1 Introduction on Cancer Immunology and Immunotherapy

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Contents

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N. Rezaei (ed.), *Cancer Immunology*, https://doi.org/10.1007/978-3-030-30845-2_1

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1.1 Introduction

Cancer is a life-threatening disease, which can involve all human organs and tissues. It is the second leading cause of death and is responsible for 25% of all deaths in the USA. It is estimated that around 1.7 million of new cases of cancer of any site will be diagnosed in 2018 in the USA, and an estimated 609,640 people will die of this disease [1]. The major cancers in adults include lung, breast, prostate, and colorectal cancer. In addition, 4613 adolescents and young adults aged 15–19 years old were diagnosed with invasive cancers. Among all invasive cancers, lymphoma was the most common cancer (20%), followed by invasive skin cancer (15%), male genital system cancer (11%), and endocrine system cancer (11%) [2]. The overall incidence of all type of cancers has been falling on average 1.1% each year over the last 10 years. In addition, death related to cancer has been decreased on average 1.5% each year over 2006–2015 [3].

Many cancer predisposing factors have been recognized; it has been found that cancer incidence is significantly associated with age from 10 to 60 years. Additionally, male gender is at higher risk of developing cancer compared to females [2]. Race is another important factor for cancer development; before 40 years of age, non-Hispanic whites and, after 40 years of age, African-Americans/blacks have the highest incidence [4]. Other risk factors include life style choices, such as tobacco use, obesity, and lack of exercise, and environmental factors, such as exposure to excessive sun, radiation during childhood, human papilloma virus (HPV), human immunodeficiency virus, and Epstein–Barr virus (EBV) infection [4].

Cancer can be a life-threatening health problem, especially when the tumor has metastasized to other organs. Its estimated number of deaths was 163.5 per 100,000 men and women per year based on 2011–2015 database of the USA. Lung and bronchus, colorectal, pancreatic, and breast cancers are responsible for approximately 50% of cancer-related deaths. Fortunately, the overall cancer-related mortality has been decreasing in recent years. Between 2011 and 2015, the death rate decreased on an average of 1.8% per year for men and 1.4% for women. Liver and intrahepatic bile duct cancer showed the greatest increase in mortality among both men and women [3].

Cancer survival significantly impacts patients' quality of life. Five-year mortality rates depend on several factors; survival is worse among males over 30 years of age, and the survival gets worse for patients over 45 years in both males and females. Non-Hispanic whites have the best survival rate and African-Americans have the worst survival with survival differences as great as 20% at 5 years after cancer diagnosis [5]. Furthermore, the type of cancer is another risk factor for patient survival. Total mortality rates vary from 6% in thyroid cancer to 97% in pancreatic cancer [6].

1.2 Cancer Immunity

Cancer immunology has been studied for a long time; however, the molecular and cellular basis of tumor immunity is not completely understood. Advances in understanding the basis of immunosurveillance and progress in the treatment of infectious disease have had a major impact on the development of tumor immunotherapy. The modern era of tumor immunology began in the 1950s when the role of T-cell responses in tissue allograft rejection was initially identified. Since then, it has been confirmed that tumors occur in association with impaired function of T-cells, indicating the importance of the immune system in the development and progression of cancer [7]. The identification of tumor-associated antigens, knowledge of effector T-cell responses, and the role of regulatory and suppressor T-cell populations are now shaping the use of the immune system to treat cancer.

In addition to an improved understanding of the immune system, significant advances in understanding the molecular basis of neoplasia have occurred. Precise control of cellular activity and metabolism is crucial for proper physiologic function. Notably, cell division is an important process that requires precise regulation. The main difference between tumor cells and normal cells is lack of growth control during the cell division process. This uncontrolled cell division can originate from various factors, such as chemical agents, viral infections, and mutations, that lead to escape of cells from the checkpoints which properly control cell division. According to the type of tumor and proliferation rate, cancers can be benign or malignant [8]. It has been found that some tumors are caused by oncogenic viruses that induce malignant transformation. These oncogenic viruses can be both RNA and DNA viruses. Also, viral infection may lead to leukopenia and immunodeficiency, increasing the risk of malignancy. Therefore, prophylactic immunization against oncogenic viruses (such as EBV, HPV, and HBV) might be a logical strategy for prevention of malignancy [9]. Indeed, a vaccine against the human papilloma virus has shown significant impact on preventing cervical intraepithelial neoplasia and may prevent development of cervical carcinoma.

