Current and future directions for cancer immunotherapy

Overview

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Theory and potential of immunotherapy

Cancer immunotherapy aims to exploit and maximise the body’s own immune system in order to target and destroy cancer cells. The immune system is a complex and effective integrated network of specialised cells, organs and factors (cytokines and antibodies) that can quickly and efficiently identify and remove foreign agents such as bacteria and viruses, and “self agents” such as cellular debris and malfunctioning cells that are dangerous to the host. There are several mechanisms in place to alert the immune system to these dangerous self cells in order to prevent damage that can be caused by the immune system when unregulated. Therefore, when immunosuppressive cytokines are inappropriately expressed, it can dampen immune responses and allow for cancer cells to avoid attack by the immune system.

Malignant cells can also up-regulate the expression of certain cell surface molecules that may not be innately antigenic but may be useful as tumour associated antigens (TAA) in future therapies such as prostate specific antigen (PSA). An example of well-studied tumour-associated antigens is the MAGE and GAGE families of genes. While these antigens were initially described in melanoma, they have been demonstrated to be present in a variety of tumour types including lung and bladder carcinoma, sarcomas, and head and neck tumours. They are, however, non-detectable in a large range of normal tissues, including brain, bone marrow and peripheral blood. Therefore, they may be used as potential targets for future therapies.

Types of immunotherapy

The aim of immunotherapy approaches is to prime the immune system to target these cancer cells specifically and without creating an autoimmune response. Immunotherapy can refer to any method in which the immune system is being altered to become more effective. Generally, there are three modes of immunotherapy that are currently being utilised – antibodies, cytokines and cellular immunotherapy.

Antibodies have been used in a variety of ways to affect cellular behaviour. They can be administered to replace naturally-occurring ligating events. When antibodies bind to cell surface molecules they can have activating, inhibiting or null effects on cell signalling. It is possible to use activating antibodies to ligate death receptors on cancer cells in order to cause these cells to die (ie Fas). It is also possible to use antibodies to ligate lymphocyte cell surface receptors in order to induce lymphocytes to expand and activate an immune response (B7.1, LFA-3, ICAM-1). In addition, blocking antibodies can be used to interfere with naturally-occurring ligation events that are activating. Using a blocking antibody to the epidermal growth factor receptor (EGF-r) has been effective in reducing the growth of several tumour types that have amplified EGF receptor expression. Further, as described in this paper by Dr Frazer, anti-viral vaccines can be administered to produce neutralising antibodies against the papilloma virus, which is responsible for alterations in their apoptotic machinery. Secondly, cancer cells can evade detection of the immune system by altering the expression of cell surface molecules. MHC molecule expression is essential to trigger an immune response by activating T lymphocytes through the T cell receptor (TCR). Therefore, it is common for cancer cells to down-regulate expression of its MHC molecules. Finally, cells can secrete immunosuppressive soluble cytokines such as IL-10 and TGF-B that can down-regulate the immune response. Generally, these cytokines act as brakes on the immune system to control the immune response in order to prevent damage that can be caused by the immune system when unregulated. Therefore, when immunosuppressive cytokines are inappropriately expressed, it can dampen immune responses and allow for cancer cells to avoid attack by the immune system.
cervical cancer. Finally, antibodies can be used to carry cytotoxic drugs to specific cells that express the ligand. This method aims to target only the cancer cells to receive cytotoxic agents by conjugating the toxic agent to the antibody that has been shown to be specific for only the cancer cell using TAAs. In each method, antibodies can be used to specifically target cancer cells and can be exploited by choosing the appropriate antibody to achieve altered cellular outcomes.

Cytokines are soluble factors that direct and modulate the nature of an immune response. Granulocyte-Colony Stimulating Factor (G-CSF) is regularly administered to chemotherapy patients to boost neutrophil counts following treatment. Furthermore, cytokines (ie FLT-3 Ligand) can also be used to differentiate cells in vivo for later harvesting for more invasive immunotherapy applications. Finally, it has been shown that cytokines can have local toxic effects in high doses and some direct applications of cytokines to tumours can cause tumour regression (IL-2). Therefore, cytokines can have both supportive and therapeutic roles in treating cancer patients.

Cellular immunotherapy involves the alteration of autologous immune cells ex vivo, which are then administered to the patient to produce a specific anti-tumour effect. Current models are focusing on the use of dendritic cells (DC), which are the most potent antigen-presenting cells and therefore the best candidates to introduce tumour-specific antigens. The enormous potential for exploiting DC for immunotherapy has been hindered until recently by the rarity of this cell type in the human body (less than 1.0% of mononuclear cells) and the lack of methods to generate DC in vitro. There are two major ways of isolating human DC:

- separation of CD34+ cells from mobilised peripheral blood mononuclear cell (PBMC) harvests; or
- isolation of monocytes from PBMC by adherence to plastic.

Both cell subsets are then stimulated to develop into DC via culture in the presence of several human cytokines, such as GM-CSF, TNF-α, SCF or IL-4.

The fundamental role of DC in orchestrating the different arms of the immune system defines them as important mediators of the immune response. Cell-mediated responses include adaptive responses facilitated by CD4+ and CD8+ T cells and the innate response facilitated by natural killer (NK) and natural killer T cells (NKT) cells. DCs engage and activate these lymphocyte subsets via separate mechanisms in order to control and define the nature of the immune response generated. Each lymphocyte subset has a unique mechanism for killing target cells, but they all produce the anti-tumour cytokine IFN-γ in response to activation. DCs present peptide antigens within the context of MHC class I and II to CD8+ and CD4+ T cells respectively. CD8+ cytolytic T cells kill quickly via granzymes when activated after ligation with MHC I and costimulation molecules such as a B7 family member. CD4+ T helper cells, when activated – also through co-stimulation molecules and ligation with peptide-MHC II – can kill target cells through Fas-FasL interactions. NKT cells recognise lipid and glycolipid antigens within the context of CD1a expressed on DC while NK cells recognise and kill cells that do not express MHC I molecules. This dynamic arrangement allows the interplay between initiators and effectors to produce a multi-pronged attack against antigen-bearing cells.

### Immunocompetency of cancer patients

The status of immune system function in cancer patients has recently been of interest with respect to new approaches of anti-cancer therapies. However, these studies have focused on immunocompetency following chemotherapy, and baseline data prior to chemotherapy is lacking. Patients with acute lymphoblastic leukaemia (ALL), Hodgkin’s disease, or solid tumours were examined for immune function after successful chemotherapy (with or without radiotherapy). Immune responses to specific antigens were lower than normal for both the humoral and cellular arms of the immune system in most patients, with only 19% demonstrating normal responses 12 months post-chemotherapy. Further studies involving the cytokine profiles of cancer patients have shown that IL-2 is deficient in PBSC after traditional chemotherapy and bone marrow transplantation, and mononuclear cells in patients with advanced cancer show deficiency in T helper 1 responses (decreased IFN-γ, IL-10, IL-12 and increased IL-4). While it is important to assess immune function following chemotherapy, baseline immunologic data is necessary to draw meaningful conclusions as to the status of immune function in cancer patients prior to therapy.

### Conclusion

There have been many advances recently in the field of cancer immunotherapy, and with the forthcoming publication of clinical trials underway we are certain to refine and improve our methods and efficacy for future therapies.

### References


