Pd 1 Blockade Therapy

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The Effects of Neoadjuvant Anti-Programmed Cell Death Protein 1 (PD-1) Therapy on the Tumor Infiltrating T Cell Compartment and Tumor Microenvironment Immune Composition in Recurrent Glioblastoma Patients Springer
Revealing essential roles of the tumor microenvironment in cancer progression, this book focuses on the role of hematopoietic components of the tumor microenvironment. Further, it teaches readers about the roles of distinct constituents of the tumor microenvironment and how they affect cancer development. Topics include neutrophils, basophils, T helper cells, cytotoxic lymphocytes, fibrocytes, and myeloid-derived suppressor cells, and more. Taken alongside its companion volumes, these books update us on what we know about various aspects of the tumor microenvironment as well as future directions. Tumor Microenvironment: Hematopoietic Cells – Part A is essential reading for advanced cell biology and cancer biology students as well as researchers seeking an update on research in the tumor microenvironment.
Cancer Immunotherapy Principles and Practice Springer
The immune system has proven valuable in the fight against cancer. Therapies that unleash a T cell response against tumors have led to durable remissions in multiple cancers. Specifically, antibodies blocking the programmed death (PD)-1 pathway have been approved for the treatment of metastatic melanoma, non-

small cell lung cancer, and renal cell carcinoma, amongst others. However, only a limited number of patients respond to these therapies. The field is now trying to determine combination strategies and biomarkers to extend the benefits of these therapies to additional patients in a rationale manner. A fundamental challenge towards this goal is that the cellular and molecular mechanisms underlying the efficacy of PD-1 pathway blockade are not well understood. In this thesis, we dissected the role of PD-1 and its ligands on multiple cell types in the tumor microenvironment. PD-1 is a receptor expressed on T cells upon activation, amongst other cells. Its ligands, PD-L1 and PD-L2, can be expressed on many cell types, including tumor cells. In the first section, we show that PD-1 pathway blockade can effectively combine with another therapy targeted at tumor cells themselves, BRAF inhibitors. This work provided support for ongoing clinical trials. In the second section, we show that tumor cells can protect themselves from immune eradication by expressing PD-L1, which directly suppresses the cytotoxicity of CD8* T cells. This establishes a key mechanism by which the PD-1 pathway prevents effective antitumor immunity. In the third section, we show that the inhibition of CD8* T cell cytotoxicity through PD-1 signaling is due in part to cell-intrinsic and cell-extrinsic suppression of T cell metabolism. Removing the inhibitory PD-1 signal on a fraction of cells enhances their metabolic state and allows them to become more cytotoxic. In turn, this creates a tumor microenvironment that allows additional CD8* T cells to become more functional. We show that pharmacologic agents that mimic these effects of metabolism can enhance CD8* T cell cytotoxicity. These mechanistic insights will assist in developing cancer therapies that combine PD-1 blockade with other approaches to broaden the benefit of PD-1 immunotherapy.

An Ex Vivo 3D Tumor Microenvironment-Mimicry Culture to Study TAM Modulation Frontiers Media SA

This book proposes immunogenomics, or immunopharmacogenomics, as the next-generation big science to uncover the role that the immune system plays in the pathogenesis of many diseases, by summarizing the importance of the deep sequencing of T-cell and B-cell receptors. Immunogenomics/immunopharmacogenomics, a genetic characterization of the immune system made possible by next-generation sequencing (NGS), will be important for the further understanding of the pathogenesis of various disease conditions. Abnormal immune responses in the body lead to development of autoimmune diseases and food allergies. Rejection of recipient cells and tissues, as well as severe immune reactions to donor cells, is also the result of uncontrolled immune responses in the recipient body. There have been many reports indicating that activated immune responses caused by the interaction of drugs and HLA are present in drug-induced skin hypersensitivity and liver toxicity. The importance of the host immune responses has been recognized in cancer treatments, not only for immunotherapy but also for cytotoxic agents and molecular targeted drugs. Hence, characterization of the T-cell receptor and B-cell receptor repertoire by means of NGS deep sequencing will ultimately make possible the identification of the molecular mechanisms that underlie various diseases and drug responses. In addition, this approach may contribute to the identification of

antigens associated with the onset or progression of autoimmune diseases as well as food allergies. Although the germline alterations and somatic mutations have been extensively analyzed, changes or alterations of the immune responses during the course of various disease conditions or during various treatments have not been analyzed. It is also clear that computational analyses to draw meaningful inferences of functional recognition receptors on the immune cells remain a huge challenge.

