A New Strategy for Immunotherapy of Cancer

Cancer immunotherapy holds out great promise, but good animal results have not been successfully translated to the clinic. This re-evaluation brings forward new ideas about immune responses in cancer patients that may improve strategies in future.

The best way to prevent and remove infections is through the natural ‘sterilising’ action of the immune system, which combines innate and adaptive immunity to ward off foreign pathogens without medical intervention. The immune system ‘remembers’ the cleared foreign antigens to speed up its response to re-infection. The immune system in most cancer patients can still completely destroy viruses and bacteria. The ferocity and specificity of this response can be witnessed in the way an inadequately suppressed immune system can completely destroy a large transplanted organ, while sparing one’s own (self) tissues. This destructive effect would be beneficial for cancer therapy if it could be directed at tumours.

The field of immunotherapy seeks methods to harness, direct and control this immunity especially against cancer. Therapeutic cancer vaccines are a form of immunotherapy designed to educate the immune system of patients with existing cancers to recognise their tumour cells as foreign rather than self. If successful, an immune response could theoretically stimulate immune cells to destroy large tumours, and also seek out and destroy metastatic tumour cells. Alternatively immunotherapy could educate the immune system to ‘remember’ tumour cells ought to eliminate any recurrence without additional treatment in much the same way as it protects against opportunistic infections.

Immunotherapy is a highly desirable alternative (or complement) to current treatment strategies. Unlike immune-mediated anti-tumour mechanisms, surgery, radiation and chemotherapy have no anti-tumour specificity at the single cell level. Therefore, it is not technologically feasible for them to eliminate every last tumour cell, without which cancer recurrence commonly occurs. Furthermore, these modalities lead to resistance rather than ‘memory’ of tumour.

The immune system promises complete tumour elimination and durable remissions with properly designed cancer vaccines. Its specificity in targeting malignant cells and avoiding normal cells also promises minimal toxicity. This is the only currently feasible approach that has the technical possibility to cure cancer.

Current immunotherapy development status

The ability to educate the immune system to remove all cancer cells has been successful in some animal models. Mice can be immunised to reject syngeneic transplanted tumours and protect against tumour rechallenge without further treatment, whereas non-immunised mice invariably die. Protection is tumour-specific, since immunised mice succumb to challenges from different tumours. Tumour-specific CD8+ cytotoxic T-cells (CTL) are mainly responsible for tumour elimination. Moreover, CTLs can specifically recognise tumour cells and do not attack normal cells of the same tissue.

While these animal studies provide “proof-of-concept” for translating these methods to the clinic, the promise of immunotherapy has not been realised. In the last two decades, immunological strategies have been designed to stimulate anti-tumour immunity in cancer patients, by vaccination with peptide-pulsed or tumour lysate-pulsed dendritic cells, cytokine-mediated immunotherapy, the administration of large numbers of T cells generated from tumour-infiltrating lymphocytes or engineered to express receptors for specific tumour-associated antigens (TAA), ‘naked DNA’, and recombinant virus. Despite numerous attempts, the success rate of clinical immunotherapy remains abysmally low. However encouraging reports of successful trials using novel cancer vaccines in prolonging survival in prostate cancer illustrates the potential of this approach, although the results fall far short of the curative potential.

Despite the poor clinical results, dozens of cancer vaccine clinical trials are currently being conducted by both industrial and academic sponsors. One of the reasons for continuing development and testing of anti-cancer vaccines is the demand for alternatives to the high morbidity associated with other modalities of treatment, since immunotherapy has little toxicity. While response rates to highly toxic chemotherapy have improved over the last two decades, the modest increase in 5-year survival [1] has come at a severe price in terms of quality of life.

Flaws in cancer vaccine development

The failure of hundreds of immunotherapy clinical trials to produce significant anti-tumour activity calls for a re-examination of the underlying principles. For over 200 years, vaccines have been used successfully to prevent numerous infectious diseases by inducing a humoral response (antibodies). The same concept is being applied to develop cancer vaccines with the intention of treating existing tumours, despite the fact that vaccines giving protection against pathogenic infection are incapable of curing existing infections with the same pathogen. Hence, modeling of cancer therapy on the basis of protective immunity is fundamentally flawed as a strategy because protective immunity does not provide therapeutic immunity. Therapeutic immunity to cancer requires a cellular immune response.

