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Journal club

ALTERED SELF: THE NOT-SO-NEO-ANTIGENS

The field of cancer neo-antigens seems to have emerged into the scientific consciousness most prominently in 2017 with the publication of two important papers elegantly showing how information from next-generation sequencing of cancer exomes could be used to design vaccines targeting antigens on cancer cells (Ott *et al.*, 2017 and Sahin *et al.*, 2017). However, the concepts underlying these groundbreaking studies have deep roots in efforts to identify and vaccinate against cancer antigens.

Approaches to generate immune responses to cancer antigens have not solely focused on random carcinogen-induced changes in DNA sequence. In 1996, my once-and-always mentor, Alan Houghton, and graduate student Clarissa Naftzger, published a paper showing how immune tolerance to self antigens on cancer cells could be overcome by using xenogeneic orthologues or altered-self antigens. Using the syngeneic B16 mouse melanoma model, Naftzger *et al.* showed that tumour immunity and autoimmunity (as indicated by coat depigmentation) could be induced by immunizing C57BL/6 mice with either the xenogeneic (human) orthologue of the melanosomal differentiation antigen gp75 (also known as TRP1) or native mouse gp75 produced in insect cells.

> “protective immunity … could be mediated by targeting a self molecule”

These studies revealed several important concepts. First, protective immunity to an otherwise poorly immunogenic cancer could be mediated by targeting a self molecule. Second, tolerance to a self molecule could be overcome by using a xenogeneic orthologue, which presumably contains neo-epitopes. Third, tolerance could also be overcome by using antigen with a wild-type DNA sequence but produced in a non-mammalian cell, hypothetically because of differences in glycosylation or processing.

Another important message from the Houghton group was that humoral immunity can have an important role in therapeutic tumour immunity, as passive administration of antibodies specific for gp75 was shown to result in tumour protection and coat depigmentation (Hara *et al.*, 1995). This point is important to recall in the current era of “T cell chauvinism”, as has been described by Stephen S. Hall (in *A Commotion in the Blood: Life, Death and the Immune System*).

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The author declares competing interests: see Web version for details.

ORIGINAL ARTICLE Naftzger, C. *et al.* Immune response to a differentiation antigen induced by altered antigen: a study of tumor rejection and autoimmunity. *Proc. Natl Acad. Sci. USA* **93**, 14809–14814 (1996)

FURTHER READING Ott, P. A. *et al.* An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature* **547**, 217–221 (2017) | Sahin, U. *et al.* Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature* **547**, 222–226 (2017) | Hara, I. *et al.* Implicating a role for immune recognition of self in tumor rejection: passive immunization against the brown locus protein. *J. Exp. Med.* **182**, 1609–1614 (1995)