Cutaneous T-Cell Lymphoma Springer

The high effectiveness of antibodies as anti-tumor therapeutic agents has led to a burst of research aiming to increase their therapeutic applications by the use of antibodies against new targets, new antibody formats or new combinations. In this e-book we present relevant research depicting the current efforts in the field.

Targeting the PD-1/PD-L1 Cancer Immune Evasion Axis: Challenges and Emerging Strategies Eliva Press

This textbook presents concise chapters written by internationally respected experts on various important aspects of cancer-associated metabolism, offering a comprehensive overview of the central features of this exciting research field. The discovery that tumor cells display characteristic alterations of metabolic pathways has significantly changed our understanding of cancer: while the first description of tumor-specific changes in cellular energetics was published more than 90 years ago, the causal significance of this observation for the pathogenesis of cancer was only discovered in the post-genome era. The first 10 years of the twenty-first century were characterized by rapid advances in our grasp of the functional role of cancer-specific metabolism as well as the underlying molecular pathways. Various unanticipated interrelations between metabolic alterations and cancer-driving pathways were identified and currently await translation into diagnostic and therapeutic applications. Yet the speed, quantity, and complexity of these new discoveries make it difficult for researchers to keep up to date with the latest developments, an issue this book helps to remedy.

Cutaneous Melanoma Frontiers Media SA

The Society for Immunotherapy of Cancer's handbook,SITC’s Guide to Managing Immunotherapy Toxicity, is a practical reference to managing side effects associated with FDA-approved cancer immunotherapy drugs. Separated into two parts, Part I contains chapter-based overviews of immune checkpoint inhibitors in the clinic, starting with anti-CTLA4 agents, anti-PD1/PD-L1 agents, and approved immunotherapeutic combinations. These chapters cover relevant mechanisms of action, indications, and toxicities seen while combating early, advanced, and metastatic stages in cancer patients. Part II is structured by common and uncommon toxicities that affect major organ sites throughout the body. It begins with a general summary of principles and management options followed by chapters focusing on specific toxicities such as rash and mucosal irritation, muscle and joint toxicity, diarrhea and colitis, pneumonitis, endocrine toxicities, neurological toxicities, cardiac toxicity, renal toxicity, hematologic toxicity, and ocular toxicities. Each chapter provides guidance on how to assess and treat the toxicity and how to support the patient through acute and chronic effects with detailed summary tables for quick reference. Part II

concludes with chapters covering management of special patient populations, including patients with autoimmune disease and geriatric patients, treatment and management of fatigue, and a final chapter dedicated to cost effectiveness and the toll of financial toxicity on patients and caregivers. With chapters written by world-recognized leaders in the immuno-oncology field, this text provides thorough coverage of the toxicity and management of adverse effects for immune checkpoint inhibitors. It is an indispensable resource for clinical oncologists, emergency physicians, hospitalists and other medical practitioners in both the hospital and community clinic settings, especially as the use of immune checkpoint inhibitors becomes a fixture in oncology care. Key Features: Outlines strategies for treating high-risk patients facing an acute or chronic side effect to immunotherapy Provides numerous tables that condense and highlight pertinent information for quick reference Describes the various clinical presentations and toxic reactions caused by immunotherapy Purchase includes access to the eBook for use on most mobile devices or computer

Translational Nanomedicine Springer Nature

In this book, leading experts in cancer immunotherapy join forces to provide a comprehensive guide that sets out the main principles of oncoimmunology and examines the latest advances and their implications for clinical practice, focusing in particular on drugs with FDA/EMA approvals and breakthrough status. The aim is to deliver a landmark educational tool that will serve as the definitive reference for MD and PhD students while also meeting the needs of established researchers and healthcare professionals. Immunotherapy-based approaches are now inducing long-lasting clinical responses across multiple histological types of neoplasia, in previously difficult-to-treat metastatic cancers. The future challenges for oncologists are to understand and exploit the cellular and molecular components of complex immune networks, to optimize combinatorial regimens, to avoid immune-related side effects, and to plan immunomonitoring studies for biomarker discovery. The editors hope that this book will guide future and established health professionals toward the effective application of cancer immunology and immunotherapy and contribute significantly to further progress in the field.

