Published in final edited form as:
Curr Opin Immunol. 2010 April ; 22(2): 212–214. doi:10.1016/j.coi.2010.03.001.

Understanding and activating immunity against human cancer

Freda K Stevenson and
University of Southampton, School of Medicine, Cancer Sciences Division, Tremona Road, Southampton SO16 6YD, United Kingdom, fs@soton.ac.uk

Karolina Palucka
Baylor Institute for Immunology Research, Dallas, TX, USA, karolinp@baylorhealth.edu

It has required the tools of modern biology to develop realistic strategies to activate immunity against cancer cells in patients. Genetic technology is now revealing new target antigens and is providing the means to deliver these effectively to the immune system. Pathways of immunity and its regulation are also being mapped by the use of genetically manipulated mice. A hurdle to progress in the past, still not fully recognized, is a mismatch between mouse and human tumors. Pre-clinical models are bedeviled by the fact that the majority of passaged tumor cell lines harbor retroviral sequences, many potentially functional. These are readily released and retroviral antigens can self-immunize, leading to induction of cytolytic T cells able to suppress the tumors [1]. There is little evidence of counterparts in most human tumors and this difference is one of the many reasons for the failure to translate promising findings in mice to patients [2,3]. It is driving investigators to focus more attention on human tumors and we have tried to reflect this in our issue.

In this edition we have brought together reviews concerning natural immunity against cancer in patients and pointing to the importance of the microenvironmental influences on induction and maintenance of effective immunity. We have then highlighted novel tumor antigens and described strategies to activate immune attack, always aware that clinical trials are the real test.

The question of whether the natural immune response has a role in modulating the progress of spontaneous tumors in human subjects has been asked for many years. Now, as discussed by Galon *et al.*, immunohistochemical analysis of colorectal cancers is revealing that both the level and distribution of T cells in the tumor tissue, described as the ‘immune contexture’, appear to have significant prognostic value. Infiltrating memory T cells in particular are associated with a good prognosis and reduced metastasis, supporting the concept that T-cell immunity is important in controlling cancer. Genes expressed during successful control of cancer should provide clues for vaccine strategies.

In terms of maintenance of immune pressure, drawing an analogy between chronic infection and cancer is informative, since, in both settings, there is persistence of antigen that can exhaust T cells. Ahmed *et al.* have described both the similarities and differences between the effects of infection and cancer on T cells, and have delineated the hierarchical molecular changes associated with progressive T-cell dysfunction. One suggestion for cancer, where tolerance to self antigens may be an added factor, is that anergy is the dominant inhibitory pathway in the early stages, with exhaustion occurring later. These findings offer prospects for reversal of inhibition, one being to block the PD-1/PD-L1 interaction during vaccination.

A key factor in the initiation and progression of cancer, and in the operation of vaccines, is inflammation. The link between the development of gastric lymphoma and the presence of Helicobacter pylori is a striking example of this [4]. The remarkable reversal of the progression of gastric lymphoma following elimination of the infection underscores the

clinical relevance of understanding this link. As described by Mantovani *et al.*, tumor-associated macrophages are likely to have a central role in pathogenesis and can be re-programmed by signals from cancer cells and by interaction with immune cells. However, macrophages can also suppress tumor growth, and they, and innate immunity in general, have a clear importance for vaccination [5]. As always, we need to be careful to consider the heterogeneity of cell populations and the plasticity of function in different settings. This review describes the potential duality of macrophages, with the balance being important for controlling immunity against cancer.

While tumor-associated macrophages are emerging as a crucial influence on tumor behaviour, they may not be the only cell type involved. Bronte *et al.* focus on myeloid-derived suppressor cells (MDSCs) that have been defined in mice on the basis of markers and on the functional ability to suppress T-cell activation. The review points out that MDSCs are part of a 'myeloid macropopulation' that includes polymorphonuclear and monocytic cells. Human MDSCs do not have the same markers, but appear likely also to contain both these populations, identified by expression of arginase and of other immunosuppressive molecules [6]. The level of maturity of myeloid cells in patients with cancer may also differ, and studies could have been hampered by loss of important cell fractions during collection and storage. Clearly there is much to learn about the components of MDSCs and their role in cancer immunity, especially in patients.

Assuming that vaccination, possibly combined with strategies to block specific inhibitory pathways, can reverse immunosuppression and take its place in treatment, there is a need for an ideal set of target antigens. In their review, Dhodapkar *et al.* discuss the pluripotent nature of cancer cells. They point out that the linkage between expression of genes associated with pluripotency and those expressed in cancer. While much has been made of the need to target stem cells among cancer cell populations, this review considers the question as to whether the quality of 'stemness', which is dynamic and could derive from the influence of microenvironmental factors on cancer cells, should be the real target. Ideal target genes would be those shared between cancer cells and embryonal cells, but not expressed in adult stem cells, and several examples are described. A corollary of the study of 'stemness' is that it could illuminate the potential risk of tumor formation as a byproduct of stem cell-based therapies.

