IMMUNOTHERAPY

Put your coat on!

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Unlike syngeneic tumour transplants, allogeneic tumour transplants (those that are from the same species but that have distinct antigens) are rejected by a robust immune response. A recent publication in *Nature* indicates that the coating of tumour cells with immunoglobulin G (IgG) is crucial for this response.

Initially, Carmi *et al.* showed that B16 melanoma cells were able to proliferate unchallenged in syngeneic C57BL/6 mice but were rejected in allogeneic 129S1 mice and vice versa: metastatic pancreatic tumour cells from 129S1 mice grew when transplanted in syngeneic hosts and were rejected in C57BL/6 mice. Allogeneic rejection was blocked by removal of either $CD4^+$ or $CD8^+$ T cells but was unaffected by the removal of natural killer cells. Moreover, mature myeloid dendritic cells (DCs) were higher in number and had an activated phenotype in allogeneic transplanted tumours compared with syngeneic tumours. However, co-culture of DCs with allogeneic tumour cells *in vitro* resulted in minimal activation of DCs, indicating that additional activation signals were present *in vivo*.

The authors noted that the allogeneic tumours were coated with IgG and IgM molecules before rejection, and this was not evident in syngeneic tumours. *In vitro* analyses indicated that activation and uptake of tumour antigens by bone marrow-derived DCs and subsequent stimulation of T cells were only triggered by allogeneic immunoglobulins and not syngeneic immunoglobulins. However, allogeneic IgG injected into tumours in autologous mice had little effect on tumour growth. Examination of tumour-associated DCs (TADCs) explanted from the mice indicated that, in the absence of DC stimuli, these cells were not activated by the presence of immunocomplexes formed by allogeneic IgG bound to tumour cells or a tumour cell lysate (alloIgG-IC). The authors used several methods (including the addition of tumour necrosis factor (TNF) and CD40L) to activate the TADCs, and this combined with alloIgG-IC resulted in tumour protein uptake and presentation by TADCs *in vitro*, as well as robust T cell activation and tumour regression *in vivo*. Allogeneic IgG given with TNF and CD40L also induced the regression of disseminated melanoma and of metastatic breast cancer in mouse models.

Is this stimulation of DCs and induction of an immune response purely a property of allogeneic immunoglobulin? The authors crosslinked syngeneic IgG to syngeneic tumour cells, and this also resulted in activation of bone marrow-derived DCs, indicating that it is the binding of IgG to the tumour cells in large quantities rather than the binding of allogeneic immunoglobulin that is important for an immune response. Moreover, binding of IgG to specific allogeneic antigens was not important for the T cell-mediated immune response, which was driven by tumour-specific antigens.

Isolation of human syngeneic IgG, tumour cells, TADCs and allogeneic IgG from healthy donors was used to show that allogeneic IgG bound to human cancer cells in the presence of TNF and CD40L also induced activation of TADCs. Moreover, bone marrow-derived DCs isolated from two patients with mesothelioma were able to stimulate the proliferation of $CD4^+$ T cells after treatment with alloIgG-IC.

These findings indicate that antibody-mediated uptake of tumour antigens by suitably activated TADCs can induce robust rejection of tumour cells. Other studies have linked the presence of immunoglobulin with tumour progression and chemotherapy resistance, indicating that the role of immunoglobulins in cancer development and treatment is complex. Nevertheless, this initial evidence that tumour cells coated with immunoglobulin can provide a means to initiate a potent antitumour immune response warrants further examination.

Nicola McCarthy
Horizon Discovery Group, Cambridge, UK

The author declares no competing interests.

ORIGINAL RESEARCH PAPER Carmi, Y. *et al.* Allogeneic IgG combined with dendritic cell stimuli induce antitumour T-cell immunity. *Nature* **521**, 99–104 (2015)
FURTHER READING Shalapour, S. *et al.* Immunosuppressive plasma cells impede T-cell-dependent immunogenic chemotherapy. *Nature* **521**, 94–98 (2015) | de Visser, K. E., Eichten, A. & Coussens, L. M. Paradoxical roles of the immune system during cancer development. *Nature Rev. Cancer* **6**, 24–37 (2006)