Seminars in Immunopathology (2019) 41:1–3
https://doi.org/10.1007/s00281-018-0711-z

INTRODUCTION

Anti-cancer immunotherapy: breakthroughs and future strategies

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Received: 10 September 2018 / Accepted: 17 September 2018 / Published online: 21 September 2018

Introduction

This special issue of *Seminars in Immunopathology*, entitled "Anti-cancer immunotherapy: breakthroughs and future strategies," focuses on the many recent breakthroughs in the field of cancer immunotherapy. New immunotherapies for the treatment of advanced cancers are being approved at a quick pace, with the promise of long-term survival. Immunotherapy will be a dominant part of future cancer treatment and lead to changes in treatment strategies for most, if not all, cancers. The current issue highlights current knowledge and the significant challenges emerging in the use of immunotherapy. This issue includes several reviews that describe the different forms of immunotherapy, as well as reviews describing key parameters for the future success of immunotherapy. In general, there are four forms of immunotherapy: cytokine therapy, cellular therapy, antibody therapy (especially immune checkpoint blockade), and therapeutic vaccines.

Cytokines are molecular messengers that allow the cells of the immune system to communicate with one another. Pro-inflammatory cytokines activate key immune effectors, such as T cells and NK cells. Cytokine treatment was the first broadly used form of immunotherapy. To date, two cytokines have obtained FDA approval as single agents for cancer treatment: high-dose IL-2 for metastatic melanoma and renal cell carcinoma, and IFN-α for adjuvant therapy of Stage III melanoma. The latter is one of the most studied cytokines and is still used in some indications, particularly Philadelphia-negative myeloproliferative neoplasms (MPNs), essential thrombocytosis, polycythemia vera, and myelofibrosis. In the current issue of *Seminars in Immunopathology*, Hasselbalch and Holmström describe and discuss the effects and perspectives of IFN-α in MPNs [1]. They describe the story of IFN in MPNs from the very beginning in the 1980s until today, and discuss the future perspectives of IFN-α in the treatment of MPNs.

Many of the immune regulatory mechanisms considered helpful in autoimmune settings are used by tumors to suppress immune responses towards malignant cells in cancerous settings. Thus, various immune-tolerance mechanisms are exploited by cancer cells to achieve immune escape, which becomes more pronounced with disease progression. The creation of an immunosuppressive microenvironment involves the actions of regulatory T cells (Tregs), dendritic cell subtypes, myeloid-derived suppressor cells (MDSCs), and regulatory B cells. Thus, both cancer cells and other regulatory immune cells release inhibitory cytokines and express checkpoint inhibitors (e.g., PD-L1) and metabolic enzymes (e.g., indoleamine 2,3-dioxygenase [IDO]) that suppress the anti-tumor activity of anti-tumor-specific T cells in the tumor microenvironment. In recent years, growing knowledge of the factors responsible for protecting cancer cells from immune destruction has led to the development of novel, immune-based, anti-cancer treatment modalities. In particular, the use of monoclonal antibodies to block either PD-1 or PD-L1 has produced outstanding clinical responses. Thus, the most widespread treatment approach using immune checkpoint inhibitors can cure patients with widely metastatic tumors. The most successful immunotherapeutic drug is currently the anti-PD1 antibody pembrolizumab. Schmidt gives a detailed description of the current use of pembrolizumab both as monotherapy and, especially, in combination in the current issue of *Seminars in Immunopathology* [2].

Although many patients respond to checkpoint blockade, a major problem is that a significant proportion of these patients, who initially demonstrate encouraging tumor regression in response to the treatment, develop resistance and

This article is a contribution to the special issue on Anti-cancer Immunotherapy: Breakthroughs and Future Strategies - Guest Editor: Mads Hald Andersen

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progress over time. In the current issue of *Seminars in Immunopathology*, Donia and colleagues summarize the current knowledge on the role of tumor intrinsic factors in the development of resistance to cancer immunotherapy [3].

IDO is a natural immunoregulatory mechanism that contributes to immune suppression and tolerance in a variety of cancer settings. Treatment with IDO inhibitors was shown to enhance anti-tumor immune responses in pre-clinical models. However, the first large phase III trial to evaluate an IDO1-selective enzyme inhibitor (epacadostat) in combination with an anti-PD1 antibody (pembrolizumab) in advanced melanoma showed no indication that epacadostat provided an increased benefit. Dr. Müller and colleagues describe in the present issue of *Seminars in Immunopathology* the potential use of IDO blockers in light of the recently failed phase III trial [4]. The review describes what was learned from the failed trial, which has stopped a lot of other investigators during similar trials. Better rationalized compounds and better rationalized trial designs will be important in the future to accurately gauge medical impact.

Adoptive cell therapy (ACT) has emerged as a powerful and potentially curative therapy for several cancers. It is already approved for the treatment of patients with B cell malignancies. In the current issue of *Seminars in Immunopathology*, Met et al. describe the different principles of ACT in cancer [5]. The goal of ACT is to generate a robust immune-mediated anti-tumor response through infusion of ex vivo-manipulated T cells. ACT strategies with the aim of utilizing T cells to destroy tumors can be divided into (1) the isolation of naturally occurring tumor-specific T cells from existing tumor masses, and (2) the genetic modification of blood-derived T cells to allow for specific recognition of tumor cells. Though immunotherapy techniques, such as adoptive transfer of tumor-infiltrating T cells and gene-modified T cells, have been shown to be capable of mediating complete and durable responses in patients with a limited number of cancer types, further advances may increase the number of patients that can benefit from this treatment modality and increase the feasibility of ACT as a standard of care for cancer. As described above, T cells are the main target for most forms of immunotherapy including ACT. However, other cell types are involved in anti-cancer immune responses, especially NK cells. In the current issue of *Seminars in Immunopathology*, Malmberg and colleagues describe the possibilities of off-the-shelf cell therapy based on natural killer (NK) cells derived from inducible pluripotent stem cells (iPSCs) [6].