Immunotherapy of Hepatocellular Carcinoma Springer

Of the two disciplines in parallel development for two decades, tumor immunology and transplantation immunology, the latter has thrived and has led to some of the most critical discoveries in immunobiology. The former continues to thwart both scientists and clinicians alike. The goal of immunologists in modern day research is to develop a simple and effective means to manipulate cancer in vivo, possibly encompassing several venues: identifying a phenotypic marker and the use of either active or passive immunization; include the use of passive reagents carrying "warheads" to selectively destroy cancer cells; or altering the basic process of cell survival. This excellent multidiscipline-authored volume presents a theme which has not been well described before. The papers include both basic and clinical science and range from sophisticated molecular biology to little more than phenomenology (e.g. the increased association of cancer in some autoimmune diseases and increased presentation of autoimmune phenomena in malignant condition). This,

however, is state-of-the-art. This collection of themes will be of use not only to bench scientists, but also to clinicians who treat patients. The book represents progress at the cutting edge of this discipline, and points the way to further developments in the "black box" of immunology.

The Role of the PD-1 Pathway in the Tumor Microenvironment Springer

Programmed cell death - 1 (PD1) is a well-studied inhibitory immune checkpoint receptor that is expressed in immune cells especially activated T-cells, resulting in increased immune tolerance. PD1 binds to its ligand PD-L1, over expressed in the tumor cells, in a 'handshake' fashion. This immune handshake facilitates the cancer cells to evade host immune surveillance. Monoclonal antibodies against either PD1 or PDL1, resulting in inhibition of PD1/PDL1 'handshake', known as immune checkpoint blockade (ICB) therapies has shown promising results against multiple cancers, including non-small cell lung cancer (NSCLC). Tumor associated macrophages (TAMs) expressing PD1 have been implicated in progressive disease states in murine models of cancer and poor prognosis in human cancers. GIV/Girdin is a multimodal signal protein known to modulate inflammation and determine whether cells migrate or proliferate. The current study highlights the phenotypic variabilities of tumor growth in myeloid-specific GIV knockout versus GIV-wild type mice, in a syngeneic lung cancer model. GIV-KO mice developed significantly larger tumors as compared to the wild type, due to higher expression of TAM-associated PD1. Upon monoclonal antibody-mediated blockade of PD1, GIV-KO mice demonstrated better response and complete recovery, as compared to the GIV-WT mice. Elaborate biochemical studies depicted that GIV's C-terminally located TILL-like BB loop (TILL) essentially binds to the putative TILL motif of PD1, which in turn initiates the cascade of endocytic pathways and affects PD1 receptor availability. This work aims at illustrating role of GIV in enhancing the efficacy of prevalent PD1 ICB therapies via effective modulation of TAM inflammatory responses in the tumor microenvironment.

Resistance to Programmed Death Protein 1 Blockade Mediated by Somatic JAK1/2 Mutations Springer

Radiotherapy plays an integral role in cancer treatment. Approximately 60% of cancer patients will receive radiotherapy at some point in their treatment. A major improvement in patient outcomes occurs with the use of combined chemotherapy and radiotherapy. The combination of targeted biological agents with radiotherapy is the latest cutting-edge extension in cancer therapy for radiation oncologists. Combining Targeted Biological Agents with Radiotherapy: Current Status and Future Directions is an overview of the current state of clinical and pre-clinical research in combining radiotherapy with targeted biological agents to fight cancer. The text provides a general overview of targeted agents, reviews the current clinical trials, and includes a look at the future of this state-of-the-art practice. This book begins with a general overview of the topic, including an introduction to the subject; the basic science rationale behind the two most important current targeted agents: epidermal growth factor (EGFR) receptors and vascular epithelial growth factor (VEGF) receptors; the dermatologic manifestations of targeted agents; and an introduction to radioimmunotherapy a treatment that has the ability to combine targeted agents directly with

