IMMUNOTHERAPY

Combinations that work

Targeted cancer therapies can modulate host immune responses, which raises the possibility that efficacy might be improved by combining these therapies with immune-stimulating agents. Preclinical data in support of such a strategy have been reported in two recent papers.

Knowing that the activity of the monoclonal antibody trastuzumab (which targets ERBB2) in breast cancer is partly due to antibody-dependent cellular cytotoxicity (ADCC), which depends on natural killer (NK) cells, Ronald Levy and colleagues investigated whether activation of the co-stimulatory molecule CD137 (also known as TNFRSF9 and 4-1BB) in NK cells could improve trastuzumab efficacy. *In vitro* studies showed that co-incubation of ERBB2-expressing breast cancer cell lines and purified human NK cells with trastuzumab upregulated CD137 on the NK cells. These activated NK cells were able to kill trastuzumab-coated ERBB2-expressing breast cancer cell lines through ADCC, and this was enhanced by a CD137 agonistic antibody. To investigate this combination *in vivo*, the authors used a xenograft model of human breast cancer cells in athymic mice, which lack functional T cells but which have NK cells. Mice were injected with trastuzumab on day 3 after tumour inoculation, and the CD137 antibody was injected on day 2, day 3 or day 4. Trastuzumab followed by CD137 antibody treatment significantly reduced tumour growth and increased mouse survival compared with either antibody alone. Interestingly, if ERBB2-expressing and non-expressing cell lines were transplanted into opposite flanks on the same mouse, the combination treatment only had an enhanced effect against the ERBB2-expressing tumour, indicating specificity for trastuzumab-bound cells, which may translate to reduced systemic toxicity. Treatment with trastuzumab followed by the CD137 antibody was also effective against a xenograft of a primary ERBB2-expressing human breast tumour in severe combined immunodeficient (SCID) mice (which have NK cells but which lack a functional adaptive immune response). Finally, the authors examined circulating NK cells in patients with breast cancer who were receiving trastuzumab therapy and, although heterogeneous, overall there was an approximately twofold induction in CD137 expression in the NK cells following trastuzumab infusion. These data suggest that the timing of antibody administration should be carefully considered in any clinical studies of this combination.

> “efficacy might be improved by combining [targeted] therapies with immune-stimulating agents”

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It is also important to bear in mind that CD137 activation can influence other immune cells besides NK cells, and this was addressed in work by Phillip Darcy and colleagues. As host immune responses can mediate the anti-tumour effects of oncolytic viruses, these authors examined the combination of a CD137 agonistic antibody with an oncolytic vaccinia virus (Vvdd, which selectively kills tumour cells but which is not tumour type-specific). In immune-competent mice, this combination significantly reduced the growth of established tumours derived from breast or colorectal cancer cell lines and increased survival compared with either treatment alone. In mice with subcutaneous breast tumours, combination therapy also significantly reduced the number of metastatic lesions in the lungs. Analysis of the immune cells present in the tumour following treatment revealed an increase in neutrophils, $CD8^+$ T cells and NK cells following Vvdd treatment alone; the addition of the CD137 antibody seemed to contribute to a sustained response by the neutrophils and $CD8^+$ T cells. Depletion of each of these immune cell types in mice prior to initiating therapy indicated that all three were required for maximal inhibition of breast tumour growth, supporting roles for both innate and adaptive immune responses. One mechanism by which $CD8^+$ T cells and NK cells promote anti-tumour responses is through the secretion of interferon-γ, and the authors also showed that tumours in mice lacking this cytokine had a reduced response to Vvdd and to the CD137 antibody.

Together, these studies further establish a rationale for clinical testing of immune stimulation by CD137 activation combined with tumour-targeted therapies.

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ORIGINAL RESEARCH PAPERS Kohrt, H. E. *et al.* Stimulation of natural killer cells with a CD137-specific antibody enhances trastuzumab efficacy in xenotransplant models of breast cancer. *J. Clin. Invest.* 13 Feb 2012 (doi:10.1172/JCI61226) | John, L. B. *et al.* Oncolytic virus and anti-4-1BB combination therapy elicits strong anti-tumor immunity against established cancer. *Cancer Res.* 7 Feb 2012 (doi:10.1158/0008-5472.CAN-11-2788)
FURTHER READING Vanneman, M. & Dranoff, G. Combining immunotherapy and targeted therapies in cancer treatment. *Nature Rev. Cancer* **12**, 237–251 (2011)