Review

Adjuvant immunotherapy for cancer: both dendritic cell-priming and check-point inhibitor blockade are required for immunotherapy

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Abstract: The immune system eliminates advanced cancer when treated with programmed cell death protein-1 (PD-1) or its ligand (PD-L1) blockade, but PD-1 therapy is effective in only ~20% of patients with solid cancer. The PD-1 antibody mainly acts on the effector phase of cytotoxic T lymphocytes (CTLs) in tumors but induces no activation of the priming phase of antigen-presenting dendritic cells (DCs). It is reasonable that both DC-priming and PD-1/L1 blocking are mandatory for efficient CTL-mediated tumor cytolysis. For DC-priming, a therapeutic vaccine containing Toll-like receptor (TLR) agonists, namely a priming adjuvant, is a good candidate; however, a means for DC-targeting by TLR adjuvant therapy remains to be developed. TLR adjuvants usually harbor cytokine toxicity, which is a substantial barrier against drug approval. Here, we discuss the functional properties of current TLR adjuvants for cancer immunotherapy and introduce a TLR3-specific adjuvant (ARNAX) that barely induces cytokinemia in mouse models.

Keywords: TLR3, PD-1/L1 blockade, polyI:C, adjuvant, cancer immunotherapy

1. Introduction

In the 1950s, Macfarlane Burnett advocated the theory of immune surveillance, where the immune system monitors not only infection but also carcinogenesis by discriminating non-self from self-cells.1) Cancer antigens originate from self-molecules that exhibit ectopic expression and/or antigenic mutations,2) and then the concept of tumor-specific antigens and immunoediting was proposed based on the surveillance theory.3) Cancer antigens are collectively referred to as tumor-associated antigens (TAAs) because they contain testis-specific antigens and differentiation antigens (self antigens) in addition to mutated antigens. Many factors are involved in the process of natural selection, whereby cancer cells escape from the immune system.4) It is currently accepted that tumor formation is suppressed by the immune system, which eliminates protumor cells throughout life, and only a very few escape from the immune network to grow into a visible mass. Immune potential decreases with age, and tumor incidence increases in the elderly. Cancer cells appear to be the target of immune surveillance by a mechanism similar to infected cells in infectious diseases.

Infections are usually accompanied by signs of acute inflammatory responses, fever, pain, headache, etc., which are largely based on the innate responses to interferon (IFN)/cytokines. Thereafter, the acquired arms of the immune response, including antibody (Ab) production and T cell proliferation, are raised to specifically eliminate pathogens. Acquired responses happen with immune cell proliferation but no manifestation. Collectively, both acute inflammation and acquired immune response have a common root in the fundamental host response to pattern recognition in innate immunity. Prophylactic vaccines with antigens and pattern molecules are effective, but those with only antigens are far less or ineffective. Pattern molecules activate pattern-recognition receptors (PRRs) on macrophages/dendritic
cells (DCs), which trigger the induction of lymphoid effectors in acquired responses. Toll-like receptors (TLRs) are a typical family of PRRs. Immune-enhancing adjuvant represents pattern molecules that activate DCs to cross-present exogenous antigens onto MHC class I and cross-prime T cells.\(^5\)

Tumor cells originate from self cells, but harbor TAAs that can be recognized by autonomous T cells. However, tumor cells barely express pattern molecules. Instead, tumor cells may secrete damage-associated molecular patterns (DAMPs) when they are dying.\(^6\) DAMPs tend to modulate the immune system and microenvironment in either a positive or negative fashion. However, the exact components of DAMPs or the pathway by which immune cells are activated for Ab production/T cell proliferation remains unknown. By contrast, individual pattern molecules and PRRs have been biochemically identified from their differences in many studies.\(^7,8\) Thus, the quality of DC-priming can be defined in terms of immune-enhancement by an exogenous adjuvant (Table 1).

This report examines the role of synthetic TLR3-specific agonist (ARNAX) in vaccine immunotherapy for cancer.

