ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Current and Future Applications of Immunopharmacogenomics

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H&O What is immunopharmacogenomics?

YN Research in the field of immunopharmacogenomics aims to develop a better understanding of how the immune system impacts the development of diseases and response to treatment. This field relies on next-generation sequencing of T-cell and B-cell receptors to identify the molecular mechanisms that underlie various disease states and drug responses. Analysis of the somatic changes in cancer cells and the characteristics of the T cells in tumors can provide important information about the disease and predict response to anticancer treatments.

Immunopharmacogenomics incorporates 2 study areas: immunogenomics and pharmacogenomics. Immunogenomics uses genomic tools, such as next-generation sequencing, to assess aspects of the immune system, including human leukocyte antigen (HLA) molecules, B-cell and T-cell repertoires, and expression levels of cytokines, chemokines, and other immune-related molecules. In oncologic disorders, the host's systemic and local immune responses can significantly influence the clinical outcome. Pharmacogenomics analyzes variations in patients' pharmacologic responses based on differences in genetic/germline characteristics, somatic mutations, and gene expression levels.

H&O How can immunopharmacogenomics be used in hematologic and oncologic disorders?

YN The study of immunopharmacogenomics will lead to a new type of immunotherapy through the identification of T-cell receptors that can recognize cancer-specific antigens. Immunopharmacogenomic analysis can identify the T cells that are able to kill cancer cells. Identification of these T cells will allow us to characterize the T-cell receptors. It might be possible to generate genetically engineered T cells that are able to kill cancer cells.

This field of study could be used to predict how a patient will respond to anticancer treatment—not only immunotherapy (eg, immune checkpoint antibodies), but also chemotherapy and radiation (see the table). It might also be used to predict whether a patient will develop adverse events.

H&O How can the immune microenvironment predict response to treatment?

YN Various aspects of the immune microenvironment can predict how a patient will respond to immunotherapy. Multiple studies aiming to identify which patients will respond to treatment based on examination of the exome, transcriptome, and immune status in cancer tissues have indicated that the number of somatic mutations correlates to outcome with immune checkpoint antibodies, including agents targeting programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4). Patients with a higher number of somatic mutations are more likely to have a strong infiltration of T cells, particularly those that express the CD8 molecule (which is predominantly expressed on the surface of cytotoxic T cells attacking the cancer cells).

Patients with the DNA repair gene mutation, a higher number of somatic mutations, more infiltration

of CD8-positive T lymphocytes into cancer tissues, and clonally expanded T cells are expected to have a better response to treatment with immune checkpoint antibodies. In addition, various studies have indicated that patients with a high CD8 cell count in cancer tissues have a good response to radiation therapy and chemotherapy.

Five years ago, there were no tools to characterize the millions of T-cell receptors in T cells or B-cell receptors in B cells. It is now possible to characterize millions of T-cell receptors with a single test. Although the next-generation DNA sequencers generate a huge amount of sequence information, the quality of each sequence read was not high enough, and the length of each read was not long enough to cover the critical regions of the T-cell receptor or B-cell receptor that can define the antigen-recognition site. However, progress in DNA sequencing technology has allowed us to obtain the variable/diversity/joining (V[D]J) combination as well as the inserted/deleted nucleotides during the recombination process of the T-cell receptor β chain (the D segment is not present in the T-cell receptor α chain). This measurement of the count of each unique T-cell receptor sequence in the T-cell population in a given sample is important when characterizing the immune environment in cancer tissues. Patients with clonally expanded CD8-positive T cells in cancer tissues can be identified by a larger number of the same T-cell receptor sequence reads. These patients can expect a better response to treatment. The B-cell receptor can be used to characterize the clonality of B cells. It is now also important to examine the expression levels of immune-related molecules, particularly γ interferon, perforin, and granzyme, which are related to the cytotoxic activities of T cells.

H&O What are some of the complexities of the human immune system?

YN The immune system is extremely complicated. The composition of T cells and B cells is different in each person. (T cells are further classified into subtypes such as killer, helper, and regulatory T cells, and B cells are also classified into several subgroups.) The T-cell and B-cell repertoires are also enormously different in each person because of variations in the HLA types that present antigens to T cells. Every T cell has a unique T-cell receptor that can recognize certain antigens presented by HLA molecules on the cell surface. One hypothesis suggests that, theoretically, 10^{15-18} different T-cell receptors can be produced in humans. (That number is higher than the number of lymphocytes in the body.) The body eliminates T cells that can recognize its own cells by negative selection in the thymus, and it also positively selects T cells that can prepare for an attack by pathogens or chemicals.

