Targeting transforming growth factor β to enhance cancer immunotherapy

T. Hahn PhD and E.T. Akporiaye PhD

KEY WORDS

DC-based vaccine, TGFβ, immunotherapy of cancer

1. INTRODUCTION

Human tumours have evolved intricate mechanisms to evade the immune system, either by avoiding recognition or by inhibiting and eliminating immune cells. Although clear evidence exists that the immune system is mobilized in response to tumour growth—a fact that is manifested in the accumulation of numerous immune cells including dendritic cells (DCs), natural killer (NK) cells, macrophages, and lymphocytes at the tumour site—tumour growth continues unabated. One of the major obstacles to the success of immunotherapy of cancer is therefore the diminished immune responsiveness of cancer patients with progressing disease.

Continued tumour growth in the presence of what appears to be a significant antitumour response suggests the existence of a microenvironment that is inhospitable to antitumour immune effector mechanisms. Several tumour-derived products present in sera and tumour extracts from cancer patients, including transforming growth factor β (TGFβ), prostaglandin E2, interleukin-10, and vascular endothelial growth factor [1–4], have been identified and employ a variety of mechanisms to promote tumour growth.

To develop effective cancer therapy modalities, an understanding of the biologic effects that these tumour-derived factors have on immune cells is essential. The challenge, therefore, is to identify the underlying mechanisms of action of tumour-promoting factors, so that effective counteractive strategies that will bolster the antitumour immune response can be developed.

Richard J. Ablin, PhD, Research Professor of Immunobiology, University of Arizona College of Medicine and the Arizona Cancer Center, Tucson, Arizona, U.S.A., and Phil Gold, PhD, MD, Professor of Medicine, Physiology, and Oncology, McGill University, Montreal, Quebec, Canada, Section Editors.

2. DISCUSSION

2.1 TGFβ and Dendritic Cells

One of the most studied and best described tumour-derived factors with potent immunosuppressive activity is TGFβ. A pleiotropic cytokine [5], TGFβ is secreted in copious amounts by murine and human cancer cells. In melanoma and in pancreatic, colorectal, lung, and breast cancers, elevated levels of circulating TGFβ have been correlated with disease progression, metastases, disease recurrence, and mortality [6–13]. The immunosuppressive activities of TGFβ include inhibition of the differentiation and effector functions of T cells, NK cells, lymphokine-activated killer cells, macrophages, and DCs [14].

The impact of tumour-derived TGFβ on DC function is of particular interest because of the foundational role that DCs play in the induction of antigen-specific tumour immunity—especially in the context of their use as cancer vaccines. Transforming growth factor β affects DCs in numerous ways that negatively affect their ability to prime tumour-specific T cells, including downregulation of cell-surface major histocompatibility complex (MHC) antigens, downregulation of co-stimulatory molecules and chemokine receptors, and impairment of maturation and migration to secondary lymphoid organs. These effects are also supported by the reported functional impairment of circulating and tumour-infiltrating DCs in tumour-bearing animals and in cancer patients such that the DCs are unable to induce T-cell responses [15–18].

Given the central role of DCs in inducing antigen-specific immune responses, the impact of tumour-derived TGFβ on DCs poses a major challenge for DC-based cancer immunotherapy. Therapeutic strategies that can successfully negate the impact of TGFβ on DCs would therefore be expected to result in enhanced DC function and to lead to improved clinical responses.

The importance of DC-mediated immune responses against TGFβ-producing tumours can be shown by systemic inhibition of TGFβ-mediated signalling using a TGFβ neutralizing antibody in combination with a DC vaccine or DCs in which TGFβ signalling is impaired by

the expression of a dominant negative TGFβ type II receptor (dnTGFβRII) transgene [15,19] (unpubl. data). These strategies have enhanced the immune response against TGFβ-producing murine breast cancer and melanoma respectively. Those results suggest that counteracting TGFβ-mediated signalling in immune cells, including DCs, may be exploited to enhance antitumour immune responses. However, tumour cell destruction by the immune system ultimately depends on an efficient cell-mediated immune response carried out by CD8+ cytotoxic T lymphocytes (CTLs). This process usually depends on MHC class-II restricted CD4+ T-cell help that provides the cytokine signals necessary for activation and clonal expansion of tumour reactive CTLs and for memory formation that can then provide the much-desired long-term antitumour protection.

