accelerations, and is considered to be capable of surpassing the standard quantum limit. Third, cavity optomechanics provides resources for both classical and quantum information processing. For instance, optomechanical devices can serve as information storage devices and act as interfaces between light beams with different wavelengths or even microwaves.

In the last few years, researchers have made considerable efforts to put mechanical systems into their quantum ground states \[5\]. Recent efforts have demonstrated optomechanically induced transparency \[6\], normal-mode splitting \[7\], quantum-coherent coupling \[8\], wavelength conversion \[9\], and measurements performed below the standard quantum limit \[10\]. Future developments will aim to integrate different quantum systems to form hybrid quantum devices, e.g. hybrid optomechanical and electromechanical systems. In this way, we can enable phonons, photons, and electrons to work together in the quantum world.

Recent years have seen rapidly growing interest in the field of cavity optomechanics. As shown in Fig. 2, the publications and citations in this field have grown exponentially. The now booming development in this field will turn the dream of manipulating macroscopic mechanical systems in a quantum manner into reality.

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IMMUNOLOGY

Targeting the immune system: a new horizon of cancer therapies

Chen Dong

INTRODUCTION

The immune system is our trustworthy army of defense against invasion of microorganisms. As the first line in this army, the innate immune system, composed of myeloid cells (dendritic cells and macrophages), some lymphocytes (NK cells and innate lymphocytes as well as some types of T lymphocytes such as NKT cells and γδ T cells) and other cells in our body, can quickly mount inflammatory responses after the specific receptors in these cells recognize the pathogen-associated pattern molecules inside or outside host cells. The adaptive immune system, consisting of B and T lymphocytes, is slower in their activation, but it is more specific in their antigenic recognition and long-lasting, owing to the generation of memory lymphocytes. Two major types of T lymphocytes that carry αβ T cell receptors have different functions—those express the CD4 molecule secrete cytokines to regulate immune function and are called helper T cells, while those express CD8 co-receptor are called cytotoxic T lymphocytes (CTL) and can directly kill cells infected by viruses.

The immune system has an intimate relationship with cancer. Immune cells, such as myeloid cells and lymphocytes, are frequently found in the tumor
tissues. There is growing evidence that the immune system may be able to recognize tumors and also attempt to control cancer development. Robert Schreiber proposed cancer editing by the immune system. Stephen Rosenberg and his colleagues recovered CD8+ CTL from tumor tissues and expanded them in vitro, which, when adoptively transferred into melanoma patients, conferred significant therapeutic effects. There is also rich literature indicating that cancer-associated inflammation by the immune cells promotes the development, angiogenesis and metastasis of cancer. Thus, the immune system is a double-edged sword in cancer, and its relationship with cancer can be very complex.

Immunotherapy has arisen in the recent years and recently regarded as a fourth therapy for cancer, in addition to surgery, radiation and chemotherapy treatments. It is important at this stage to review the scientific basis for cancer immunotherapies and rationalize future strategies and combined approaches.

**CURRENT STRATEGIES OF IMMUNOTHERAPIES**

Attempts have been made in the past several decades in applying the immune system to fight against cancers with variable degrees of success. I summarize here the recent efforts, which may enlighten future developments.

**Cancer vaccines**

Immunologists have successfully used vaccines to eliminate infectious diseases. It has long been thought to develop vaccines against cancer. Indeed, preventive vaccines against HBV and HPV have helped reduce the incidence of liver and cervical cancers, respectively. For non-viral transformed cancers, however, there exists limited success so far. It is a major challenge to identify cancer-specific antigens for many tumors. One exception is B cell tumors such as lymphoma or myeloma where the tumor cells produce the same immunoglobulins, which can be produced as tumor-specific antigens for vaccination [1].

The other challenge is the use of adjuvants. To elicit strong T-cell-mediated immunity, vaccines will have to first activate the pattern recognition receptors expressed by the innate immune system, which not only process and present the antigens to T cells but also upregulate costimulatory molecule expression to enhance the effector differentiation of T cells. The best example for pattern recognition receptors is toll-like receptors (TLR), which upon activation stimulates pro-inflammatory cytokine expression and induces robust T cell activation. Imiquimod, which activates TLR7/8, is being used topically to treat skin cancers [2]. Another possibility is CpG, which activates TLR9. These TLR agonists may activate dendritic cells infiltrating into the tumor tissues and convert them from immune tolerance inducers to immune activators. However, they may be more powerful or specific in their immune-activating effects if combined with tumor antigens or debris of tumor cells.

Dendritic cells are the most potent T cell activators. Strategies have been developed to utilize these cells for cancer vaccines. GM-CSF is a cytokine that stimulates the development of dendritic cells, which is being used as an adjuvant for cancer vaccines. A dendritic cell-based vaccine against prostate cancer has been developed and approved for clinical use.

**T cell therapies**

T cells are frequently found in solid tumors and they may be more superior to blood-circulating T cells in their tumor specificity. Stephen Rosenberg and his colleagues have developed protocols to expand CD8+ T cells from melanoma using high dose IL-2. Transfer of these expanded T cells into patients has led to shrinkage of tumors. These studies have provided direct evidence for T-cell-mediated immunity to cancers.

