Yoshiyuki Yamaguchi
Editor

Immunotherapy of Cancer

An Innovative Treatment Comes of Age

Springer

Immunotherapy of Cancer

Yoshiyuki Yamaguchi
Editor

Immunotherapy of Cancer

An Innovative Treatment Comes of Age

Springer

Editor
Yoshiyuki Yamaguchi
Department of Clinical Oncology
Kawasaki Medical School
Kurashiki, Japan

ISBN 978-4-431-55030-3 ISBN 978-4-431-55031-0 (eBook)
DOI 10.1007/978-4-431-55031-0

Library of Congress Control Number: 2015960813

Springer Tokyo Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer Japan KK is part of Springer Science+Business Media (www.springer.com)

Preface

Preparation of this book started in October 2013, when the 51st Annual Meeting of the Japan Society of Clinical Oncology (JSCO) was held in Kyoto, Japan. When the editorship was offered to me, I thought, Why me? I was too inexperienced to complete such a great book, with so many Japanese experts in this field. However, I decided to take on the challenge of producing the book with much help from my dedicated older and younger colleagues. Here, I want to express my sincere thanks to all the authors who contributed.

This book contains the history, current status, and future perspective of cancer immunotherapy. The reader may understand easily, I hope, what you should know about the immune system when you treat a cancer patient. Immunotherapy has now come of age as the fourth modality of cancer treatment. Its role in cancer treatment, I believe, will grow day by day, and a future revolution in cancer treatment will occur as all the other treatments, including surgery, chemotherapy, and radiotherapy, may exist with and for the success of cancer immunotherapy.

About 30 years ago, when I was still a young surgeon, I was absorbed in research for tumor immunology. My Ph.D. thesis was titled "An Analysis of Suppressor Factor–Receptors on Peripheral Blood Lymphocyte Surfaces of Cancer Patients". My esteemed professors had thought in those days that there could be no success in cancer immunotherapy without modulation of immunosuppressive mechanisms. Now, they do seem to have been right! I dedicate this book to my two most important professors, the late Takao Hattori and the late Tetsuya Toge. I also dedicate this book to all my sincere researchers who helped me to develop in this field.

Kurashiki, Japan — Yoshiyuki Yamaguchi
July 2015

Contents

Part I
Overview, History, Classification

Chapter 1
Overview of Current Cancer Immunotherapy

Yoshiyuki Yamaguchi

Abstract Immunotherapy has been investigated worldwide as the fourth cancer treatment modality, following the standard modalities of surgery, chemotherapy, and radiotherapy. Recently, the significant progress in our fundamental understanding of tumor immunology and the recent clinical advances in cancer immunotherapy trials have opened new avenues of cancer immunotherapy. At last, cancer immunotherapy has come of age, now. There is no longer any doubt that the immune system does work in tumor eradication. In this chapter, the progress made in cancer immunotherapy during the past half-century and the many types of cancer immunotherapy are summarized. A brief review of important nomenclature in tumor immunology is also provided, which may further facilitate the reader's understanding of the later chapters. Moreover, a future perspective for cancer immunotherapy development is discussed. Finally, I would say now that one lymphocyte, one dendritic cell, one antigen, and one drug can change the cancer treatment, immunotherapy, together.

Keywords Cancer immunotherapy • Mutation • Immunosurveillance • Immunocheckpoints • Personalized immunotherapy

1.1 Introduction

Immunotherapy has been investigated worldwide as the fourth cancer treatment modality, following the standard modalities of surgery, chemotherapy, and radiotherapy. Over the past five decades of research into cancer immunotherapy, several novel and promising discoveries have been investigated but then found to have disappointingly limited efficacy in clinical trials. Nevertheless, the significant progress in our fundamental understanding of tumor immunology and the recent clinical advances in cancer immunotherapy trials have opened new avenues of cancer immunotherapy, at last [1]. There is no longer any doubt that the immune system does work in tumor eradication.