radiotherapy. The second half of the book focuses on specific disease sites, including malignant gliomas, head and neck, lung, pancreatic, cervical, and endometrial cancers. Biologically targeted agents promise to be the next significant breakthrough in cancer therapy. Written by leading experts in the field, Combining Targeted Biological Agents with Radiotherapy is a comprehensive evaluation of the entire field.

Management of Endometrial Cancer Springer Science & Business Media

This book focusses on the different types of immunotherapeutics that are currently being used and developed for the treatment of melanoma. In recent years, immunotherapy has revolutionized the treatment of metastatic melanoma and other types of cancer. Discussing treatment options for melanoma and the success of immunotherapy along with the challenges of immunotherapy, this book covers epidemiology, susceptibility genes, and treatment recommendations from Society for Immunotherapy of Cancer, as well as immune based therapies such as aldesleukin, Intron-A, Sylatron, Yervoy, Opdivo, Keytruda, Imlygic, DC vaccines and adoptive cell therapy. The detailed information included on the key immune cells involved in anti-tumor immune response and immune-inhibitory mechanisms in tumor microenvironment will aid the understanding of tumor immunology. Both academic as well as industry-based researchers, developing novel anti-cancer therapies, will also benefit from the details of promising molecular targets and immunotherapeutic strategies under investigation. With 132 illustrations including synopsis tables for important information, over 1200 references (majority of which are openly accessible) and details of more than 150 ongoing clinical trials, this book is a valuable source of information for health care providers as well as cancer biologists interested in learning about melanoma and the significant advances made by immunotherapy.

Successes and Limitations of Targeted Cancer Therapy Frontiers Media SA

This book addresses the most pressing current questions in the management of urologic malignancies. The rapid advances in imaging and molecular markers are placed into a clinical context, with explanation of their effects on prognosis and treatment planning. Similarly, progress in immunotherapy is carefully examined, focusing in particular on the role of immune checkpoint inhibitors in both early- and late-stage urologic malignancies. Looking beyond the improvements in minimally invasive techniques for urologic cancers, the impacts of care coordination pathways and enhanced recovery after surgery protocols are reviewed. Readers will also find enlightening discussion of the decision algorithm for the treatment of early-stage, high-grade bladder cancer, taking into account evidence on the most advanced treatment options and the circumstances in which surgery may need to be expedited. The penultimate chapter discusses the Cancer Genome Atlas project for bladder cancer, and the book closes by considering contemporary medical and surgical management of testicular cancer.

Combination Targeted Radionuclide Therapy and Immunotherapy for Prostate Cancer Elsevier

Tumor-associated macrophages (TAMs) accumulate in the solid tumor microenvironment (TME) and have been shown to promote tumor growth and dampen antitumor immune responses. TAM-

mediated suppression of T-cell antitumor reactivity is considered to be a major obstacle for many immunotherapies, including immune checkpoint blockade and adoptive T/CAR-T-cell therapies. An ex vivo culture system closely mimicking the TME can greatly facilitate the study of cancer immunotherapies. Here, we report the development of a 3D TME-mimicry culture that is comprised of the three major components of a human TME, including human tumor cells, TAMs, and tumor antigen-specific T cells. This TME-mimicry culture can readout the TAM-mediated suppression of T-cell antitumor reactivity, and therefore can be used to study TAM modulation of T-cell-based cancer immunotherapy. As a proof-of-principle, the studies of a PD-1/PD-L1 blockade therapy and a MAO-A blockade therapy were performed and validated.

