precondition the tumour immune micro-environment to subsequent immune checkpoint blockade

IMMUNOTHERAPY

Viral reprogramming

Only a minority of patients with solid cancers benefit from immune checkpoint inhibition, and tumour response correlates with pre-existing tumour-infiltrating cytotoxic T cells and expression of programmed cell death 1 ligand 1 (PDL1). Therefore, it has been suggested that combinations of immunotherapeutic strategies might provide superior outcomes in more patients. Testing this theory, two studies have used oncolytic viruses to precondition the tumour immune microenvironment to subsequent immune checkpoint blockade in breast and brain tumours — two cancer types that, to date, have not been successfully treated with immune checkpoint inhibitors.

Bourgeois-Daigneault et al. looked at the potential of using Maraba rhabdovirus to induce antitumour immunity in a window-of-opportunity preclinical model that follows the course of treatment for patients with triple-negative breast cancer (TNBC). Intratumoural injection of the virus into syngeneic orthotopic

TNBC mouse models resulted in tumour killing but not overall tumour control or long-term survival of the mice. As surgery is the standard of care for newly diagnosed patients with TNBC, the authors surgically resected primary lesions from the mice following virus treatment and found a reduction in spontaneous lung metastases compared with untreated tumour-bearing animals.

To assess whether virotherapy could prevent tumour recurrence, the authors developed a rechallenge model whereby secondary tumours were orthotopically implanted after removal of the primary lesion initially treated with virus. A single virus injection was sufficient to protect against secondary tumour formation, and this protection was dependent on a T cell immune response.

Samson et al. carried out a phase 1b window-of-opportunity clinical trial where nine patients with recurrent high-grade gliomas or brain metastases were intravenously infused with human *Orthoreovirus* before debulking neurosurgery. Previous trials with oncolytic viruses for glioma have been undertaken with technically challenging intratumoural injections, owing to concerns that the blood–brain barrier would restrict virus delivery. Yet, these authors demonstrated that intravenous reovirus infusion resulted in viral RNA detection in multiple peripheral white blood cell subsets and in resected brain tumours.

Furthermore, systemically delivered reovirus led

to increased interferon release in patient sera.

Importantly, both studies identified that virus infection triggered the upregulation of immune response genes (such as chemokines), which is indicative of virus-induced recruitment of leukocytes to tumours. Consistent with this observation was the greater number of tumour-infiltrating T cells and other immune cells detected in both human brain tumours and mouse TNBCs after virus treatment. Concurrent elevated PDL1 expression mediated by interferons in infected brain and breast tumours relative to control tumours led the authors to hypothesize that the therapeutic activity of tumour-infiltrating T cells might be lessened by the increased T cell inhibitory signalling. In identifying an approach to overcome this obstacle, Samson et al. showed that sequential treatment with intravenous reovirus and programmed cell death protein 1 (PD1) antibody improved survival in an orthotopic mouse model of glioma compared with the individual monotherapies. Similarly, Bourgeois-Daigneault et al. showed that intratumoural Maraba infusion before primary TNBC tumour resection and immune checkpoint blockade led to a complete response in 60–90% of mice after tumour rechallenge. Notably, without prior virotherapy, immune checkpoint inhibition was ineffective in TNBC models after primary tumour resection.

Together, these two studies justify why rational, complementary combination immunovirotherapies warrant further clinical testing.

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ORIGINAL ARTICLES Bourgeois-Daigneault, M.-C. et al. Neoadjuvant oncolytic virotherapy before surgery sensitizes triple-negative breast cancer to immune checkpoint therapy. *Sci. Transl. Med.* **10**, eaao1641 (2018) | Samson, A. et al. Intravenous delivery of oncolytic reovirus to brain tumor patients immunologically primes for subsequent checkpoint blockade. *Sci. Transl. Med.* **10**, eaam7577 (2018)