Y. Yamaguchi, M.D., Ph.D. (✉)
Department of Clinical Oncology, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan
e-mail: shogo@med.kawasaki-m.ac.jp

Y. Yamaguchi (ed.), *Immunotherapy of Cancer*,
DOI 10.1007/978-4-431-55031-0_1

Cancer immunotherapy has only recently obtained a steady hold in the field of cancer treatment. Moreover, there is currently a fresh breeze of innovation in the field of immunotherapy as cancer treatment, and clinicians and researchers should thus be aware of the paradigm shift in our ways of thinking about how best to treat the many varieties of cancer. In this chapter, the progress made in cancer immunotherapy during the past half-century and the many types of cancer immunotherapy are summarized. A brief review of important nomenclature in tumor immunology is also provided, which may further facilitate the reader's understanding of the later chapters.

1.2 What Is the Immune System? Cells, Molecules, and Receptors Are Involved

The immune system plays a key role in human host-defense mechanisms, by which invaders such as viruses and bacteria are eradicated as not-self entities. Along with this eradication, antigenic information is saved in the memory of the host immune system, which can ensure the host's prompt immune response against the next attack of the same invaders. The host is also protected from cancer by this mechanism, which is known as the immunosurveillance mechanism [2].

The immune system consists of many types of functional cells, molecules, and receptors (Table 1.1), which together make the immune system quite complicated. The cells involved include granulocytes, natural killer (NK) cells, γδT cells, macrophages, T and B lymphocytes, and dendritic cells (DCs). Granulocytes and NK cells "look around" the body and attack invaders in an antigen-nonspecific manner. Macrophages are organ-specific phagocytes that also attack and collect the antigenic information of invaders as well as injured cells, old dying cells, and mutated cells, locoregionally. T lymphocytes work under the direction of DCs in an antigen-specific manner, and they can be classified into many functional cell types including helper T cells, cytotoxic T cells, inducer T cells, regulatory T cells, suppressor T cells, and more. It has been well established that T cells are highly involved in tumor eradication. B lymphocytes function as a producer cell of antigen-specific antibodies after antigenic stimulation through their differentiation into plasma cells. DCs are known as professional antigen-presenting cells (APCs). Immature DCs migrate, capture, and process antigens and then differentiate into mature DCs that present antigenic information to antigen-reactive T cells in regional lymph nodes, resulting in antigen-specific T-cell activation. DCs play a crucial role in the antigen-specific machinery of immune responses.

The immune molecules to be understood in cancer immunotherapy include antibodies, cytokines, and antigen peptides. Antibodies are molecules that are produced by B cells through their differentiation to plasma cells. Antibodies bind to antigens in an antigen-specific manner, and they then attack or neutralize the antigens. Antibodies also exist on the surface of B cells as a B-cell receptor (BCR).

Table 1.1 Representative cells, molecules, receptors, and their functions in immune system

1. Cells	Granulocytes, NK cells, γδT cells:	Systemic patrol
	Macrophages	Locoregional patrol
	T and B cells	Specific functions offered
	Dendritic cells	Director in immune reactions
2. Molecules	Antibody	Bind to target and neutralize antigens
	Cytokine	Intercellular stimulatory or inhibitory signaling
	Peptide	Essential target recognized by effector T cells
3. Receptors	TCR	Antigen-reactive receptor on T cells for recognition and signaling
	BCR	Antibody on B cells
	TLR	Danger signal transduction
	Cytokine receptor	Signaling specific for corresponding cytokine

NK natural killer, *TCR* T-cell receptor, *BCR* B-cell receptor, *TLR* toll-like receptor

Cytokines are molecules that mediate intercellular communications such as stimulatory or inhibitory signals. Many cytokines have been identified to date, including interferons, interleukins, tumor necrosis factor, growth factors, colony-stimulating factors, and more. Some cytokines are directly cytotoxic to cancer cells, but a few cytokines are approved for use in cancer treatment. Antigen peptides are a part of the antigenic mother protein. They can stimulate antigen-reactive T-cell precursors in regional lymph nodes to become effector T cells, which then migrate to a target site and recognize the antigenic epitopes on target cells, including cancer cells. Many clinical trials using antigen peptides are now being conducted to determine the potential clinical benefits.

These immune molecules function in the immune system through their specific receptors. Antigen peptides are recognized by T-cell receptors (TCRs) specific to the antigen. A BCR is a receptor on B cells, a molecule of which is an antibody, as mentioned above. In addition, toll-like receptors (TLRs) are molecules that transduce danger signals of invaders into immune cells. Each cytokine has a corresponding receptor on the cell surface, through which functional signals are transduced into the cells.