Anti-cancer vaccines have raised hopes from the start of immunotherapy but have not yet been clinically successful. In general, cancer vaccines represent a way to eliminate minimal residual disease without inducing critical toxicity and secondary malignancies. However, thus far, a significant improvement in patient outcome has not been demonstrated. This probably reflects the ability of malignant cells to suppress the function of induced immune cells. The few positive results of anti-cancer vaccines have been observed in clinical situations of low tumor burden or preneoplasia. However, the success of immune checkpoint blockers may also increase the effect of cancer vaccines. Cancers that respond to anti-PD-1/PD-L1 (20–30%) are those that are infiltrated by anti-tumor T cells with an inflammatory infiltrate. However, 70% of cancers do not appear to have an anti-tumor immune reaction in the tumor microenvironment. To induce this anti-tumor immunity, therapeutic combinations between vaccines and anti-PD-1/PD-L1 are being evaluated. Tartour and colleagues discuss this in their review entitled, "Therapeutic cancer vaccine: building the future from lessons of the past," in the current issue of *Seminars in Immunopathology* [7]. The review describes the novel possibility of identifying patient-specific neoepitopes against which the immune system is less tolerated. Although the clinical position of vaccines in cancer therapy remains limited, this review highlights the many reasons to be optimistic regarding the future use of therapeutic vaccines as a clinical strategy against cancer.

Cancer vaccines aim to activate specific T cells towards cancer cells, but a novel approach to target the tumor microenvironment with specific T cells was recently suggested by Andersen. Andersen and colleagues have reported that the immune system has an established mechanism to counteract the variety of immune-suppressive feedback signals: self-reactive, pro-inflammatory T cells that target immune-suppressive cells. As these T cells can directly react against regulatory immune cells, such cells were termed *anti-regulatory T cells* (anti-Tregs) [8]. In the current issue of *Seminars in Immunopathology*, Andersen describes how the activation of anti-Tregs, e.g., by vaccination, may offer a novel alternative to directly target immune inhibitory pathways in the tumor microenvironment, modulate immune regulation, and potentially alter tolerance to tumor antigens [9]. Thus, if successfully targeted, a therapeutic vaccination approach to activate anti-Tregs can, like the other approaches that target immune suppression, contribute to anti-tumor immunity by relieving immune suppression and potentiating effective anti-tumor T cell responses. However, unlike other approaches, it actively attracts pro-inflammatory T cells into the tumor microenvironment in addition to actively killing tumor cells because anti-Tregs can be cytotoxic. Thus, the novel understanding of anti-Tregs may lead to a translatable strategy for making checkpoint blockade useful in a much broader population of cancer patients. An anti-Treg-activating vaccine would attract T cells into the tumor, thereby inducing Th1 inflammation, which would further induce PD-L1 expression in cancer and immune cells, generating targets more susceptible to anti-PD1/PDL1 immunotherapy.

Until recently, the main focus of cancer immunotherapy has been solid tumors. Less is known about how different immune escape mechanisms influence tumor immune evasion

in hematological malignancies, and the extent of their impact on ongoing immune responses. However, recent developments in the field of hematology have highlighted immunotherapy as an important treatment modality. This is highlighted in two reviews in the current issue of *Seminars in Immunopathology*. Holmström and Hasselbalch describe the current status and future perspective of cancer immune therapy for myeloid malignancies [10], and Klausen et al. focus on lymphoid malignancies [11]. All of the immune therapy modalities described above are currently being examined in hematological cancers, and the approval of cellular therapies with CAR-T cells for ALL and diffuse large B cell lymphoma have been particularly major therapeutic achievements.

In summary, the development of novel immunotherapies for cancer treatment modalities requires a detailed understanding of the factors that permit tumor cells to evade immune destruction under malignant conditions, a situation that becomes increasingly pronounced with disease progression. One important but often overlooked factor is the age of cancer patients. In the current issue of *Seminars in Immunopathology*, Pawelec describes the troubles (or benefits) of old age in relation to anti-cancer immunotherapy [12]. He describes and discusses age-associated differences in peripheral immune parameters (immunosenescence) and their potential clinical impact, and further highlights the possible mechanisms that determine whether a treatment response is better in this segment of the population. The next milestones in tumor immunotherapy include novel strategies to promote strong anti-tumor immunity without inducing clinically significant autoimmunity. Achieving such anti-tumor immunity will require the elimination or suppression of regulatory immune cell function. We are rapidly accumulating knowledge regarding the biology of various regulatory network protagonists that maintain immune system homeostasis. The coming years will likely bring new insights into this complex system, which will undoubtedly guide future therapeutic interventions that can harness the immune system to fight cancer. Acute and chronic treatment-related immunotoxicities represent a significant clinical problem, and patients treated in registration clinical trials hardly represent the majority of real-life cancer patients, making the impact of novel immunotherapies in the real-world hard to predict. Finally, the financial burden of immunotherapies on health systems is becoming unsustainable. Overall, for both clinical and financial reasons, there is a need to establish new immunotherapeutic strategies, direct treatments to the right patient subgroups, and manage side effects effectively. The current issue provides an up-to-date summary of the current knowledge regarding the rapidly growing field of anti-cancer immunotherapy.

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