Lymphocyte Activation Springer

Cutaneous MelanomaImmunotherapy of Hepatocellular CarcinomaSpringer

Merkel Cell Carcinoma Frontiers Media SA

Tumor-Induced Immune Suppression - Prospects and Progress in Mechanisms and Therapeutic Reversal presents a comprehensive overview of large number of different mechanisms of immune dysfunction in cancer and therapeutic approaches to their correction. This includes the number of novel mechanisms that has never before been discussed in previous monographs. The last decades were characterized by substantial progress in the understanding of the role of the immune system in tumor progression. Researchers have learned how to manipulate the immune system to generate tumor specific immune response, which raises high expectations for immunotherapy to provide breakthroughs in cancer treatment. It is increasingly clear that tumor-induced abnormalities in the immune system not only hampers natural tumor immune surveillance, but also limits the effect of cancer immunotherapy. Therefore, it is critically important to understand the mechanisms of tumor-induced immune suppression to make any progress in the field and this monograph provides these important insights.

Oncoimmunology Frontiers Media SA

This eBook is a collection of articles from a Frontiers Research Topic. Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact.

Immune Checkpoint Molecules and Cancer Immunotherapy Frontiers Media SA

Cutaneous T-cell lymphoma (CTCL) is a general term for many lymphomas of the skin including mycosis Fungoides and Sezary syndrome. This book presents the state of the art in CTCL epidemiology, clinical features, pathology, immunochemistry, diagnostic molecular techniques, staging and prognosis, and treatment. Edited by one of the leading experts in the disease, Cutaneous T-Cell Lymphoma: Mycosis Fungoides and Sezary Syndrome provides comprehensive coverage of the disease and

presents techniques for diagnosis and state-of-the-art treatment modalities, such as ultraviolet light, steroids, and topical chemotherapeutics.

Is the Recent Burst of Therapeutic Anti-Tumor Antibodies the Tip of an Iceberg? National Academies Press

Glioblastoma (GBM) is the most common malignant tumor in the central nervous system and has poor patient survival rates. Unlike other cancers, immune checkpoint therapies, such as PD-1 checkpoint blockade, have been largely ineffective in GBMs for several reasons: an immunosuppressive tumor microenvironment, a lack of suitable neoantigens, and poor intratumoral T cell infiltration and activity. However, there is evidence that using anti-PD-1 therapy in the neoadjuvant setting may generate a more robust anti-tumor immune response, though characterizing how the GBM tumor microenvironment changes with such therapy is incomplete. As such, we performed high dimensional analysis using CyTOF mass cytometry and single-cell RNAsequencing to study the intratumoral immune populations in GBM patients treated with or without neoadjuvant anti-PD-1 therapy. Characterizing PD-1 expressing tumor infiltrating T cell populations showed that PD-1 was associated with markers of T cell activation and dysfunction regardless of treatment and that this association existed less strongly in peripheral PD-1 expressing T cells. We studied the effects of neoadjuvant anti-PD-1 therapy on a large patient cohort of tumor infiltrating immune cells and found that neoadjuvant anti-PD-1 therapy significantly increased the proportion of several intratumoral T cell sub-populations, including a TCF7-expressing progenitor exhausted population. Downstream effects of neoadjuvant anti-PD-1 therapy on T cells, namely increased production of IFN-g, included transcriptionally altering the myeloid and dendritic cell populations to be more immune suppressive but also potentially more vulnerable to other immune checkpoint therapies, specifically anti-TIGIT and anti-CTLA-4 therapies. Due to the impact of neoadjuvant anti-PD-1 therapy on intratumoral T cell populations, we examined whether we could detect tumor-reactive T cells by cloning TCRs from transcriptionally defined populations in a patient treated with neoadjuvant anti-PD-1 and testing reactivity to the patient-derived gliomasphereline. Among TCRs cloned, we discovered that T cells arising from the activated and exhausted population showed tumor reactivity, suggesting that utilizing transcriptional phenotypes can guide selection of potential tumor-reactive TCRs in GBM patients treated with neoadjuvant anti-PD-1 therapy. In conclusion, neoadjuvant anti-PD-1 therapies alters the immune landscape in these tumors and can be potentially used in combination with other immunotherapies to more effectively treat this malignancy.