1.3 Classification of Immune Systems and Cancer Immunotherapy

There are two different classifications with which one can understand the immune system in terms of the comparative counterpart nomenclatures of immunity: they are humoral immunity versus cellular immunity and innate immunity versus acquired immunity. Each of these types of immunity consists of the different cell types, molecules, and receptors mentioned above (Table 1.2).

Table 1.2 Classification of immunity and cancer immunotherapy based on cells and molecules involved

1. Humoral immunity versus cellular immunity	Humoral:	Antibody
	Cellular:	Functional T cells, macrophages, NK cells, NKT cells, γδT cells, DCs, granulocytes
2. Innate immunity versus acquired immunity	Innate:	Granulocytes, NK cells, NKT cells, γδT cells, macrophages, DCs
	Acquired:	T cells, B cells
3. Active immunotherapy versus adoptive immunotherapy	Active:	Vaccine, immunocheckpoint inhibitor
	Adoptive:	Antitumor antibody, antitumor cytokines, antitumor lymphocytes

Humoral immunity is an immune response that depends on antigen-specific antibody production by B cells in concert with type 2 helper T cells (Table 1.2). Although there is evidence that the antibody response is involved in tumor responses, humoral response-based cancer immunotherapy has not been actively developed, except for research concerning monoclonal antibodies specific to tumor growth factors and growth factor receptors on the surfaces of tumor cells. Cellular immunity is an immune response involving many types of cells, including antigen-specific functional T cells (cytotoxic T cells and type 1 helper T cells) and antigen-nonspecific macrophages, NK cells, NKT cells, γδT cells, DCs, and granulocytes. Cellular immunity-based cancer treatment has been the main focus of investigation in the development of cancer immunotherapy.

The counterpart nomenclature, i.e., innate immunity versus acquired immunity, is also important. Innate immunity involves granulocytes, NK cells, NKT cells, γδT cells, macrophages, and DCs, whereas acquired immunity involves T- and B-cell responses (Table 1.2). Both of these types of immunity are quite important to the body's eradication of invaders including cancer cells, as well as in the overall understanding of cancer immunotherapy.

When we classify the current types of cancer immunotherapy, two nomenclatures of immunotherapy types are used: active immunotherapy and adoptive immunotherapy (Table 1.2). Active immunotherapy includes cancer vaccines, where therapeutic vaccines indirectly attack tumor cells with the emergence of immune activation specific to tumor antigens. Immune cells that are stimulated and activated by the cancer vaccines "actively" function in tumor eradication in a host. In terms of an "indirect" working property, the immunocheckpoint inhibitors described below can also be considered to belong to the active immunotherapy category. In contrast, adoptive immunotherapy is a treatment using tumor-reactive immune molecules (cytokines or antibodies) or cells, which themselves directly attack tumor cells for eradication. When treating a host undergoing cancer immunotherapy, more attention must be paid to the patient's immunocompetency in active immunotherapy compared to adoptive immunotherapy.

1.4 Eradication of Invaders Including Cancer by the Immune System

A scheme showing the eradication of invaders including cancer is shown in Fig. 1.1. When invaders enter a host, an initial response to the invaders is processed by the host's innate immunity, usually in an antigen-nonspecific manner. Antigenic information obtained in the initial response is further presented to the acquired immunity system by DCs, which are antigen-presenting cells. This presentation results in the activation and differentiation of T and B cells to function in an antigen-specific manner, which strengthens the eradication of invaders as a secondary response. After the initial and secondary immune responses, antigenic information is recorded in the memory of the host immune system to varying extents depending on the antigens. Thus, invaders including cancer can be completely eradicated with both initial and secondary immune responses in antigen-nonspecific and antigen-specific manners by the innate and acquired immunity, respectively. Cancer immunotherapy is a treatment that uses these precise machineries of the immune system.

Importantly, there is a regulatory immunity that controls both the initial and secondary immune responses (Fig. 1.1). The regulatory immunity consists of cellular and molecular systems, including regulatory T (Treg) cells, myeloid-derived suppressor cells (MDSCs), and immunocheckpoint molecules, for example, cytotoxic T-lymphocyte-associated protein (CTLA)-4 and programmed death (PD)-1. These cells and molecules are highly involved in the prevention of the emergence of effective antitumor immune responses (Fig. 1.1).