Like DCs, CTLs and CD4+ helper T cells are both functionally impaired in the presence of TGFβ, as evidenced by reduced cytokine production and proliferative potential, blunting the effectiveness of the cell-mediated immune response. The importance of this process and the impact of neutralizing the immunosuppressive effects of TGFβ on T cells to enhance an antitumour immune response *in vivo* has been demonstrated by Flavell's group. Their studies [19,20] targeted expression of dnTGFβRII in transgenic mice to T lymphocytes, leading to immune-mediated rejection of TGFβ-producing EL-4 thymoma and B16 melanoma tumours. In a study by another group, sub-lethally irradiated mice transplanted with dnTGFβRII-expressing bone marrow cells demonstrated improved survival over mice receiving wild-type bone marrow when challenged with B16 melanoma or TRAMP-C2 prostate tumours [21]. Furthermore, adoptive transfer of tumour-specific, dnTGFβRII-expressing CD8+ T cells into TRAMP-C2 tumour-bearing mice led to improved survival and a reduction in the number of pulmonary metastases [22].

2.2 Novel Human Therapies

Promising findings of augmentation of the antitumour immune response by inhibition of TGFβ leads us to examine how such augmentation may be translated into novel human therapies. Although the described animal models are useful for studying *in vivo* DC, T-cell, and TGFβ biology, they do not easily lend themselves to translation to the clinic for the treatment of human malignancies. One approach would be to generate tumour-specific T cells in combination with antigen-pulsed DCs for adoptive cell transfer (ACT).

Current ACT involves the transfer of either *ex vivo* activated T cells or antigen-pulsed DCs into cancer patients. Adoptive transfer of tumour-specific T cells has been accomplished by first vaccinating patients with autologous tumour cells, harvesting the vaccine-draining lymph node cells, expanding the recovered lymphocytes *ex vivo*, and re-infusing the activated T cells into the patient [23,24]. In similar studies, treatment with *ex vivo*–stimulated tumour-infiltrating T lymphocytes was well tolerated, and the transferred T cells persisted in the circulation for several months [25]. The DC-based ACT has used tumour lysate, tumour antigen, or peptide-pulsed DCs, and has demonstrated robust immunologic antitumour responses accompanied by modest clinical outcomes in patients with cancers of various histologic origins [26–29].

These adoptively transferred DCs and T cells would be expected to encounter significant amounts of tumour-derived TGFβ in the peripheral circulation and at the tumour site that could impair their ability to efficiently prime the immune system or mediate effector functions. A combinatorial approach in which both DCs and T cells are protected from the deleterious effects of TGFβ would be expected to improve the therapeutic efficacy of ACT. Several different classes of TGFβ antagonists are now in development, such as TGFβ-neutralizing monoclonal antibodies [30,31], soluble TβRII:Fc fusion proteins, and antisense TGFβ oligonucleotides [32,33].

Of particular interest is the recent development of small-molecule TGFβ receptor kinase inhibitors. These molecules resemble dnTGFβRII expression in that they inhibit TGFβ-mediated signalling at the cellular level [34–36]. They are particularly promising because of their ease of manufacture and use as compared with larger-molecular therapeutics such as antibodies.

3. CONCLUSION

The observations presented here show that therapeutic approaches that neutralize or abrogate tumour-derived products such as TGFβ significantly enhance the effector activity of immunocytes in the tumour microenvironment. Studies are underway to combine these novel anti-TGFβ therapies with adoptive cell transfer to devise better therapeutic approaches that, in conjunction with established treatments, will provide oncologists with additional therapeutic options in the future.

4. REFERENCES

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Corresponding author: Emmanuel T. Akporiaye, Department of Microbiology and Immunology, University of Arizona, 1501 N. Campbell Avenue, PO Box 245049, Tucson, Arizona 85724 U.S.A.
E-mail: akporiay@u.arizona.edu