2. PD-1/L1 antibody therapy

Recently, basic research on immunochemistry has contributed to proving the presence of cancer immune-surveillance with regard to what makes cancer cells non-self. Allison et al., demonstrated in clinical trials that an anti-CTLA4 Ab (ipilimumab) is effective in the treatment of some advanced cancers.\(^9\) Honjo et al., designed clinical trials in patients with melanoma based on the mouse finding that the PD-1 pathway leads to the regression of transplanted cancer. An initial report on a clinical trial with an anti-PD-1 Ab (nivolumab) was published in 2012 and surprised cancer researchers worldwide.\(^10\) Melanoma with systemic metastasis achieved a remission rate of 60\% by treatment with PD-1 Ab. It was shown that anti-PD-1 Ab was also effective for Hodgkin’s lymphoma with high expression of PD-L1, a ligand of PD-1.\(^11\) The anti-PD-1 Ab was also noted to have fewer side effects than the anti-CTLA4 Ab. The concept is accepted that PD-1 blocking relieves lymphocyte PD-1-mediated suppression of CD8\(^+\) killer T cell activity and active CTLs prohibit tumor progression. Unlike the anti-PD-1 Ab, the anti-PD-L1 Ab acts on both cancer cells and DCs, suggesting that the anti-PD-L1 Ab might be more effective than PD-1, depending on the cancer type.

The cases of success with PD-1 and PD-L1-inhibiting Abs clearly show that responders to PD-1/L1 therapy harbor “cancer-specific CTLs”, which are activated and/or reinvigorated in response to PD-1 blockade. PD-1 is a receptor for a suppressive signal that is evoked in lymphocytes, which was consistent with the finding that PD-1 blockade leads to the recovery of T cell function to enhance CTL cytotoxicity. It is likely that because the rate of cancers permitting T cell entry and reinvigoration are limited in frequency, therapies with anti-PD-1 or anti-PD-L1 Abs may accomplish only 20–30\% remission in patients with solid cancers.\(^12\) To succeed in immunotherapy, it is essential to devise a way to induce anti-tumor CTL activation/proliferation in patients with progressive cancer, in order to help some of the remaining ~70\% patients with resistance to PD-1 therapy.

Recently, anti-PD-1 Ab therapy was approved for the treatment of lung cancers. Smokers frequently have squamous cell lung cancer with genomic mutations.\(^13\) In 1 year, anti-PD-1 Ab therapy produced remission in nearly 30\% of advanced cancers (including partial remission), a much higher rate than that with docetaxel.\(^14\) Even adenocarcinoma and large cell carcinoma responded slightly better to PD-1 therapy than docetaxel based on a comparison of their 2-year survival rates.\(^15\) The remission rate of patients with cancer cells positive for PD-L1 expression was nearly 40\%, and cancer PD-L1 positivity was a good prognostic parameter.\(^14\) That is, if cancer has an antigen mutation with high PD-L1 expression, there is a high possibility of remission with the anti-PD-1/L1 Abs in patients.\(^16\) The problem is still that ~60\% of patients with advanced cancers that barely enter remission with the anti-PD-1 Ab despite being PD-L1 positive. Again, the problem may be that the CTLs are not fully primed. Research on priming adjuvants could be the key to bringing the ~60\% patients to remission.

3. Need for a priming adjuvant for immunotherapy

Sequential trials of cancer peptide vaccines for two decades have suggested that a CTL-inducing peptide vaccine is not established by administration of the antigen alone.\(^17\) Innate immunity activation (immune-enhancer, generally referred to as an adjuvant (Table 1)) becomes essential in the context of DC-priming.\(^5,18\) As with prophylactic vaccines against infections, antigens and adjuvants are needed
for therapeutic vaccines where immune memory is established (Fig. 1). Adjuvants are roughly divided into inflammatory adjuvants and DC-priming adjuvants. So far, no DC-priming adjuvant has been approved for use in humans, leaving only inflammatory adjuvants, such as aluminum salt (alum) and oil (Montanide, etc.), approved as supplements for vaccines. Most studies of cancer vaccines containing inflammatory adjuvants have failed to reach the criteria of efficacy and safety for therapeutic aims. At least one of the reasons for the failure of cancer vaccines is due to the selection of inappropriate adjuvants.