Cancer vaccination has followed classical development strategies by focusing on finding unique antigens on tumours not found on normal cells, i.e. tumour-specific antigens (TSA), or by seeking tumour-associated antigens (TAA) overexpressed by cancer cells. TSAAs have only been found in tumours induced by infectious agents (e.g. EBNA-1 antigen from Epstein Barr virus-induced Burkitt’s lymphoma). However, many TAAs have been identified, including CEA, MUC1, HER-2/neu and α-fetal protein, of which some are expressed on many tumour types, but not on
normal tissues, with the exception of spermatogonia (e.g. MAGE family, GAGE family and NY-ESO-1 antigens). TAAs are self antigens and thus do not mark tumours as foreign, but nevertheless enable immunological distinction between tumour and normal cells.

Cancer vaccines containing TAA can also contain agents that augment the ability of these antigens to stimulate anti-tumour immune responses. These have included mixture with immunological adjuvants (such as MF59, incomplete Freund’s adjuvant, saponins QS-21, and bacillus Calmette-Guerin [BCG]), synthesis of more immunogenic derivatives, conjugation to immunogenic proteins, and pulsing directly to dendritic cells, but without much success.

The perceived need for ‘augmenting’ TAA is based on the assumption that, since TAAs are derived from self tissues, rather than from foreign pathogens as in previous vaccines, they are relatively weak. Methods that enhance the immunogenicity of TAA are thought to be essential for eliciting stronger responses that can have a clinical anti-tumour effect. The assumption is that cancer is a disease of a weakened immune system and, therefore, methods are required to ‘boost’ the immune system to treat cancer. Traditional immunology has taught us that the main purpose of the immune system is to distinguish between “self” and “non-self”, and since cancer is “self”, there should be no immune response against it, a concept which is also fundamentally flawed.

**Cancer: a disease of a weak immune system?**

When a normal cell transforms into a tumour cell, changes occurring in the surface expression of antigens give rise to TAAs that can theoretically be detected by immune cells. Ehrlich first postulated in 1909 that the immune system protects the host against cancer, a concept modified in the 1950s by Lewis Thomas and later by Nobel laureate Sir Macfarlane Burnet, who proposed that the immune system has a “surveillance” mechanism for eliminating precancerous and cancerous cells. The fundamental tenet of this hypothesis is that tumours arise constantly in the body and the immune system must recognise and eliminate cells that express TAAs. It predicts that in circumstances where the immune system is weak or suppressed, surveillance is compromised, tumour cells take hold and clinical disease results. This has been the basis on which the immune system in cancer cases is seen as weak, and so the immune system must be strengthened to mount an attack against cancer. However, there is much evidence to the contrary.

While a few rare cancers occur in immunosuppressed individuals, most human cancers form in immunocompetent individuals. Additionally, there is no doubt that many neoplasms, particularly those of epithelial origin, have a significant inflammatory cell component. This includes a diverse leukocyte infiltrate of macrophages, neutrophils, eosinophils, and mast cells, often in association with lymphocytes. Tumours are usually abundantly infiltrated with immune cells, which argues against weak recognition of their antigens. Further, many attempts to augment the immune response enhance rather than suppress tumour growth [2,3]. In mice, a newly induced in situ tumour, both of mesenchymal and epithelial derivation, can be stimulated to grow faster if it engenders an immune response. Even highly immunogenic tumours left undisturbed in their original hosts can grow faster than tumours with little or no immunogenicity. Therefore, the idea that tumours are “invisible” to the immune system, which therefore needs to be boosted, is misconceived. The problem may be that the immune response to the tumour, while strong, may be of the wrong type. In attempting to boost an immune response that has already failed to protect against tumour formation, it is not surprising that tumour growth may be enhanced rather than suppressed. This is another flaw in the strategy of cancer vaccine development.