1.3 Cancer and Immune System Impairment

It has been reported that impaired immune response can induce tumor growth and prevent effective antitumor suppression, possibly through a process of "sneaking through" which allows improved growth of small tumors rather than large tumors [10]. Tumors may also produce immunosuppressive factors, such as interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and alpha-fetoprotein, which suppress innate immune responses against cancer. This has led to investigations using neutralizing antibodies against these immunosuppressive factors [7]. In contrast, tumor-specific cytotoxic T lymphocytes (CTLs) can be genetically altered to become resistant to the TGF-β inhibitory effect by transgene expression of a mutant-dominant-negative TGF-β type II receptor (DNR). In addition, specific T-cells genetically manipulated to produce IL-12 can overcome the inhibitory effects of IL-10. On the other hand, tumors may express FasL and stimulate apoptosis of tumor-infiltrating effector T-cells. Small interfering RNA (siRNA) can be used to knock down the Fas receptor in tumor-specific CTL, leading to a significant decrease in their susceptibility to Fas-/FasL-mediated apoptosis [11].

The interaction between the immune system and established cancers is complex, because in addition to increasing carcinogenesis by various carcinogens among compromised subjects, cancer cells themselves can lead to severe immunosuppression. It has been reported that patients involved with primary immunodeficiency syndromes have higher risk of cancer development. In a report by Kersey et al., subjects that had an inherited abnormal lymphoid system were susceptible to malignant transformation and impairment of tumor immunosurveillance [12]. In addition, tumors produce soluble factors which downregulate the interleukin-2 receptor-α (IL-2Rα), leading to suppression of T-cell function. Furthermore, established tumors may result in severe protein expenditures in hosts, contributing to impairment of immune system function [13].

1.4 Immune System Reaction to Cancer

A critical question is whether cancer cells are sufficiently different from their normal cellular counterparts and can thus be recognized by the immune system. The immune system also produces a group of complementary markers with protective effects against cancer and other immunologic or inflammatory stresses. These markers include proteins released by T-cells and are generally classified as "cytokines." Cytokines include interleukins, interferons, tumor-necrosis factors (TNF), and lymphocyte-derived growth factors. The production of tumor-specific antibodies and/or activation of tumor antigen-specific T-cells target tumor-associated antigens typically found on the cell

membrane. Studies have suggested that vaccination in the presence of complements can lead to tumor lysis. While incompletely defined, several soluble and cellular mediators of tumor rejection have been described, including complement factors, active macrophages, T-cells, and NK cells. While T-cells require antigen specificity, the soluble and cellular mechanisms of the innate immune response can recognize the malignant phenotype in the absence of antigen specificity [14].

Since most tumor-associated antigens are self-proteins, the immune response is largely weak and patients may develop immune tolerance to tumor-associated antigens. Furthermore, the cells of the immune system may not adequately penetrate to the internal tumor microenvironment, resulting in slower immune-mediated tumor elimination. However, it is possible that the immune system may be more effective in controlling tumor growth rate rather than tumor regression [10]. Recently, it has been found that nutrition also plays a crucial role in protection against human cancer, and normal levels of zinc are required for protection against the detrimental effects of various immunosuppressive cytokines [15].

1.5 Genetic and Environmental Carcinogenesis

It has been found that genetic factors are as important as environmental carcinogens. Trials have tested carcinogenesis of retrovirus infection between different breeds of animals. A unique carcinogen resulted in disparate outcomes among different breeds, indicating the importance of genetic background in the progression of cancer. Environmental factors may also suppress immune responses and dysregulate immunosurveillance mechanisms [16].

1.5.1 Cancer Cells Escape from Host Immunosurveillance

Antigens that distinguish tumor cells from normal cells depend on the histologic origin of the tumor. Tumor-associated antigens may be viral in origin, represent mutated self-antigens, be cancer-testis antigens which are expressed only by tumor cells and normal testes, or be normal differentiation antigens. Thus, tumor cells may express similar antigens to normal cells, allowing tumor cells to escape immune system attack through induction of innate and/or peripheral tolerance. A corollary to this is that immunotherapy or stimulation of immune responses to some tumor-associated antigens may lead to damage of normal tissues and organs, as exemplified by the development of autoimmunity induced by anti-CTLA-4 or anti-PD-1 monoclonal antibody (mAb) treatment [17].

A number of complex mechanisms have been suggested for the escape of cancer cells from host immunosurveillance. Tumors alter their characteristics by decreased expression of immunogenic tumor-associated antigens, MHC class I molecules, beta2-microglobulin, and costimulatory molecules, which mediate the activation of T-cells. Another strategy resulting in failure of tumor immunosurveillance could be the expression of very low levels of antigens, unable to stimulate an immune response. Under some circumstances, such as failure of the immune response to induce a rapid response, cancer cells may proliferate rapidly. Further strategies for escape of tumor cells from immunosurveillance are based on inhibitory tumor-mediated signaling by CTLs, as occurs through changes in cell death receptor signaling. Other strategies which allow tumor cells to evade the immune system are the secretion immunosuppressive molecules dampening tumor-reactive effector T-cells and the induction of regulatory and/or suppressor cells [18].