Alum was reported in the 1920’s by Glenny et al. as an enhancer of the immune responses. Although it is generally understood among immunologists that immune activation is strongly potentiated by “contaminating” impurities in antigens,²⁰ the physical properties and functions of the impurities have not been determined until recently. Many immune-enhancing substances besides alum have been reported, and most of these have been collectively referred to as pattern molecules of microbes (Table 1). Hence, microbial components as well as minerals can be immune enhancers. Moreover, immune adjuvants can be synthesized based on the structures of microbial patterns, and functionally identified as an agonist for receptors such as TLR in innate immunity.²¹ Thus, studies on the mechanism and signal of adjuvanticity began recently, and elucidation of the science of DC-priming adjuvants is in progress in the academic field. Ten kinds of TLR proteins (11 transcripts) have been identified in humans. Of these, only TLR2 and TLR3 are expressed in antigen-presenting DCs in humans²¹ (Table 2). TLRs other than TLR3 utilize adapters called MyD88 (Table 1), which is closely associated with inflammation. Ligand-stimulation of TLR3 or part of TLR4 recruits an adapter called TICAM-1 (also called TRIF).⁷⁻⁸ MyD88 induces inflammatory cytokines (i.e., IL-6, TNF-α, IL-10, etc.) using NF-κB as a transcription factor.⁸,²² In addition, MyD88 triggers the production of IL-1β in association with Caspase 1 (inflammasome) activation.²³ MyD88 stimulation by TLR agonists usually induces Th2 polarization and regulatory cells. Notably, TLR stimulants cause side reactions of cytokines in host immune responses secondary to infection. Toxins other than pattern molecules may be involved in the development of inflammation in infections with bacteria or viruses. Finally, by-

| Category | Adjuvant | Receptor | Adaptor | Cytokine | Reference |
|----------|----------|----------|---------|----------|-----------|
| Lipid    | MPL      | TLR4     | MyD88   | IL-12    | TICAM in TLR4 pathway predominantly activated |
| Lipopeptide | TLR2 (+TLR1) or TLR6 | MyD88 | Undefined | IL-12    | Similar to BCG-polygalactoside-functionally |
| Oil, squalane | Undef | TLR5 | MyD88 | IL-12    | Undefined |
| Protein  | Flagellin | TLR5     | MyD88   | IL-10    | Undefined |
| Nucleic acid | Virus dsRNA | TLR3, MDA5, TICAM-1/MAYS | MyD88 | IL-12    | Provoking systemic IFN-γ cytokinemia, via |
| Polycl | TLR3, MDA5, TICAM-1/MAYS | MyD88 | IL-12    | Poly I:C TLR3, MDA5, TICAM-1/MAYS | |
| Mineral | Alum | NLR, PG? | ASC | IL-12    | BAFF-F/F-IL-12 |
stander activation of DCs occurs with infection, which is attributable to the systemic response of cytokines, IFN-α/β, and prostanoids. Similarly, vaccination (although there are individual differences in immune response) appears to make it evident that the vaccine is not effective only by the input of antigen molecules,17),19) but they can be effective with antigen plus innate immune activation, such as TLR stimulation7),8) (Fig. 1). Effective vaccines in this scenario always harbor inflammatory toxicity.

