Understanding T lymphocytes inner workings to harness therapeutic potential

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Leslie J. Berg, PhD from the University of Colorado, Anschutz School of Medicine, sheds light on understanding the inner workings of T lymphocytes to harness their therapeutic potential

In the past two decades, we have witnessed the powerful impact of years of research to uncover the mechanisms regulating our immune responses to infections. This research has revealed opportunities to harness our immune systems to fight cancers, leading to many therapies for autoimmune and inflammatory diseases.

The prevalence and impact of these treatments are highlighted by their descriptor, ‘immunotherapies’, now a common word familiar to the broader public. At the heart of this research is studying immune cells, including lymphocytes and myeloid cells, that implement our immune responses to pathogens, cancers, and self-tissues.

The power of T lymphocytes

Much of this research has focused on one subset of immune cells, the T lymphocytes. These cells are a major component of the adaptive immune response, which provides protection from microbial infections in a pathogen-specific manner. A vital aspect of the function of these cells is their highly specific recognition of individual pathogens and their ability to persist long after the pathogen has been eliminated, thereby providing what immunologists refer to as ‘long-term immune memory’.

In a healthy individual, T cells also recognize and eliminate malignant cells to prevent the outgrowth of cancers. The specialization and extreme longevity of T cells is an enormous strength for a complex, long-lived organism like humans. However, this strength can be turned against us when T cells aberrantly recognize and attack otherwise healthy cells or organs, causing autoimmune diseases.

As our knowledge about the mechanisms regulating T lymphocytes accumulates, opportunities to manipulate T cell-mediated immune responses continue to arise. The research leading to these interventions encompasses studies focused on each phase of the T cell response, from initial recognition of a foreign pathogen to production of cytolytic and inflammatory mediators.

This information, garnered from years of research, has provided the biotechnology and pharmaceutical industries with a plethora of targets for developing novel therapeutics.

Triumphs in T Lymphocyte Activation and Function Research

At the current time, the list of drugs targeting the immune system encompasses a broad range of strategies. For many autoimmune, inflammatory, or atopic (allergic) conditions, treatments often include the administration of proteins, frequently antibodies, that block or interfere with soluble mediators made by immune cells; these therapies are referred to as 'biologics', as they are protein-based rather than the small chemicals characteristic of most previous drugs.

The category of treatments known as 'immunotherapies' are those that target the functions of T lymphocytes, and are largely used to treat cancer patients. The predominant subset of these are also antibodies or inhibitory proteins. Still, instead of targeting soluble factors made by immune cells, these proteins bind to and interfere with the functions of receptors expressed on the surfaces of T cells, receptors whose normal function is to dramatically reduce a T cell's ability to recognize and kill target cells.

By blocking these inhibitory receptors, a poorly responsive T cell can be reinvigorated to destroy a cancer patient's malignant tumor cells. Not surprisingly, the identification of the receptors currently targeted by these immunotherapies and the elucidation of their role in down-regulating otherwise potent T cell responses were the products of many research labs focused on understanding the basic biology of T lymphocytes.

A second category of immunotherapy treatments, currently also used for cancer patients, is adoptive T cell therapy. In this case, a patient's own T cells are isolated and engineered to express an antigen receptor that recognizes a protein made by the patient's tumor cells. These T cells are then expanded in culture to generate highly activated anti-tumor T cells, after which large numbers of these cells are re-introduced into the patient.

This technology has been remarkably successful at eradicating tumor cells in the weeks and months following infusion of the engineered T cells. For this approach, the knowledge of how to design a substitute antigen receptor that would function in any T cell relied on years of studies dissecting the biochemical signaling pathways normally used by T cell antigen receptors following their recognition of infecting pathogens.

The gaps in knowledge constraining current endeavors

Despite these known successes, immunotherapies are a work in progress with substantial room for improvement. Those therapies that act to re-awaken the function of a patient's anti-tumor T cells are not specific to only that set of T cells, and also enhance the functions of T cells recognizing normal cells and tissues. Due to this broad activity, many patients suffer

from ‘immune-adverse events,’ manifesting as mild to extremely severe symptoms of autoimmunity. The high incidence of these immune-related toxicities underscores the need to refine better and focus the action of treatments that manipulate T cell anti-tumor responses.

Adoptive T cell therapies also have far to go to achieve a more consistent record of success. While the vast majority of patients show remarkable responses to the treatment, approximately half of those individuals will ultimately undergo relapse.

A common cause of relapse is the poor long-term persistence or loss of function of the engineered T cells. These findings highlight our need to understand better the mechanisms and signaling pathways that determine each T cell function. What are the signals needed to generate long-lived memory T cells that will persist in patients? How can we alter the signaling pathways in T cells to prevent their loss of function? More detailed knowledge of these ‘inner workings’ of the T cell is necessary to improve and ultimately optimize the durability of adoptive T cell therapies.

The dark underbelly of current successes

One of the unforeseen consequences of the inordinate success of biologics and immunotherapies is the powerful push to focus more and more resources on translating current knowledge into the development of drugs. Unfortunately, this comes at the expense of supporting basic research aimed at furthering our understanding of immune cell regulation and function.

The inevitable outcome of this imbalance between these two equally important endeavors is that the pipeline of new information will ultimately dry up, and efforts to translate emerging knowledge of immune cells into disease treatments will hit the proverbial wall.

The way forward: Balancing discovery and application

A key element in achieving the appropriate balance of discovery and application is to improve communication between the research community and the general public. Given the achievements of recent years, this message should resonate broadly. The connection between basic research and translation to therapies will undoubtedly gain even more visibility and impact in the near future, as there are currently over 1,500 ongoing clinical trials for cell and gene therapies.

The conditions targeted include everything from cancer to cardiovascular and neurological diseases, and are likely to touch nearly every family. As such, the continuing efforts to develop new therapies, efforts that rely on both discovery and application, is a goal that should garner widespread support.

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