Thus, tumor eradication by the immune system is finally completed when the regulatory immune system of cellular and molecular interactions is overcome. The

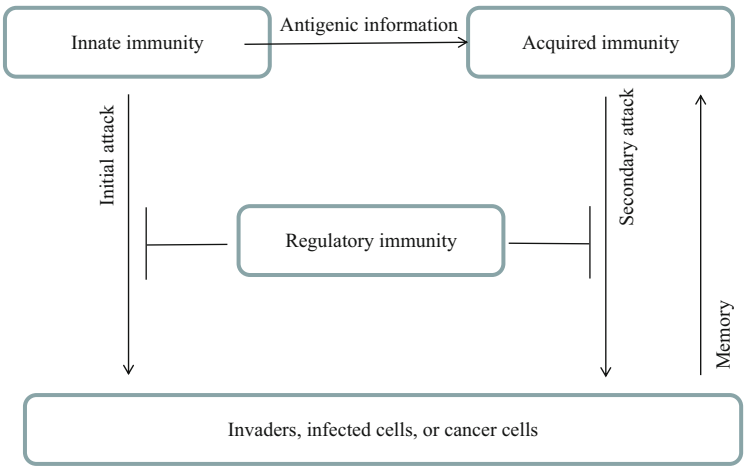

Fig. 1.1 Scheme of effector and regulatory systems for eradication of invaders including cancer. Scheme of immune system against invaders including cancer is indicated. It consists of effector (innate and acquired immunity) and regulatory systems

concept of cancer "immunoediting" advocates that the "three Es" of elimination, equilibrium, and escape play dual roles in promoting host protection against cancer and facilitating tumor escape from immunosurveillance [3]. The immunoediting concept may help us to determine what is happening at the tumor site at the time of tumor recognition and eradication by the immune system.

1.5 Machinery of Antigen Presentation and Recognition

The machinery of antigen presentation and recognition is very important to the concept of cancer immunotherapy (Fig. 1.2). Exogenous and endogenous antigen proteins are processed randomly into peptides consisting of 8–12 amino acids at the proteasome of professional APCs, such as DCs. The processed antigen peptides meet with a human leukocyte antigen (HLA) molecule at the endoplasmic reticulum of the APCs to make an HLA-peptide complex that then moves to the cell surface of the APCs. The antigen peptides in context with an HLA molecule on APCs can stimulate antigen-reactive T-cell precursors to become effector T cells, in which HLA class I- and class II-peptide complexes can stimulate antigen-reactive

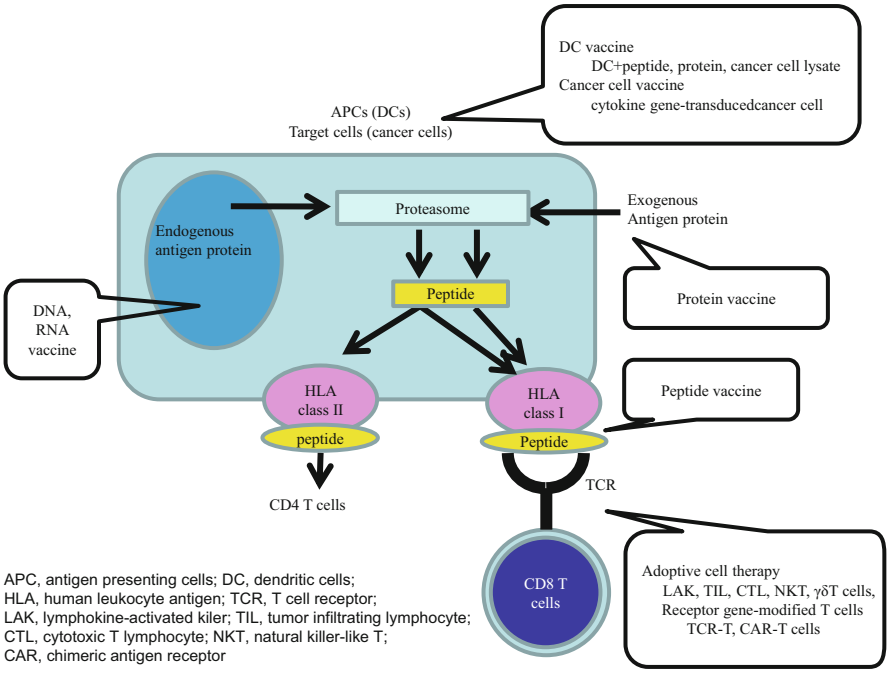

Fig. 1.2 Machinery of antigen presentation and possible cancer immunotherapy. Machinery of antigen presentation and recognition is summarized. Possible cancer immunotherapies including vaccine therapy and adoptive cell therapy are also indicated