4. DC maturation by current adjuvants in the context of inflammation

A whole-body response by the innate immunity system is not required for immune activation, only for the prevention of systemic spread by infections. For immune activation, local DC-priming in lymph nodes and CTL entry and reinvigoration of T cells in the microenvironment may be prerequisites. Adjuvant facilitates the provocation of CTL proliferation, then PD-1 is silenced without systemic inflammation in antitumor immunity (Fig. 1). Thus, the chemical synthesis of immune adjuvant should aim to reduce the inflammatory response to keep DC function intact and CTLs locally reinvigorated, at least in cancer immunotherapy.23)

DCs are representative antigen-presenting cells, discovered by Ralf Steinman.24) Human antigen-presenting DCs are positive for CD141 (a thrombomodulin epitope) and do not express TLR7/9, unlike those of mice20),21) (Table 2). Antigen-presenting DCs strongly express TLR3 across species,21),25),26) Selective DC-priming can be achieved by activating TLR3 (followed by the TICAM-1 pathway) localized on CD141+ DCs23) (Fig. 2). Double-stranded (ds)RNA is a good tool for the activation of TLR3,27) but exogenously added dsRNA (mostly viral dsRNA except polyI:C) hardly enters the endosome in DCs (where TLR3 is localized). Once dsRNA enters cells, as has been shown with polyI:C,27),28) robust cytokines are generated via cytoplasmic RNA sensors.8),29) The RNA sensor-response occurs in viral infections in response to cytoplasmic dsRNA in whole-body cells.30) External dsRNA released from infected cells barely enters DCs unlike polyI:C. Studies on polyI:C and viral infections have suggested that cytokines and mediators promote systemic defense against infection but do not target only antigen-presenting DCs (Fig. 2). DC maturation in infection occurs in the context of activation of the cytokine network.31) Cytokines thereafter are expressed in a spatio-temporal order, culminating in the immune response. Random input by a single cytokine for therapy makes no sense for immune activation. In fact, cytokine monotherapy has not succeeded in trials using from IL-2 to IL-12. Many adverse events have also been reported with the use of IFN-α/β in hepatitis therapies.32),33) Even if cytokines do not induce systemic inflammation or side effects from vaccination, local secretion of cytokines/IFNs could be sufficient for immune-enhancing vaccine therapies to induce the maturation of localized DCs.

5. Ideal adjuvants for immunotherapy

Conventional inflammatory adjuvants are activators of innate immunity as well as inducers of inflammatory mediators; nonetheless, their role in DC-primed immune activation has not been clarified. Both the MyD88 and TICAM-1 pathways sufficiently prime DCs, but their qualitative differences remain unknown. In comparison with the MyD88 pathway, TLR3-TICAM-1 mainly works in antigen-presenting DCs,27),34) which is of benefit for their specificity, with no need to abstract DC-stimulating activity from the whole molecule of adjuvant.

The quality of adjuvanticity in compounds that complement vaccines, such as alum, has been assessed through their efficacy to induce cytokine responses, which do not always reflect their immune-enhancing ability, or in other words their DC-priming ability. Multivalent metal ions, not limited to aluminum, induce contact dermatitis, which reflects an adverse effect of metals on human cells. The current adjuvants are good for Ab production,
Fig. 1. Functions of priming adjuvants. The priming adjuvant targets DCs in draining lymph nodes and induce IL-12 and type 1 IFN to facilitate Th1 skewing, CD8⁺ T cell proliferation and reinvigoration (upper panel). The priming adjuvant promotes DC cross-presentation of external antigens from patients’ cancer cells to proliferate tumor-specific CTLs (lower panel). DC-priming is triggered independent of inflammation or cytokines induced secondary to adjuvant injection (upper panel). Administration of DC-priming adjuvant also resets the tumor microenvironment, which is indispensable for CTL invigoration and migration to tumors (lower panel). PD-1 in T cells and its ligand PD-L1 on tumor cells control CTL tumoricidal activities, and block excess CTL activation (lower panel). Regulatory T cells (Treg) and damage-associated molecular patterns (DAMPs) may control these CTL reactions toward cancer.

Fig. 2. TLR3-specific DC-priming induced by ARNAX. PolyI:C is a virus dsRNA mimic, and it evokes mitochondrial antiviral signaling-mediated systemic cytokine production all over the body (right panel). Selective activation of TLR3 in DCs is accomplished by GpC DNA-capped short dsRNAs (left panel). These enter human cells just by addition to the medium. Of note, human cells do not take up viral dsRNA with no 5’- or 3’-stretch. TICAM-1 is a TLR3-specific adaptor for the induction of IL-12 and type I IFN. It also cross-presents in exogenously added antigens onto MHC class I to cross-primed CD8⁺ T cells (lower inset).
which is partly independent of TLRs, but inappropriate for CTL proliferation. This can raise a question as to why an inflammatory poison is regarded as an adjuvant.