However, T cells recovered from tumors may have already been suppressed by tumors in their activities, even after *in vivo* expansion. To avoid this disadvantage, multiple methodologies have been developed. For example, T cell receptors specific for tumors can be added to virus-specific T cells. More recently, Carl June and his team utilized chimeric antigen receptors to allow activated T cells to target tumor cells, and this personalized approach has led to impressive remission of leukemia in many patients [3].

**Costimulation modulations**

Activation and function of T cells requires engagement of clonotypic T cell receptor by antigenic peptides presented on MHC molecules on antigen-presenting cells (APC). In addition to this interaction, an array of cell-surface costimulatory molecules is expressed on APC and engages their corresponding receptors on T cells. Some of these molecules enhance T cell activation, including CD28 and ICOS. Many more molecules identified by others and us inhibit T cell activation and function. In addition to maintain immune tolerance and avoid autoimmunity, extensive literature suggests that these inhibitory pathways may be present in the tumor microenvironments and function to restrict the function of anti-tumor immunity. James Allison has pioneered the study in targeting these molecules to boost tumor immunity and found that anti-CTLA4 enhanced tumor immunity. Humanized anti-CTLA4 has been shown in clinical trials to extend the life of metastatic melanoma patients and has been proved by FDA.

PD-1 is another immune inhibitory receptor expressed by activated T and B lymphocytes. Unlike CTLA4, one ligand for PD-1, B7-H1/PDL1 was shown to be upregulated in cancer tissues [4]. Anti-PD-1 has been developed and was shown in recent clinical trials to effectively prolong the survival of human cancer patients [5]. Of note, the response rates appeared to differ among various cancers. Combination of PD-1 and CTLA4 blockade has even more remarkable effects [6].

**ADDITIONAL CONSIDERATIONS**

Various strategies have been developed to boost T-cell-mediated immunity to cancers and have achieved considerable, promising effects in the treatment of can-
cancer patients. In contrast to these good benefits, the immune system also possesses tumor-promoting effects. Restricting these side effects of the immune system is of considerable interests in developing future immunotherapies for cancer.

**Tumor-associated inflammation**

Chronic inflammation has been a strong predisposing factor for many types of cancers. In tumor tissues, myeloid cells, including tumor-associated macrophages and myeloid-derived suppressor cells (MDSC), may promote tumor development and suppress tumor immunity [7]. How to target or eliminate them and modulate tumor-permissive microenvironment is one possible direction for future development.

T cells that regulate chronic inflammation have been identified in the past decade. CD4+ T cells that produce IL-17, so-called TH17 cells, are found to be important for inflammatory diseases in human, including psoriasis. Elevated expression of IL-17 and TH17-regulating cytokine IL-23 has been associated with many cancers [8]. Although in some tumors such as melanoma, TH17 cells are protective, inhibition of IL-17 was found to reduce the development of colon cancers. Interestingly, in a recent study, anti-IL-17 had good therapeutic effects in a model of lung cancer, which was associated with reduced MDSC recruitment into the tumor tissue [9]. Targeting IL-17 or TH17 cells may be considered as a novel immunotherapy in cancers.

**Regulatory T cells**

In addition to pro-inflammatory TH17 cells, Foxp3+ regulatory T (Treg) cells are also frequently found in tumor tissues [10]. They may function to suppress cytotoxic T cell responses to tumors. The nature of these cells and selective targeting of the tumor-associated Treg cells but not those in peripheral tissues that restrict autoimmune responses are a major challenge. Further investigation is needed before any development can be attempted along this direction.

**SUMMARY AND FUTURE PERSPECTIVES**

There has been good progress in eliciting and modulating the immune system to treat cancers, in particular, via T cell adoptive therapy or checkpoint blockade. These data from human studies have offered proofs of concepts in that the immune system can recognize cancers and can eliminate cancers. Cancer immunotherapy can witness a rapid growth in the next decade.

Benefited from the studies thus far, I think that the following can be considered in the future development.

First, the immune system is a double-edge sword. We may consider how to boost good immune function, as well as limit bad influence of the immune system, including chronic inflammation or Treg generation. In addition, crosstalk or regulation of immune components ought to be considered.

Second, immunotherapy is unlikely to become the sole therapy for cancer patients. Surgery may be combined with cancer vaccine approaches. How to combine existing radiation, chemotherapy, targeted therapy or antibody-mediated tumor killing with immune modulations will be a major direction of future research, which ultimately will maximize the patient survival.

Third, personalized cell- or antibody-based therapy will be desired. Cancers vary. We cannot afford to guess the best medicine for patients. Careful immune profiling analysis may help rationalize our treatments. More investigations are needed to correlate patient responses and their immune features to improve our abilities to prescribe.

In general, I believe that the future direction is the combination and personalization in our immunotherapy treatment.

Cancer immunotherapy is a new area of research and development. China has ample resources of patients and unique environments associated with cancer development. There should be a national strategy in this area to organize our translational research and to advance our drug industry with a goal to help our patients from devastating diseases. It is time to act and research.

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