To date, most direct evidence on tumor immunosurveillance originates from experimental studies in animal models. These models have supported the potential for antitumor immunity via vaccination, as, for example, by administration of inactivated cancer cells or through removal of a primary tumor. In addition, antitumor immunity can be adoptively transferred through administration of tumor-reactive T lymphocytes. The complexities of immunotherapy are evident as nearly all immune system components can influence tumor growth and progression. Although there is evidence for antitumor immunity in humans, and

several new agents have gained regulatory approval for cancer therapy, further investigation is warranted to increase the impact of tumor immunotherapy for more cancer patients [19].

1.5.2 Cancer Immunodiagnosis

Nowadays, new immunomolecular diagnostic approaches have been suggested for tumor detection. Monoclonal antibodies marked with radioisotopes have been used for in vivo diagnosis of small tumor foci. In addition, monoclonal antibodies have been used for in vitro recognition of the cell of origin for tumors with poor differentiation. Immunodiagnostics have also been used to determine the extent of metastatic disease, especially metastasis to the bone marrow [20].

1.6 Cancer Treatment

Systemic cancer treatment is based on four general therapeutic approaches: (1) chemotherapy, which contains a wide group of cytotoxic drugs that interfere with cell division and DNA synthesis; (2) hormonal therapy, which contains drugs that interfere with growth signaling via tumor cell hormone receptors; (3) targeted therapy, which involves a novel group of antibodies and small-molecule kinase suppressors that principally target proteins crucial in cancer cell growth signaling pathways; and (4) immunotherapy, which targets the induction or expansion of antitumor immune responses [21].

1.6.1 Cancer Immunotherapy

Tumor immunotherapy is a novel therapeutic approach for cancer treatment, with increasing clinical benefits. Tumor immunotherapy is based on strategies which improve the cancer-related immune response through either promoting components of the immune system that mediate an effective immune response or via suppressing components that inhibit the immune response. Two current approaches commonly used for immunotherapy are allogeneic bone marrow transplantation and mAbs targeting cancer cells or T-cell checkpoints [22]. Recently, various other approaches have been tested such as injection of cytokines. FDA recently approved injection of PEG-IFN-a2b in high-risk melanoma [23].

Initially, anticancer vaccines were considered for prevention and treatment of various tumors [22]. It is estimated that more than 15% of human cancers are caused by viral infection [24]. Vaccine-based immunotherapy may, thus, be most useful for virus-induced cancers. Consistent with this hypothesis, a 50% complete remission (CR) of HPV-associated vulvar intraepithelial neoplasia grade III (VINIII) has been reported [25]. An attenuated, oncolytic herpes simplex type 1, which is genetically engineered to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), has been developed for cancer therapy. This oncolytic immunotherapeutic agent has been injected to the tumor mass and has had beneficial effects in the treatment of melanoma and head and neck squamous cell carcinoma [26]. Although vaccine-based therapy has not been effective in some types of cancer, there are studies that have shown an overall survival benefit compared to placebo therapy [27]. FDA recently approved a vaccination therapy using dendritic cells for prostate cancer [28].

Another immune-targeted approach is mAbs which blocks T-cell checkpoints functioning to suppress T-cell responses. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is a member of a large family of molecules regulating T-cell immune responses. CTLA-4 is expressed on CD4+ and CD8+ T-cells, as well as on FOXP3+ regulatory T-cells [29]. Administration of mAbs targeting human CTLA-4 leads to the rejection of established tumors in a small cohort of patients with metastatic melanoma and demonstrated improved overall survival in patients with metastatic melanoma, resulting in US FDA approval for the treatment of metastatic melanoma [30]. Recent trial showed survival benefit of ipilimumab, a CTLA-4 inhibitor, in setting of metastatic melanoma and also after resection of stage III melanoma [31, 32].

Monoclonal antibodies which block other T-cell checkpoints, such as the programmed cell death protein 1 (PDCD1/PD-1), programmed cell

death ligand 1 (PD-L1/CD274), CD276 (B7H3) antigen, V-set domain-containing T-cell function inhibitor 1 (B7x), and B and T lymphocyte attenuator, have also entered clinical trials. In addition, recent trials have demonstrated significant therapeutic activity in several types of cancer, including melanoma, metastatic urothelial carcinoma, gastric cancer, hepatocellular cancer, colorectal cancer, renal cell carcinoma, non-small cell lung carcinoma, and ovarian cancer [33–38]. It has been reported that PD-L1 expression by tumor cells is associated with poor clinical outcome and may be associated with clinical response to anti-PD-1 and anti-PD-L1 therapy. Also, ligation of PD-L1 leads to inactivation of tumor-infiltrating cells [39]. On the other hand, regulatory T-cells have an immunosuppressive role in the tumor microenvironment. Studies of anti-PD-1 and anti-PD-L1 are in progress. Moreover, the combination of these agents with anti-CTLA-4 and other immunotherapy strategies has yielded promising results.

