Multiple approaches to immunotherapy - the new pillar of cancer treatment

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Surgery, radiation and chemotherapy have long been considered the three pillars of cancer care, but a fourth pillar could soon expand this foundation and provide an exciting new treatment option for some patients. This new pillar, cancer immunotherapy, uses antibodies, small molecules, cells and viruses to stimulate the host immune system to attack and destroy tumour cells.

In this Special Feature, we present a series of reviews that highlight some of the recent advances in practice and theory concerning the more effective means to mobilize effective host immunity to cancer. The diversity of approaches covered represents only a small minority of the enormous efforts being undertaken by clinicians, academics and pharmaceutical companies world-wide to explore the potentially broad applicability of cancer immunotherapy in cancer treatment.

Mounting evidence suggests that the major barrier to more successful cancer immunotherapy is the tumour microenvironment (TME), where chronic inflammation may play a significant role in tumour immunosuppression, tumour survival and proliferation, and angiogenesis. Our understanding of cancer-related inflammation has significantly improved, and now we have a number of new therapeutic options tailored to interfering with inflammation in the TME. These strategies include the following: re-educating the TME, inhibiting inflammatory mediators or their downstream signalling molecules, blocking the recruitment of myeloid cells, and modulating immunosuppressive functions in myeloid cells. In the review by Nakamura et al., the role of cancer-related inflammation (intrinsic and extrinsic regulators) as a potential target in the era of immunotherapy is discussed.

Tumour cells use various ways to evade anti-tumour immune responses. Adenosine, a potent immunosuppressive metabolite, is often found elevated in the extracellular TME. Therefore, targeting adenosine-generating enzymes (CD39 and CD73) or adenosine receptors has emerged as a novel means to stimulate anti-tumour immunity. This is a large field, but Allard et al. nicely focus on the therapeutic potential of targeting the adenosine A2 receptors. They present a comprehensive review of A2 receptor signalling, A2 receptor expression, the role of A2 receptor in immunity and cancer progression, and the development of highly specific A2 receptor antagonists for use in cancer treatment alone and in combination with immune checkpoint blockade antibodies. Targeted therapies directed against A2a, A2b or against upstream ecto-nucleotidases CD39 and CD73 responsible for adenosine catabolism have proven to be effective in various pre-clinical cancer models. Combinations with other treatments, including immune checkpoint inhibitors, chemotherapy and adoptive cell therapy, have also demonstrated therapeutic synergy. The first results with A2A receptor antagonists in advanced cancer patients will be available early this year. These will be awaited with great anticipation.

Antibodies are increasingly important vehicles for targeting elements of the immune system in tumours. One of the most obvious, but surprisingly poorly recognized, mechanisms of antibody activity is via its Fc portion. Stunning experiments in mice using antibodies with a variety of Fc isotypes and mice gene-targeted for various Fc receptors have highlighted the critical role that Fc-FcR cross-linking plays in the therapeutic activity of antibodies that target host immune cells (for example, anti-CTLA-4, anti-GITR and antibodies reactive with the TNF superfamily of receptors). In these instances, mechanisms may include depletion of immune cells expressing the antigen by antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis or FcR cross-linking, and signalling or antigen internalization. Barnhardt and Quigley and Ochoa et al. present two wonderful reviews on this subject area, with Ochoa et al. particularly focusing on ADCC and the means to enhance the function of NK cells in cancer. Barnhardt and Quigley produce some really useful reference figures and facts concerning the complex family of IgG molecules and Fc receptors and outline the questions a pharmaceutical company has to pose itself when designing the optimal antibody to match the cancer patients TME. Ochoa et al. discuss some of the better-known monoclonal antibodies (for example, CD20, Her2, EGFR) targeting cancer associate antigens and the utility of their Fc. They go on to discuss bispecifics and the use of cytokines and other strategies to enhance ADCC, as well as genetic modification and adoptive transfer approaches for NK cells.

Lastly, adoptive cellular therapy (ACT) in the context of allo-transplantation and cellular therapies based on tumour antigen or virus antigen-specific T cells has already produced some spectacular responses in haematological cancers. The genetic modification of these T cells through several generations of improvement with chimeric antibody receptors has improved the sophistication of the approach in tailoring the cellular product for the patient’s particular TME. Yong et al. detail these advancements and present the challenges that lie ahead for this approach to the treatment of solid cancers. They present a useful table of current trials that demonstrate the vast amount of new activity in this area. The common problems for all T-cell-based therapies such as tumour-induced immunosuppression, ineffective trafficking and poor tumour penetration are all discussed. The more rapid characterization of neo-antigens for human tumours and the ability to clone T-cell receptors that recognize them rapidly will pave the way for some next-generation technology for designer T cells that can more specifically attack tumour tissue and reduce off-target toxicity.

In parallel, ACT for EBV-associated post transplant lymphoproliferative disorders has shown great promise and set the scene for new
strategies to target virus-associated cancers in non-immuno-compromised patients. Smith and Khanna6 beautifully review the efforts to translate this approach into clinical practice in diseases such as nasopharyngeal carcinoma, cervical and head and neck cancer, glioblastoma, and hepatocellular carcinoma. The potential uses of newly generated off-the-shelf cellular products from healthy donors are discussed, as are opportunities to marry this approach with the revolutionary immune checkpoint blockade therapies.

In summary, cancer immunotherapy is at a critical and exciting stage of development, intersecting with developments in high-throughput genetics, bioinformatics and imaging. For the first time therapeutic responses in patients can be studied, samples collected and interrogated, completing a virtuous cycle of knowledge from the bench to bedside and back. The cancer treatment armamentarium has expanded and the opportunities for immunologists to make a lasting contribution to medicine in this area are immense.

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