Table. Potential Uses of Immunopharmacogenomics

Prediction of drug-induced adverse reactions (eg, skin hypersensitivity, liver toxicity)
Selection of patients for immunotherapy, as well as monitoring during therapy and predicting adverse reactions
Better understanding of mechanisms of rejection after organ transplantation, which could lead to novel therapies
Better understanding of severe immunologic reactions, including autoimmune diseases and food allergy, which could lead to new therapies
Prediction of efficacy of chemotherapy and radiation therapy by integrated analysis of somatic mutations in cancer, as well as the immune signature in cancer cells

T cells are divided into 2 classes by the T-cell receptors: the α/β T-cell receptor and the γ/δ T-cell receptor. Most lymphocytes (95%) possess the α/β type of T-cell receptor. The α/β receptor genes contain a large number of exons, including V and J exons. For example, the T-cell receptor α has nearly 60 V exons.

During the differentiation of lymphocytes, genes for the T-cell and B-cell receptors undergo a process known as recombination to generate receptors. During this process, a V exon, a D exon (only for the β chain), and a J exon combine. In addition, nucleotides are deleted or inserted in a random manner at V(D)J junctions. The V(D)J combination and insertion/deletion of each chain, as well as the α/β chain combination, define the characteristics of each T-cell receptor, including their ability to detect a specific antigen on the HLA molecule. The T-cell receptor α chain can generate 3000 different V-J combinations. The β chain can generate nearly 2000 different V(D)J combinations. In addition, during recombination, nucleotides are inserted and deleted between the V-J junction for the α chain and between the V-D and D-J junctions for the β chain, generating various types of T-cell receptors even with the same V(D)J combinations.

Cancer has many somatic mutations, some of which generate certain amino acid changes. The amino acid change can create cancer-specific antigens on the cell surface. Some T cells can recognize these newly generated cancer-specific antigens (called neoantigens). When this recognition occurs, such T cells are activated and proliferate, and then are likely to find and kill cancer cells.

Cancerous tissue is characterized by 2 types of T cells: active and suppressive. Active T cells are able to kill cancer cells, whereas suppressive T cells protect the cancer cells from host immune attack. The balance between the active T lymphocytes and the protective or suppressive T cells significantly influences the clinical response to cancer treatment. Growth of cancer cells reflects the dominance of the immunosuppressive side. Immune checkpoint

antibodies inhibit the activity of the suppressive side and thereby alter the balance between the immunoactive side and the immunosuppressive side. By making the immunoactive side dominant, this treatment can be very effective.

H&O What are some other potential applications of immunopharmacogenomics?

YN Immunopharmacogenomics will be important not only in oncology but also in autoimmune diseases. In Crohn's disease, we have identified clonal T-cell receptors that are expanded in the inflamed tissues.

In addition, immunopharmacogenomics can be used to predict the risk of graft-vs-host disease after bone marrow transplantation. It may be useful for investigating the graft-vs-leukemia effect. It will also provide important information for molecular mechanisms of rejection after organ transplantation.

It should also be important for food allergies. The incidence of food allergies has been increasing. For example, peanut allergy is quite common among white ethnicities, but rare in Asian countries, such as Japan. This disparity indicates that immune differences are key factors in the development of peanut allergies. If it is possible to analyze the detailed immune response that occurs in patients with peanut allergies (in this case, probably with B-cell receptor analysis), we may be able to discover the cause of the food allergy and develop new strategies for prevention and treatment.

H&O What are the challenges involved with the application of immunopharmacogenomics in clinical practice?

YN The immunopharmacogenomic approach is not yet used in clinical practice. Because of the high complexity and variability seen in HLAs, antigens, the T-cell repertoire, and the B-cell receptor repertoire, it will be necessary to accumulate a huge amount of data. In the next 10 years, however, I am confident that immunopharmacogenomics will become an important aspect of hematology/oncology.

Disclosure
Dr Nakamura has no real or apparent conflicts of interest to report.

Suggested Readings

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