Table 1.3 Molecules involved in antigen presentation and recognition

Reaction	APC, target cell	Lymphocytes
Specific	HLA + peptide	TCR
Co-stimulatory	CD80 (B7-1), CD86 (B7-2)	CD28(stimulatory), CTLA-4 (inhibitory)
	CD40	CD154 (CD40L)
Adhesion	HLA class II	CD4
	HLA class I	CD8
	CD54 (ICAM-1)	CD11a/CD18 (LFA-1)
	CD58 (LFA-3)	CD2 (LFA-2)

TCR T-cell receptor, *CTLA-4* cytotoxic T-lymphocyte-associated protein-4, *LFA* lymphocyte function-associated antigen, *ICAM* intercellular adhesion molecule

CD8 and CD4 T cells, respectively (i.e., HLA restriction) [4]. Activated T cells then migrate to a target site and recognize the antigen epitopes on target cells, including cancer cells, to eradicate them.

Important molecules involved in the antigen presentation and recognition are summarized in Table 1.3. The machinery of antigen presentation and recognition consists of molecules needed for the antigen-specific reaction, co-stimulatory reaction, and adjunctive adhesion reaction, which together make a strong immunological synapse formation that can transduce efficient activation signals into antigen-reactive T cells [5].

Based on the above information, several treatment modalities for cancer immunotherapy have been proposed, including vaccines and adoptive cell therapy (ACT) (Fig. 1.2). The vaccine modalities include DC vaccines, cancer-cell vaccines, protein vaccines, peptide vaccines, and DNA/RNA vaccines. The ACT modality includes the transferal of cells of several effector cell types, including lymphokine-activated killer (LAK) cells, tumor-infiltrating lymphocytes (TILs), cytotoxic T lymphocytes (CTLs), NKT cells and γδT cells, and TCR gene- and chimeric antigen receptor (CAR) gene-modified T cells, all of which are described in detail in the following chapters.

1.6 History of Cancer Immunotherapy Development

The history of the development of cancer immunotherapy is of interest. According to the literature, the first immunotherapy for cancer was conducted in 1891 by Dr. William Coley, who administered a bacterial preparation to patients [6]. I would say, however, that the development of cancer immunotherapy based on the current understanding of tumor immunology has been most active since the 1970s. Events that have contributed to the development of cancer immunotherapy are shown in Fig. 1.3, and the cancer immunotherapies currently approved in Japan are shown in Table 1.4.

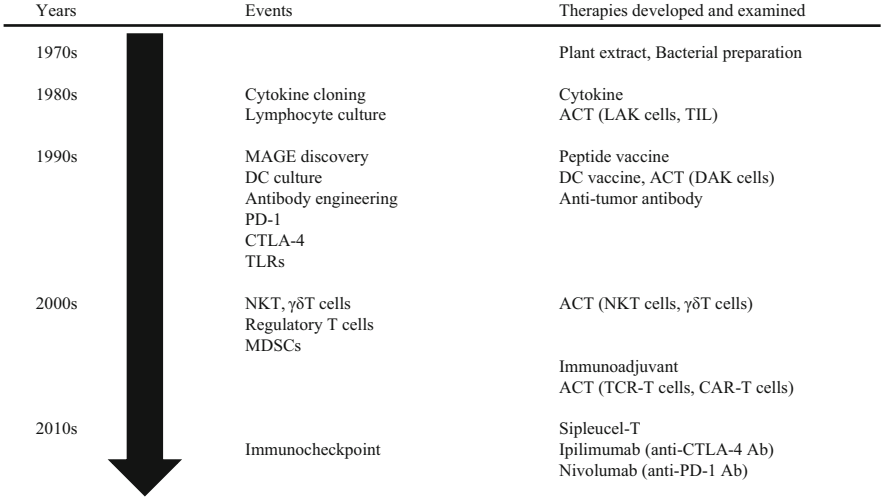

Fig. 1.3 History of cancer immunotherapy development. History of cancer immunotherapy development is shown. Milestone discoveries in tumor immunology are also indicated