Even when an ideal target is identified, the challenge of activating immunity in the patient remains. One way of avoiding this is to generate specific T cells *ex vivo* and then transfer these to the patient. Heslop *et al.* have used this approach successfully for preventing or treating Epstein-Barr virus-associated lymphomas post-transplantation, and they now review how this strategy has developed for cancer antigens. A promising approach is to clone the T-cell receptor α and β chain genes from tumor-reactive cytotoxic T cells into fresh T cells via an integrating vector. While these artificial T cells can be produced quite rapidly, and show some efficacy *in vivo*, questions of survival, migration, efficacy against tumor, and toxicity, remain and are considered.

Active immunization has been a successful strategy for prevention of infectious diseases [7]. One example showing great promise is prevention of HPV+ve cervical cancer by vaccinating with a recombinant viral capsid protein [8]. Therapeutic vaccination is always more difficult especially as most cancer antigens are weak and immune capacity in the patient may be tolerized or damaged by treatment. Two reviews consider separate options for activating immunity: the first, by Palucka *et al.*, focuses on the use of dendritic cells to initiate immune responses. The second, by Stevenson *et al.*, describes an alternative approach using DNA vaccination. Both articles share the concept that, even with a single antigen, the delivery system will influence outcome. For DCs, dermal CD14+ DCs tend to

induce superior humoral responses, while Langerhans cells are more efficient in inducing CD8+ T cells responses. For DNA delivery, full length antigen sequence, fused to foreign sequences, induces strong humoral responses, whereas MHC Class I-binding peptide sequences fused to a minimized foreign sequence, generates high levels ofCD8+ T cells. It evidently pays to know the antigen and to plan the vaccine design according to the desired outcome.

Both DC-based vaccines and DNA vaccines are now in clinical trials, and each review stresses the need for objective measures of immune response profiles linked to assessment of clinical effect. The overall theme of the issue is to bring together and evaluate the ingredients necessary for success in using the immune system to attack cancer cells. Clearly our understanding is evolving and our ability to engineer T cells or vaccines has advanced.

Cancer vaccines are indeed in a renaissance era owing to a number of recent phase II and phase III clinical trials that show promising immunological data and some clinical benefit to the patients. For example, an active immunotherapy product sipuleucel-T (APC8015) appears to contribute to prolonged median survival in phase III trials in patients with prostate cancer [9]. Similarly, a randomized phase II trial of a poxviral-based vaccine approach targeting PSA (PROSTVAC) in men with metastatic castration-resistant prostate cancer showed improved overall survival in patients who received PROSTVAC compared to patients receiving control vectors [10]. While these first generation positive randomized phase II/III clinical trials need further analysis and mechanistic studies, they underline the therapeutic potential of the immune system that can be tapped into. Trials of efficacy in patients are now proceeding and the outcomes will drive the next phase of this long journey.

Biographies

Freda K Stevenson obtained her DPhil degree from the University of Oxford, UK. After lecturing in the University of Sydney, she returned to Oxford to the Department of Biochemistry with a lectureship at Oriel College. She was then involved in establishing a new laboratory at the University of Southampton, which now has a strong reputation in the study of human B-cell malignancies. Her particular focus is the development of DNA vaccination as a strategy to suppress a range of tumors in patients.

Karolina Palucka obtained her MD degree from the Warsaw Medical Academy in Poland. She completed the medical-oncology residency programme at the Maria Sklodowska-Curie Memorial Institute of Oncology in Warsaw, and obtained her PhD in tumor immunology from the Karolinska Institute in Stockholm (Sweden). She completed her postdoctoral training in dendritic-cell biology at the Immunology Laboratory of the Hospital Pitie-Salpetriere in Paris. Her main focus is the biology of dendritic cells in cancer and their utilization as vectors for therapeutic vaccination.

References

1. van Hall T, van Bergen J, van Veelen PA, Kraakman M, Heukamp LC, Koning F, Melief CJ, Ossendorp F, Offringa R. Identification of a novel tumor-specific CTL epitope presented by RMA, EL-4, and MBL-2 lymphomas reveals their common origin. J Immunol. 2000; 165:869–877. [PubMed: 10878361]
2. Steinman RM, Mellman I. Immunotherapy: bewitched, bothered, and bewildered no more. Science. 2004; 305:197–200. [PubMed: 15247468]
3. Davis MM. A prescription for human immunology. Immunity. 2008; 29:835–838. [PubMed: 19100694]
4. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. Lancet. 1991; 338:1175–1176. [PubMed: 1682595]

5. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420:860–867. [PubMed: 12490959]
6. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009; 9:162–174. [PubMed: 19197294]
7. Steinman RM, Banchereau J. Taking dendritic cells into medicine. Nature. 2007; 449:419–426. [PubMed: 17898760]
8. Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, Jenkins D, Schuind A, Costa Clemens SA, Dubin G. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet. 2006; 367:1247–1255. [PubMed: 16631880]
9. Higano CS, Schellhammer PF, Small EJ, Burch PA, Nemunaitis J, Yuh L, Provost N, Frohlich MW. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer. 2009; 115:3670–3679. [PubMed: 19536890]
10. Kantoff PW, Schuetz TJ, Blumenstein BA, Glode LM, Bilhartz DL, Wyand M, Manson K, Panicali DL, Laus R, Schlom J, et al. Overall survival analysis of a phase II randomized controlled trial of a poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol. 2010; 28:1099–1105. [PubMed: 20100959]