**Right versus wrong immune response to cancer**

Before designing a cancer vaccine of therapeutic potential, the type of immunity that is required for tumour elimination needs to be understood. Immune responses are generally described by two polarised responses, the T-helper type 1 (Th1) and the T-helper type 2 (Th2). A Th1 response mediates cellular immunity and is critical for immune-mediated tumour eradication; a Th2 response mediates humoral immunity, the type of immunity that can protect against some infectious diseases, but is the “wrong” or inappropriate response to a tumour. Tumour-mediated deviation of T-helper cell differentiation to Th2 is a tumour strategy for immunovoidance and survival. In fact, an ineffective Th2 response can be detected in most patients with advanced cancer and metastatic disease. This explains why simply boosting the immune response in cancer patients fails, as this only serves to enhance a resident Th2 response that has already failed to protect against tumour formation and is incapable of eradicating cancer.

Th1 and Th2 responses are counter-regulatory, increased Th1 responses downregulate Th2 responses and vice versa. Therefore, we propose that one function of a successful cancer vaccine candidate would be to avoid enhancing an existing “wrong” Th2 response, and...
In the past, immunotherapy methods have been translated from animal models to the clinic, but without significant anti-tumour efficacy. Understanding human immune mechanisms involved in normal pregnancy and spontaneous abortion provides a model for designing vaccine immune responses to overcome self-tolerance.
presence of Th1 cytokines, as occurs in the curative GVT effect after allogeneic BMT. The presence of Th1 cytokines can drive uncommitted T-cells to develop a Th1 cytokine profile, while simultaneously inhibiting cells with the reciprocal phenotype; e.g. IFN-γ, a Th1 cytokine, can selectively expand Th1 cells and inhibit proliferation of Th2 cells. Further, breaking of tolerance to autologous tissues is also feasible in a sustained Th1 inflammatory environment, as evidenced by Th1-mediated spontaneous abortion and Th1-mediated GVHD, which acts as an adjuvant to the curative Th1 anti-tumour effect in allogeneic BMT procedures.

These mechanisms are consistent with the new concept called the “danger theory”, which proposes that the regulation of tolerance and tolerance is not determined by recognition of self versus foreign antigens as previously thought, but by the context in which the antigens are presented to the immune system [4,5]. Thus antigen expression with Th1 rather than Th2 context in dendritic cells (DC) in an appropriate environmental context prompts a strong Th1 immune response regardless of whether the antigens are self- or foreign-derived. In contrast, antigen capture by DC in a non-inflammatory context leads ultimately to immunotolerance. A tumour “conditions” the microenvironment for the tolerant response, but where normal cells are being destroyed as in GVHD, an active Th1 response is favoured.

A new experimental cancer vaccine protocol

To elicit anti-tumour immunity, it is necessary to engineer the microenvironment where DCs are processing tumour antigens to contain sufficient inflammatory “danger signals” potent enough to downregulate tumour-mediated immunosuppressive cytokine production and related tolerogenic mechanisms. This should enable the development of a Th1 immune response against the tumour, whose magnitude and duration will also control whether it is sufficient to downregulate tumour immunovoidance mechanisms. This depends on the extent and quality of the local inflammatory response and the maintenance of a systemic inflammatory response over a long duration to disable immunoavoidsance.

Based on concepts derived from actual human immune mechanisms leading to curative anti-tumour immunity and the breaking of natural immunotolerance, we propose a novel approach to cancer vaccine development, proof-of-concept having been shown in animal tumour models [6,7]. The protocol has three separate phases, the first designed to increase the circulating numbers of Th1 immune cells in cancer patients, shifting the balance from Th2 to Th1. The second elicits anti-tumour specific Th1 immunity. The third relies on activating components of the innate and adaptive immune cells in cancer patients, shifting the balance from Th2 to Th1. The second elicits anti-tumour specific Th1 immunity. The second elicits anti-tumour specific Th1 immunity. The protocol incorporates these new concepts for the development of cancer vaccines is about to be tested in the clinic. The results might, in due course, bring us closer to realising the promise of immunotherapy in cancer.

References

14. Richmond Prehn has discussed this problem in an earlier issue of Oncology news (Prehn RT. A cancer vaccine or just wishful thinking? Oncology News 2006;1;8-10).

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