Perspective

A new rat model of prostate cancer

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The current status of immunotherapy of cancer dictates that tumour cells should express appropriate antigenic peptides on the cell surface associated with MHC class I antigen. Therapies designed to activate immunity against cell surface expressed target peptides are required to induce antigen specific cytotoxic T-lymphocytes (CTL) capable of mediating tumour rejection and that such immune responses should produce immunological memory. The necessity for both MHC class I (CTL response) and class II (T-helper response)—restricted responses has been well documented and the nature of tumour antigens expressed on a wide variety of human cancers widely reported.

For prostate cancer several differentiation antigens have been proposed as suitable targets for immunotherapy, these include prostate specific membrane antigen (PSMA), prostate specific antigen (PSA) and prostatic acid phosphatase (PAP). The latter has been the subject of recent interest since vaccination against PAP has resulted in clinical trials demonstrating efficacy in prolonging overall survival of patients. This led to FDA approval for PROVENGE (sipuleulel-T), a dendritic cell- PAP vaccination protocol, however, the results, although encouraging, are not dramatic and there is considerable scope for improving patient response. PROSTAC is a PSA based vaccine using pox viruses as a vehicle for immunisation and is currently in phase three trials. Given the unmet need to treat patients with advanced disease and the potential of immunotherapy to programme the immune system to recognise tumour associated antigens, an essential element of research will rely on pre-clinical evaluation of cancer vaccines in appropriate models. This will lead to a greater understanding and optimisation of vaccine formulation and the necessity to target specifically immunity that destroys metastatic tumours together with strategies to control tumour escape mechanisms, for example, abolition of the functional activity or number of T-regulatory (Treg) lymphocytes.

Prostate cancer is an intractable disease and the most prevalent male cancer worldwide, where 1 in 4 patients will die from widespread metastasis, usually involving secondary tumour development in the bone. In men with castration-resistant prostate cancer, the treatment options are limited and the demand for new effective therapeutic intervention strategies is increasing. For progress to be made in the development of new therapies for advanced disease, efficacy in pre-clinical models of spontaneously arising cancer is a pre-requisite. The TRAMP mouse model of prostate cancer has been widely used and the progression of pathological changes in the prostate from epithelial hypoplasia to poorly-differentiated cancer has been well documented. It would therefore be an advantage to have alternative and additional models for assessing new therapeutic strategies. Until now the rat model of prostate cancer has only been developed in "outlined" strains, which restricts the scope for immunotherapy studies.

The publication by Johnson *et al.* in this issue of *Chinese Clinical Oncology* is concerned with the development of a Lewis rat model that provides advantages over the previous rat prostate cancer model and an alternative to the mouse TRAMP model. In order to generate a syngeneic rat model of prostate cancer Johnson and colleagues utilised the outbred of Sprague Dawley strain of rat, transgenic for the SV40 *T Ag* gene inserted downstream of the prostate-specific probasin promoter. These rats were back-crossed with a non-transgenic Lewis strain of male rats for ten generations, resulting in a transgenic rat on a Lewis strain background (Lew-TRAP). This study reports spontaneous

prostate tumours developing in 100% of transgenic Lew-TRAP rats, the establishment of prostate tumour cell lines and the demonstration, at least for PAP tumour associated antigen, that peptide specific responses could be generated following immunisation with a DNA vaccine encoding human PAP protein sequences.

Not yet fully explored in this Leu-TRAP rat model, is the development of castration-resistant tumours, which are likely to develop late in the natural history of tumour development, although preliminary data from Johnson *et al*. alludes to this possibility. The Leu-TRAP rat cancer model may share several features with the widely used TRAMP mouse model, making it an attractive alternative system for developing new therapies, especially useful for assessment of immunotherapy and combination therapy. Should androgen-independent tumours arise later in the course of disease, this will be highly relevant for assessing the potential of new therapies for clinical translation.

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