First, crude biological response modifiers including plant extracts and bacterial preparations were investigated in clinical trials. Some agents demonstrated a clinical benefit, and they were consequently approved as drugs for cancer treatment in Japan. Most of them have been used in combination with cytotoxic chemotherapy or radiation therapy. However, none has become a standard cancer treatment except for bacillus Calmette-Guérin (BCG) for superficial bladder cancer, despite the accumulation of evidence of some agents' effectiveness (as described in Chaps. 2, 3, and 4).

In the 1980s, advances in molecular cloning and gene-engineering technology enabled the use of cytokines, including interferons and interleukins, in cancer treatment [7]. Some of these agents showed clinical benefit and were approved for use in clinical practice. A few of them have become a standard treatment for several cancer types including renal cell cancer (see Chap. 5). A crucial cytokine, interleukin (IL)-2, has permitted us to use ex vivo-activated autologous lymphocytes for cancer treatment as ACT. Representative treatments of ACT include LAK cell therapy [8], TIL therapy [9], and tumor-sensitized T cells [10] (see Chaps. 5, 6, 7, 8, and 9). ACT using TILs and tumor-sensitized T cells showed efficacy for treating malignant effusion and advanced cancer, resulting in their approval in Japan as the advanced medicine.

In addition to the clinical use of IL-2, studies of IL-2 enabled the establishment of tumor antigen-specific lymphocyte clones in vitro, which contributed to the first discovery of a melanoma antigen-encoding gene, MAGE, in 1991 [11]. This major

Table 1.4 Cancer immunotherapy approved in Japan (at Nov. 2014)

Immunotherapy	Diseases approved
1st generation	
Polysaccharide-K	Stomach (PAC), colorectal (PAC), small cell LC (+C)
OK-432	Stomach (PAC), NSLC (+C)
	Head and neck, thyroid, malignant effusion, ascites
Lentinan	Stomach (+C)
Ubenimex	Adult acute non-lymphatic leukemia (+C)
Sizophiran	Cervix (+R)
BCG	Bladder (superficial)
2nd generation	
IFN-α-2β	RCC, MM, CML, Hairy cell, hepatitis B, hepatitis C
IFN-β	Brain tumor, melanoma, hepatitis B, hepatitis C
IFN-γ-1α	RCC
Teceleukin	RCC, angiosarcoma
3rd generation	
Advanced medicine (A)	
ACT	Malignant effusion, advanced cancer
DC+peptide vaccine	Esophageal, stomach, colorectal, metastatic liver, pancreas, biliary,
	breast, lung
Advanced medicine (B)	
Tailer-made peptide vaccine	HLA-A24+ hormone-resistant prostatic cancer
NKT ACT	Lung, head and neck squamous cell cancer
γδT ACT	NSLC
4th generation (immunocheckpoint inhibitor)	
Nivolumab	Melanoma

Antitumor antibodies are excluded. Advanced medicine A is obligated to be reapplied for B until Mar. 2016

PAC postoperative adjuvant chemotherapy, *+C* with chemotherapy, *+R* with radiation, *RCC* renal cell cancer, *MM* multiple myeloma

discovery in concert with the establishment of DCs cultured in vitro [12] resulted in many new lines of research into cancer vaccine development (see Chaps. 10, 11, 12, 13, and 14). The technique of culturing DCs was also introduced in ACT for stimulating naïve T cells to generate antigen-reactive DC-activated killer (DAK) cells (see Chap. 5).

From the late 1990s to the 2000s, antibody-engineering technology enabled the use of antitumor monoclonal antibodies in cancer treatment, and nowadays, many antitumor antibodies are used in daily practice as a standard treatment for cancer. However, antitumor antibodies are not described in detail in this book.

In the 2000s, immunoadjuvants have been actively investigated, where TLRs play a key role [13] (see Chaps. 15, 16, and 17). In addition, novel effector cells including NKT cells [14] and γδT cells [15] were discovered and introduced into