Immune adjuvants that prime DCs for robust immune-enhancement are similar to poly I:C but without inducing cytokinemia or toxicity are just now being developed. DC-targeting is achieved by the synthesis of a DNA-dsRNA hybrid molecule that selectively activates TLR3 without activating the mitochondrial antiviral signaling pathway. The design of the molecule is intended to prevent systemic inflammation. TLR3 does not link to MyD88 but does to TICAM-1 in antigen-presenting DCs. Adjuvants that specialize in DC-priming and activate antigen-specific immunity could significantly reduce adverse events in immunotherapy, particularly for patients with cancer. However, the results from studies on mouse models are still far removed from actual clinical use. In the future, the designs of adjuvants will become more sophisticated in order to accomplish fine DC-priming safely in a form that can be applicable to patients.

6. Summary

In this review, we examined priming adjuvants for DCs, which are indispensable for the induction of TAA-specific CTLs, and that conventional alum or oil adjuvants are inflammation-inducing agents but they do not always have direct immune enhancing effects, with their specificity for DCs being secondary. We have discussed the mechanism whereby cytokinemia occurs in association with inflammation, which never correlates with the degree of specific immune responses. PD-1/L1 blockade therapy necessitates pre-existing cancer-specific CTLs. An ideal CTL inducer would be a non-inflammatory, DC-priming adjuvant, such as a less-toxic RNA adjuvant (see our review on poly I:C vs. ARNAx, a non-toxic TLR3 ligand). In fact, combination therapies with anti-PD-L1 Ab and ARNAx+TAA have contributed to additive tumor regression in mouse models.

Elderly patients generally suffer from chronic diseases including cancer and cardiovascular diseases, both of which result from inflammation. The elderly could benefit from adjuvants with lower inflammatory or cytokine toxicity, enabling them to enjoy a longer life with high immune-potential and quality. Good immune adjuvants guarantee healthy life and help us to avoid exacerbating chronic diseases including cancer.

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Profile

Tsukasa Seya was born in Fukushima prefecture, Japan, and grew up in Hokkaido. He graduated from Hokkaido University Graduate School of Medicine in 1976, and majored in immunology and internal medicine. He obtained his Ph.D. from the School of Pharmaceutical Sciences and MD from the School of Medicine at Hokkaido University. After 3 years of studying abroad (Washington University, St. Louis, U.S.A.), he was appointed to the research institute of Osaka Medical Center for Cancer (now Osaka International Cancer Center). He was promoted to Director of the Institute in 1998. Concurrently, he had temporary professorial positions in Nara Institute for Science and Technology (NAIST) and Osaka University. He was appointed as a full professor of the Department of Immunology at Hokkaido University Graduate School of Medicine in 2004. He has continued studying innate immunity, with the discovery of self–nonself discrimination mechanisms, including the complement and innate-immune systems. He first identified CD46 as part of the complement system (with Prof. J.P. Atkinson in 1986). He has worked on immunotherapies for cancer and infectious diseases for a long time. He has made a marked contribution in establishing a harmless adjuvant, namely “DC-priming adjuvant”, for vaccine immunotherapy with Dr. M. Matsumoto. Together, they established the internationally accepted antibody against human Toll-like receptor 3 (TLR3.7), and synthesized the novel DC-priming adjuvant “ARNAX” to support vaccines for patients with cancer or infectious diseases. He received the Hokkaido Science and Technology prize and the the Sabro Kojima Memorial prize, among others. In 2016, he retired from the Medical School of Hokkaido University, and is concentrating on the refinement of ARNAX as an immune-enhancing adjuvant to further support clinical test.