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Revolutions in cancer treatment:
how can they be integrated?

Are immunotherapies a true medical revolution?

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Abstract

Modern immunotherapy emerged from the discovery and characterisation of the immune "checkpoints" CTLA-4 (cytotoxic T lymphocyte-associated protein 4) and programmed cell death 1 (PD-1), which, when unlocked, reinvigorate patients' immune reaction against cancers. Infiltration of tumours by memory T lymphocytes is the most powerful prognostic factor for patient survival. Based on these fundamental discoveries, modern immunotherapy has brought about a paradigm shift in cancer treatment away from attempting to eliminate tumours, towards being replaced or supplemented by strategies to reinvigorate the immune system or infuse effector lymphocytes whereby patients reject their cancer. This revolutionary approach is based on the pathophysiology of the host-tumour reaction, is partly independent of the tumour histology, and is intended to be curative even in metastatic cancers. There are major challenges associated with immunotherapy, including identification of biomarkers to indicate response, primary and acquired forms of resistance, toxicity, and financial cost, but immunotherapy has already become an essential pillar of cancer treatment.

Immunotherapy is an old concept, dating back to the beginning of the 20th century when William B. Coley reported the regression of an osteosarcoma in a patient presenting with an acute infection. Attempts to stimulate the immune system using Bacillus Calmette–Guérin (BCG) vaccine, interleukin 2 and interferon resulted in some spectacular regressions but only in rare cases. The success of allogeneic bone marrow grafts in acute leukaemias confirmed that lymphocytes were capable of controlling advanced cancers. In 1975, Georges Koehler and Cesar Milstein created monoclonal antibodies to study the physiology of B lymphocytes.[1] However, it was not until 1997 and the results achieved with rituximab, an anti-CD20 monoclonal antibody, that the number of therapeutic monoclonal antibodies began to increase. Initially viewed as just another form of chemotherapy, researchers gradually realised that long-term responses to these antibodies depended on inducing a host immune response and not simply on destroying tumour cells. Treatments involving monoclonal antibodies are now based on the recognition of T-cell receptors. One very effective method of killing tumour cells is chimeric antigen receptor T-cell (CART) therapy, which involves integrating a fragment of antibody linked to signalling receptors in circulating T lymphocytes.[2] CART has revolutionised the treatment of many refractory haematological malignancies, with response rates of around 80% to 90% after a single injection.[2]

REINVIGORATING THE IMMUNE SYSTEM

A tumour is not simply a proliferation of tumour cells, but it also involves a complex network of epithelial cells, blood and lymphatic vessels, cytokines and chemokines, and immune cells. This tumour micro-environment comprises all the inflammatory and immune cells: T lymphocytes, mast cells, NK cells, B cells, macrophages[3] (**Figure 1**). A tumour is therefore essentially a "lymphoid organ". While the tumour can dampen the immune response using immune checkpoints, the various types of infiltrating immune cells make it possible to interrupt the cycle of antitumour immune response with variable effects depending on the type of cancer.

There is a consistent correlation between the density of infiltrating CD8+ T-cells in the tumour and a good prognosis for patients with cancer.[4] This correlation has led to the use of immunotherapy to modify the tumour's microenvironment at primary and/or metastatic sites by increasing the ratio of memory T-cells specific to the tumour (and in particular CD8+ effector T-cells) to inflammatory suppression factors and their mediators. Immunotherapy also makes it possible to induce or augment a long-term systemic immune response that can control any residual malignant cancer cells. In this way, immunotherapy represents a paradigm shift compared with other cancer treatment approaches: the aim is no longer to try to eliminate the tumour cells directly, but to reinvigorate the immune system long term.

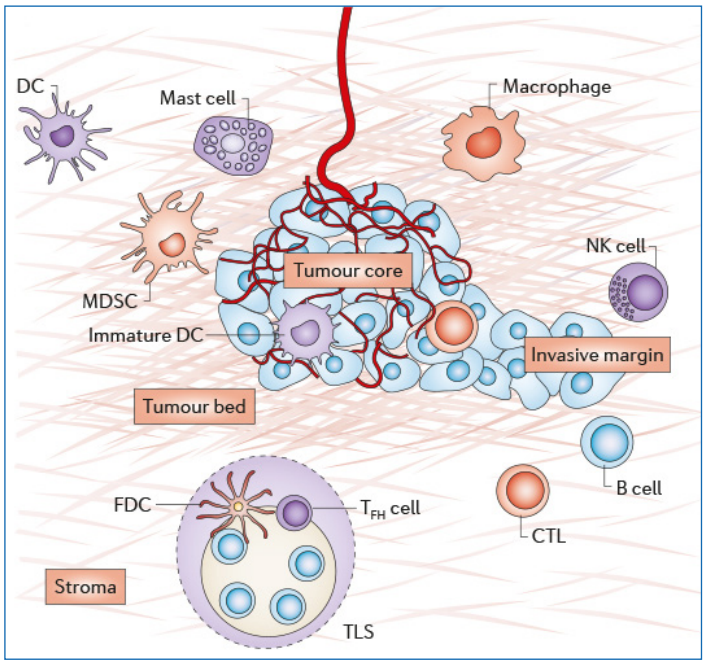

Figure 1. Immune microenvironment of tumours. Tumours develop within a complex network of epithelial cells, blood and lymphatic vessels, cytokines and chemokines, and infiltrating immune cells. The various types of infiltrating immune cells have different effects on the progression of the tumour, which may vary depending on the type of cancer.
Reproduced by permission from Springer Nature: Reference [3] Nat Rev Cancer 2012;12:298-306. Fridman et al. The immune contexture in human tumours: impact on clinical outcome. © 2012.

