both $CD8^+$ and $CD4^+$ T cells that were enriched in a memory phenotype. Surgery post-vaccination showed a significant increase in tumour-infiltrating T cells. Analysis of T cell receptor (TCR)-repertoire sequences

Credit: Lara Crow/Springer Nature Limited

demonstrated clonal expansion of neoantigen-reactive T cells in the tumour identical to circulating T cells, suggesting successful trafficking of vaccine-induced T cells to the tumour site. However, these infiltrating T cells also expressed markers of exhaustion, potentially explaining why all of the patients eventually died of progressive disease.

Hilf et al. treated 15 patients with glioblastoma, of which 11 received both the APVAC1 and APVAC2 vaccines. Analysis of the circulating immune response showed that most of the patients developed an increased number of $CD8^+$ T cells reactive to at least one unmutated immunizing peptide that was accompanied by a shift to a memory phenotype. Most patients also developed a neoepitope-specific response that was, however, predominantly a $CD4^+$ T cell response of T helper 1 type. Analysis of the tumour-infiltrating lymphocytes in one responding patient at relapse surgery post-vaccination showed higher T cell infiltration, a favourable $CD8^+$:regulatory T (T_{reg}) cell ratio and $CD4^+$ T cell reactivity against one immunizing peptide. The median overall survival in this study was 29 months, suggesting a potential clinical benefit over other available options.

These studies show that, through personalized vaccines, cold tumours characterized by a low mutational burden can be successfully infiltrated by antigen-specific T cells that have the potential to kill cancer cells. However, once tumour-reactive T cells are brought into place, further treatments might be necessary to remove the inhibitory pressure exerted by the tumour microenvironment in order to produce a lasting clinical benefit.

Maria Giuseppina Baratta, Senior Editor, Nature Communications

ORIGINAL ARTICLES Hilf, N. et al. Actively personalized vaccination trial for newly diagnosed glioblastoma. *Nature* **565**, 240–245 (2019) | Keskin, D. B. et al. Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. *Nature* **565**, 234–239 (2019)