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CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***Parallels between Cancer and Infectious Disease**

Richard S. Hotchkiss, M.D., and Lyle L. Moldawer, Ph.D.

Infectious diseases and cancer have multiple similarities. Both infectious organisms and cancer cells express many proteins that are recognizable by host T cells,¹ and both elicit T-cell-mediated inflammation. An essential aspect of T-cell homeostasis is that the responses of these cells must eventually diminish to avoid toxicity from excessive T-cell proliferation and cytokine release. Unfortunately, this can lead to a loss of appropriate T-cell responses, especially in advanced cancer and chronic infections.

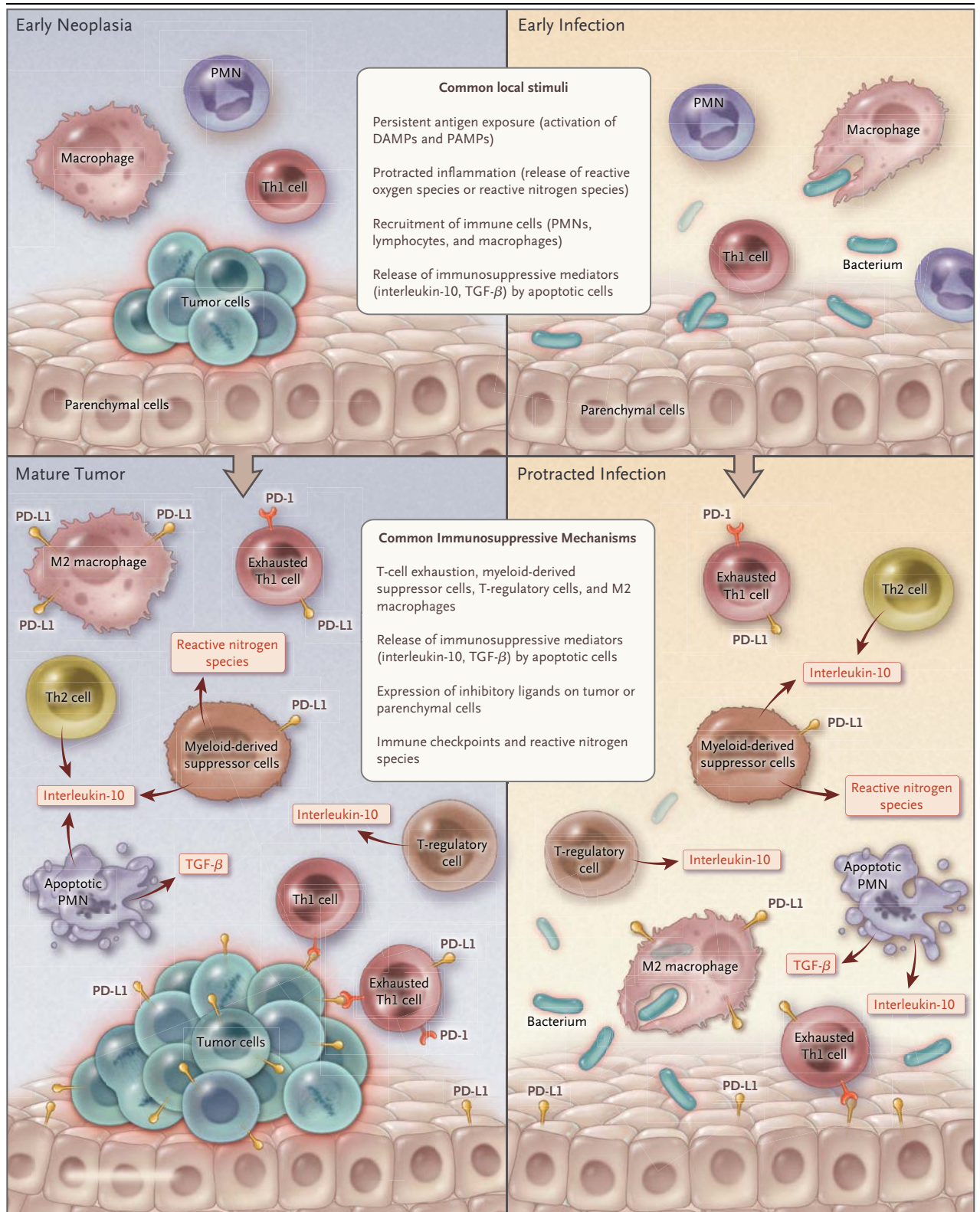
Scientists have identified many of the normal mechanisms in cancer and indolent infections that ordinarily limit T-cell responses. These findings have led to the development of agents that can overcome the limiting mechanisms to “unleash” or amplify ongoing T-cell responses under conditions of adaptive immune suppression.² These agents are designed to alleviate or reverse such events as “T-cell exhaustion” brought about by inhibitory molecules (e.g., programmed cell death 1 [PD-1] and programmed cell death ligand 1 [PD-L1]), an increased number of myeloid-derived suppressor and T-regulatory cells, decreased expression of HLA-DR by antigen-presenting cells, and a shift from M1 (killer) macrophages to M2 macrophages, which dampen the immune system by secreting antiinflammatory cytokines such as interleukin-10 (Fig. 1). Many of the agents that can expand the T-cell response are being developed for cancer therapy.³ Similarly, agents that block immunosuppressive proteins or cytokines that suppress T-cell responses (e.g., antibodies that counter interleukin-10 and transforming growth factor β) are also being developed as potential drugs for treating cancer. Several of these agents are also likely to be efficacious in patients with chronic infectious diseases.

