Towards Engineering Immunity

Thesis by

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To My Parents

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ABSTRACT

The aim of engineering immunity is to harness and engineer the immune system to treat infectious diseases and cancer. Towards this goal, accumulating evidence shows that the immune system can be manipulated to achieve the desired and improved functions. In the context of cancer therapy, many strategies have appeared to utilize the principle of immune defense to safely and effectively target tumor cells for destruction. These strategies fall into two categories: active immunotherapy and passive immunotherapy. Active immunotherapy involves activating the effectors in the host immune system to inhibit cancer cell growth and reject tumors (e.g., cancer vaccination), while passive immunotherapy is a term for directly providing the host with effectors to react against cancer (e.g., adoptive transfer of in vitro expanded antitumor T cells).

We propose a concept of instructive immunotherapy for cancer. This concept is to use a strategy to guide the host in developing in vivo effector cells capable of targeting cancer. This strategy arises from combination of gene therapy, stem cell therapy and immunotherapy to program hematopoietic stem cells (HSCs) to develop into lymphocytes with desired antitumor specificity. Therefore, taking advantage of the longevity and self-renewal of HSCs, life-long supplies of tumor-specific lymphocytes can be generated in vivo, which exceed the current methods of repetitive immunization and adoptive transfer.

To test the feasibility of this approach, I describe in Chapter 2 the procedure of retrovirus-mediated gene transfer of TCR cDNA into RAG1-deficient HSCs. Subsequent transfer of these genetic modified HSCs into RAG1-deficient mice allows the long-term production of functional antigen-specific T cells.

Chapter 3 describes a method to impart anti-tumor specificity to the wild-type mouse T cell repertoire. To achieve this, genes encoding a CD8 T cell receptor with the desired anti-tumor specificity were delivered into wild-type HSCs via a retroviral vector. When transferred into host mice, these genetically modified HSCs generated a large population of anti-tumor cytotoxic T cells, accounting for more than 20% of peripheral CD8 T cells. These cells displayed a normal response to antigen stimulation and had the ability to generate and maintain long-term memory. Significant tumor rejection was observed in mice containing these T cells, demonstrating feasibility of instructive cancer immunotherapy.

In recognition of the important roles of helper T cells in anti-tumor immunity, Chapter 4 elaborates a two-arm model to augment tumor-specific immune responses. In the experiment, the two arms, both anti-tumor CD4- and CD8 T cells, were generated by HSC gene transfer method. The resultant immune system in mice could not only suppress tumor growth, but could also eradicate large, solid and vascularized tumors. Coupled with results described in Chapter 3, we demonstrated the great potential of instructive cancer immunotherapy and expanded the scope of engineering immunity.

Successful immunotherapy relies on understanding the molecular mechanisms that control immune responses. For instance, although IL-2 has been approved by FDA to treat renal cancer and melanoma, many results from mice show that the physiological role of IL-2 is complex and unpredictable, hindering the design of better strategies, that would maximize the therapeutic impact of IL-2. I address the role of IL-2 in negative regulatory function and T cell memory in last two chapters, both of which are important for achieve the overall success of immunotherapy and engineering immunity. Chapter 5

describes the role of IL-2 in maintaining regulatory T cell homeostasis and self-tolerance, and correlates this role with the signaling molecule STAT5. The final chapter (Chapter 6) details the role of IL-2 in generation of CD4 T cell memory.

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