Optimizing Breast Cancer Management S. Karger AG (Switzerland)

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Tumor-Induced Immune Suppression Cutaneous MelanomaImmunotherapy of Hepatocellular Carcinoma

Merkel cell carcinoma (MCC) is a deadly, virus-associated skin cancer with a 5-year relative mortality rate of 46%. The Merkel cell polyomavirus (MCPyV) is clonally integrated into 80% of MCCs and persistent expression of MCPyV T-antigen oncoproteins is required for tumor survival and growth, potentially providing ideal targets for immune based therapies. In the remaining 20% of MCCs that are virus-negative, remarkably high numbers of UV-induced neoantigens are detected, suggesting that both MCC subsets harbor immunogenic epitopes. Over the last few years, this hypothesis has been strongly supported by extraordinarily high response rates to agents blocking the PD-1 pathway in patients with both virus-positive and virus-negative MCC. However, still roughly half of patients do not benefit from these modalities, indicating an urgent need to identify biomarkers predictive of response and immune evasion mechanisms that underlie PD-1 blockade resistance. While much of the work presented here was initiated and/or completed prior to the use of these novel therapies, these data provide the basis for ongoing efforts to delineate predictors and mechanisms of resistance to PD-1 blockade therapy. Within the opening chapters, we explore pathogen-driven cancers more broadly (Chapter 1) before delving specifically into MCPyV-induced MCC, its rising incidence rate (Chapter 2) and known mechanisms of immune evasion (Chapter 3). Previous studies have indicated that a robust CD8 T cell response is associated with dramatically improved MCC outcomes, therefore, we sought to characterize several mechanisms of CD8 T cell dysfunction. The first is described in Chapter 4 in which we show that the downregulation of the adhesion molecule E-selectin within MCC tumor vasculature is associated with intratumoral T cell exclusion and reduced survival. However, even if CD8 T cells can infiltrate tumors, there is abundant literature to indicate that effective CD8 T cell responses require CD4 help and that this ‘help' is often impaired in the setting of cancer. Consequently, Chapters 5-8 focus upon elucidation of the CD4 helper T cell response against MCC. Specifically, in Chapter 5 we discuss the multitude of CD4 subtypes that have been described and their relevance in the setting of cancer and cancer therapies. In order to elucidate the phenotype and function of MCPyV-specific CD4 T cells in the context of MCC, we needed to first identify CD4 T cell epitopes within MCPyV and develop reagents enabling their isolation. This work is the focus of Chapter 6. In Chapter 7 we examine an especially fascinating, newly identified CD4 epitope ‘WEDLFCDESLSSPEPPSSSE’ locating within the MCPyV Large T-antigen. This epitope is highly immunogenic and has several key features which make it an ideal target for immune-based therapies such as a therapeutic cancer vaccine. Discovery of this epitope also resulted in the generation of HLA class-II tetramers allowing for the first time isolation of MCPyV-specific CD4 T cells directly ex vivo without antigenic stimulation. However, in many patients the frequency of these cells was found to be below the limit of the detection by standard methods. As a result, in Chapter 8 we describe the development of a novel method using a digital scanning microscope to specifically and sensitively

identify rare antigen-specific T cells. Finally, in Chapter 9, we shift away from the CD4 T cell describe a unique subset of MCC patients who present without a detectable primary skin lesion and who have a remarkable 50% higher rate of survival as compared to stage-matched patients with primary skin lesions. These patients have several elevated markers of immunity suggesting that clearance of the primary skin lesion is immune-mediate. This past year (2017) historically marked the first FDA approval of an agent for the treatment of advanced MCC. Therefore, as we continue to treat more MCC patients with this agent (avelumab; anti-PD-L1) and other immune checkpoint inhibitors, the findings described in this dissertation will allow us to evaluate potential biomarkers of response and resistance including E-selectin downregulation and evaluation of CD4 T cell phenotype and function. For patients who do not respond to PD-1 blockade, these studies will help inform the use of existing therapies in potentially novel combinations and support the development of new approaches, such as a therapeutic cancer vaccine. Ultimately, we believe that these efforts will translate to improving patient outcomes.