ANTI-CTL-A4 AND ANTI-PD-1 THERAPIES

In 2018, the Nobel Prize for Physiology or Medicine was awarded to James P Allison and Tasuku Honjo for their discovery of a treatment to combat cancer by inhibiting negative immune regulation. It should also be remembered that Pierre Golstein in Marseille discovered the CTL-A4 receptor through subtractive analysis of the genes expressed in activated cytotoxic T lymphocytes. This fundamental research work led to the development of anti-CTL-A4 and anti-PD-1 antibodies that block "immune checkpoints" whose role is to limit or attenuate antitumour immune responses.[5]

In the past, clinical approaches to anticancer immunotherapy concentrated on vaccines intended to initiate or amplify a specific host response against growing tumours. Blocking immune checkpoints using monoclonal antibodies was first seen as an interesting clinical strategy in 2010. During a phase 3 study, the anti-CTL-A4 ipilimumab administered with or without a peptide vaccine to glycoprotein 100 (gp100) was compared to gp100 alone in 676 patients with non-resectable, previously treated stage 3 or 4 melanoma. The median overall survival was 10 months in the patients who were given ipilimumab (with or without gp100) compared with 6.4 months in the patients who were given gp100 alone.[6] The efficacy of ipilimumab appeared after several months, but persisted, with 20% of the patients still alive after 4 years. A similar survival curve was achieved using nivolumab, an anti-PD-1 antibody, in patients with non-small cell lung cancer.[7] Since then, research has shown that more than 30 types of cancer are sensitive to anti-PD-L1 therapies, and this is the first time that a class of drugs has shown such a wide spectrum of activity when given as monotherapy in oncology.

In 2018, studies began to investigate combinations of immunotherapies, such as nivolumab plus ipilimumab, which had a more significant effect on overall survival than sunitinib in patients with advanced chemotherapy-resistant clear cell renal cancer.[8] With this new focus on combined immunotherapies[9] and next-generation therapies, there has been a revolution in the speed at which marketing authorisations (MAs) are granted. For example, ipilimumab and nivolumab took 12 years from the start of clinical development until MA, but nowadays treatments are often registered as soon as results are obtained from phase 1 trials, significantly reducing the time to registration.[10]

In view of the multiplicity of potential targets on T lymphocytes and also on Treg cells, NK cells, antigen-presenting cells, neutrophils and macrophages, a large number of treatment approaches have been tested, resulting in an unprecedented increase in the number of clinical trials of combined immunotherapies to treat cancer.[11]

NEW CHALLENGES IN IMMUNOTHERAPY

Today the key challenges of immunotherapy are understanding the mechanisms of primary and secondary resistance, and identifying the specific toxicities of treatments.

Recent progress in the technologies, analytical methods and equipment used in immunology has made it possible to identify the patients who are likely to respond to immunotherapy. The efficacy of immunomodulatory strategies depends on the presence of a basic immune response and pre-existing immunity, with effector T-cells playing a central role in anti-cancer responses. Immunoscores do, however, vary between tumours.[12] Neoantigens synthesised by cancer cells also induce an immune reaction against the tumour; this mutation load varies between cancers.[13] The neoantigen load may be a biomarker to predict response to immunotherapy: melanomas, lung cancers and colorectal cancers with microsatellite instability, which have the most neoantigens, respond best to immunotherapies. This correlation between the number of mutations in tumours and the response to immunotherapy is not, however, absolute.[14]

The influence of the tumour's microenvironment on its response to immunotherapy was recently illustrated in patients with soft tissue sarcomas. These sarcomas are a heterogeneous group of cancers; there are more than 50 histological subtypes with highly variable responses to immunotherapies. Researchers investigated the gene expression profiles of 608 tumours from different sub-types of soft tissue sarcoma.[15] They classified these into five distinct phenotypes, based on the composition of the tumour's micro-environment: tumour types with weak immunity

(A and B), high immunity (D and E), or high vascularisation (C). Class E was characterised by the presence of tertiary lymphoid structures (TLS) containing T-cells and follicular dendritic cells and with particularly high concentrations of B-cells. The presence of B-cells was the prognostic factor that best predicted the response to immunotherapy, irrespective of whether or not CD8+ T-cells were present. A phase 2 clinical trial in 47 patients has also shown a more marked response to pembrolizumab in patients with class E tumours compared with other classes (D: 25%; C: 22%), as well as an improvement in survival. The presence of TLS rich in B-cells may therefore guide the management of patients with soft tissue sarcomas.

Primary and secondary resistance, which develop via a number of mechanisms,[16] may limit the efficacy of immunotherapy. As the molecular mechanisms behind these forms of resistance are elucidated, strategies are being developed to improve the clinical efficacy of immunotherapy. For example, researchers are currently decoding the mechanisms underlying the role of TLS in the anti-tumour adaptive immune response. The aim is to exploit TLS to promote infiltration by lymphocytes, activation by tumour antigens and differentiation to improve the anti-tumour immune response. Several approaches are being developed, using chemokines, cytokines, antibodies, antigen-presenting cells or synthetic scaffolding to induce formation of TLS.[17] These strategies are promising approaches to optimise the treatment of cancer using immunotherapies.

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