The combination of antitumor vaccines with agents targeting the IL-12 receptor resulted in conflicting results. This may be due to the upregulation of IL-12 receptor by both activated T effector cells and regulatory T-cells [40]. Thus, new approaches focused on more specific targeting of regulatory T-cells which reduce their suppressive effects on the immune system are necessary. Adoptive T-cell therapy (ACT) has been described as an effective therapeutic approach for cancer immunotherapy in early phase clinical trials. In this method, a large number of tumor-specific T-cells derived from peripheral blood, or preferably from the tumor microenvironment (with or without genetic manipulation to express a high-affinity antigen-specific T-cell receptor, or TCR), are adoptively transferred to patients with established tumors [41]. ACT mostly relies on endogenous T-cell repertoire; recent advancements allow induction chimeric antigen receptors (CARs). In CAR T-cell (CAR-T) therapy, T-cells of patients with B-cell tumors are transfected with anti-CD19 and in result, T-cells will gain the capacity to recognize B-cells in all stages of development. The first CAR-T was recently approved by FDA based on phase 2 trial which showed a dramatic complete response in 83% of patients within 3 months of infusion [42, 43]. Chemotherapy-mediated cell death leads to immune responses in a drug-induced biochemical cell death cascade-dependent manner, suggesting beneficial effects of chemotherapy and immunotherapy, in combination [44]. It seems that future goals of tumor immunotherapy are headed towards chemoimmunotherapy. Potential candidates for this combination approach include antitumor vaccines, Toll-like receptor (TLR) signaling pathway agonists/antagonists, cytokines, and mAbs targeting T-cell checkpoints, such as CTLA-4, PD-1, or PD-L1/2 [45]. Also, it seems that radiation and radiofrequency ablation are future candidates for combination therapy with immunotherapy [46]. Although immunotherapy and its combination with other therapeutic approaches such as radioimmunotherapy may be beneficial for tumor treatment, there are several limitations that need to be addressed; defining the optimal target patient, optimal biological dose, and schedule, the need for better trial designs incorporating appropriate clinical endpoints, and the identification and validation of predictive biomarkers are just a few points to note [22].

1.6.2 Cancer Cell "Switch"

Cancer cells can switch on genes mostly related to the earlier embryonic stages of development. During rapid proliferation of cancer cells, precise orchestrated enzyme formation needed for suitable metabolism of its different components might get unbalanced, and products which are not observed in normal dividing cells are produced [47]. Recently, it has been reported that these biochemical "switches" lead to uncontrolled multiplication of cancer cells. One switch has been found for a type of leukemia. It has been suggested that targeting tumor switches can make treatment of cancers very simple [19]. Nonetheless, it is unclear how this may be used to optimize tumor immunotherapy.

Since cancer immunology is a highly complex process, further research is needed to more completely understand how the immune system recognizes and eradicates cancer. In this book, we will describe a variety of novel mechanisms cur-

rently under investigation for mediating aspects of tumor immunology with a particular focus on promising therapeutic approaches, producing a complete comprehensive up-to-date textbook.

1.7 Concluding Remarks

Cancer is a life-threatening health problem which is related to several genetic and environmental risk factors that manipulate immune system function. Cancers themselves produce immunosuppressor factors to impair cells division check points, leading to uncontrolled proliferation of cancer cells. Importantly, tumor cells have learned how to escape from immune system attack via presenting of similar antigens to normal cells and expression of very low levels of antigens. Therefore, diagnosis of tumors and their progression is not easy. Recently, immunodiagnostic methods are shown to be helpful in the diagnosis of cancers and determining the extent of metastasis. On the other hand, classic treatment of cancers led to unsatisfactory results, and intelligent immunological approaches, such as regulatory T-cell targeting, adoptive T-cell administration, and combination of immunotherapy and chemotherapy are addressed. Results of antitumor vaccines, Toll-like receptor (TLR) signaling pathway agonists/antagonists, cytokines, and mAbs targeting T-cell checkpoints, such as CTLA-4, PD-1, or PDL-1/2 are promising. However, due to the high complexity of the cancer immunology, still a lot of gaps exist in this field that indicate the necessity of further research for complete understanding of cancers' immunological behaviors and emerging of more novel immunotherapeutic strategies.

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