ANTICANCER DRUGS

Cracking the combination

> these studies describe new combinations of immuno therapies that can effectively treat established tumours

Tumours can evade the immune system by exploiting the regulatory networks that protect healthy host cells from immune-mediated attacks. Targeting such pathways holds promise for treating patients with cancer, but it is becoming increasingly clear that a combination of therapies is likely to be required for clinical efficacy. Two recent studies, published in *Science* and *The Journal of Clinical Investigation*, now describe promising new strategies for combining immunotherapies for cancer treatment.

CD47 is expressed by host cells and functions as a 'don't eat me' signal to macrophages, which recognize this molecule via signal regulatory protein-α (SIRPα; also known as SHPS1). Antibodies that block CD47–SIRPα interactions can promote the phagocytosis of tumour cells by macrophages, but these antibodies also have off-target effects. Weiskopf *et al.* sought to improve existing CD47-based therapies, initially by using the monomeric CD47-binding domain of human SIRPα as an antagonist for CD47. After finding that this interaction was of weak affinity, they engineered variants of human SIRPα that bound CD47 with high affinity.


GETTY

In co-cultures of macrophages and tumour cells, the high-affinity SIRPα monomers did not enhance the phagocytosis of tumour cells by themselves. However, when co-delivered with various tumour-specific antibodies, the monomers significantly increased the phagocytosis of tumour cells. Notably, many of these tumour-specific antibodies are already licensed for the treatment of diverse cancers, including trastuzumab (used to treat breast cancer), cetuximab (used to treat colorectal cancer) and rituximab (used to treat lymphoma).

The authors also tested the efficacy of the combination therapy in a mouse model of lymphoma. Treatment with either rituximab or SIRPα monomers slowed tumour growth, but combining both therapies completely eliminated tumours in most mice. Similar results were obtained in a humanized mouse model of breast cancer. Importantly, the SIRPα monomers were not toxic to healthy host cells. These data suggest that high-affinity SIRPα monomers could be used as a universal adjuvant for antibody-based cancer therapies.

The study by Marabelle *et al.* investigated whether targeting regulatory T (T_{Reg}) cells in tumours could enhance the antitumour effects of CpG oligodeoxynucleotides (ODNs), which are Toll-like receptor 9 agonists. Previous studies had shown that directly injecting CpG ODNs into tumours promoted an antitumour response, but the efficacy of the response was shown to be limited by tumour-associated T_{Reg} cells.

The authors found that tumour-infiltrating T_{Reg} cells from mouse and human lymphomas expressed high levels of cytotoxic T lymphocyte antigen 4 (CTLA4) and OX40 ligand (OX40L; also known as TNFSF4), particularly T_{Reg} cells that were specific for tumour antigens. They showed that the direct injection of CpG ODNs with OX40L-specific or with CTLA4-specific antibodies could deplete T_{Reg} cells and eradicate tumours in mice. Furthermore, the greatest antitumour response was seen when all three reagents were combined.

An interesting aspect of this study is that targeting T_{Reg} cells at a single local tumour site (by direct intratumoural injection of the antibodies and CpG ODNs) prompted a systemic antitumour response and long-lasting protection in mice. By contrast, although the systemic delivery of antibodies and CpG ODNs had an immediate antitumour effect, mice later relapsed. Strikingly, in a model in which mice had both established central nervous system (CNS) lymphomas and subcutaneous lymphomas, the injection of antibodies and CpG ODNs into the subcutaneous tumours also eliminated the CNS tumours. Low doses of the antibodies were found to be effective when they were administered at the local tumour site. This is an important finding as clinical trials have shown that CTLA4-specific antibodies have toxic effects when they are systemically delivered.

Taken together, both of these studies describe new combinations of immunotherapies that can effectively treat established tumours in mice. It will be important to determine whether these strategies show similar promise in patients with cancer.

Yvonne Bordon, Senior Editor, Nature Reviews Immunology

This article originally appeared in *Nature Rev. Immunol.* (doi:10.1038/nri3481)

ORIGINAL RESEARCH PAPERS Weiskopf, K. *et al.* Engineered SIRPα variants as immunotherapeutic adjuvants to anticancer antibodies. *Science* 30 May 2013 (doi:10.1126/science.1238856) | Marabelle, A. *et al.* Depleting tumor-specific Tregs cells at a single site eradicates disseminated tumors. *J. Clin. Invest.* 24 May 2013 (doi:10.1172/JCI64859)

FURTHER READING *Nature Reviews Cancer* and *Nature Reviews Immunology* Focus issue on tumour immunology and immunotherapy: http://www.nature.com/reviews/focus/tumourimmunology/index.html