Why do cancer and many infectious disor-

ders induce similar immunologic responses? Persistent immune activation and inflammation play key roles. Chronic antigenic stimulation caused by damage-associated molecular pattern (DAMP) and pathogen-associated molecular pattern (PAMP) molecules occurs in cancer and infectious disorders, respectively. DAMPs and PAMPs bind to similar or, in some cases, identical toll-like receptors (TLRs) and NOD-like receptors (NLRs), which unlike most receptors are able to respond to a variety of conserved foreign

Figure 1 (facing page). Immune Phenotypes of Cancer and Protracted Infection.

Tumor and pathogen antigens persistently activate T cells, which ultimately leads to T-cell exhaustion. Chronic release of damage-associated molecular pattern (DAMP) molecules and pathogen-associated molecular pattern (PAMP) molecules occurs in cancer and infectious disorders, respectively, leading to activation of common signaling pathways mediated by toll-like receptors (TLRs) and NOD-like receptors (NLRs), which regulate immunity (see the Glossary). Protracted inflammation that is caused by reactive oxygen and nitrogen species also occurs in both disorders. Apoptotic tumor or immune cells are engulfed by phagocytic cells, which subsequently release immunosuppressive cytokines. Collectively, these processes lead to an immunosuppressive environment with “exhausted” T cells expressing inhibitory molecules (e.g., programmed cell death 1 [PD-1] and programmed cell death ligand 1 [PD-L1]), increased numbers of T-regulatory cells and myeloid-derived suppressor cells, and a shift from type 1 helper T (Th1) cells to type 2 helper T (Th2) cells and from M1 to M2 macrophages. Tumor cells, vascular endothelial cells, myeloid-derived suppressor cells, and infected parenchymal cells express PD-L1, which associates with the inhibitory receptor, PD-1, to induce the suppression of T cells and natural killer cells, thereby preventing the destruction of tumors or pathogens. Red arrows represent the secretion of molecules with inhibitory function. PMN denotes polymorphonuclear leukocyte, and TGF- β transforming growth factor β .



Glossary

Programmed cell death 1 (PD-1): Inhibits T-cell function and can trigger apoptosis; is present on T-cells.

Programmed cell death ligand 1 (PD-L1): Binds to or activates the PD-1 receptor, which is present on antigen-presenting cells and, less frequently, on T cells.

Cytotoxic T-lymphocyte antigen 4 (CTLA4): Inhibits T-cell function and is present on T cells.

Granulocyte–macrophage colony-stimulating factor (GM-CSF): Stimulates the production of granulocytes and monocytes.

NOD-like receptor (NLR): Intracellular pattern-recognition receptor of PAMPs and DAMPs.

or host ligands. Binding of TLRs and NLRs leads to the activation of common signaling pathways that regulate immunity. DAMPs and PAMPs mediate and amplify inflammation, which results in the release of similar proinflammatory and antiinflammatory cytokines, increased levels of reactive oxygen and nitrogen species, tissue wasting, and increased apoptosis. The totality of these processes has detrimental effects on host protective and antitumor immunity.

In considering new experimental approaches, a central challenge is how to boost host immunity without causing potential adverse effects associated with an overreactive immune system. Serious autoimmune disorders develop in some patients with cancer who have been treated with immune checkpoint inhibitors of PD-1 and cytotoxic T-lymphocyte antigen 4 (CTLA4) (see the Glossary). It is believed that such disorders result from the unleashing of ongoing or nascent autoimmune-like T-cell responses.³ Similarly, boosting immunity in patients with sepsis might worsen inflammation and organ injury in those who have not entered the immunosuppressive phase. Thus, identifying the right candidates for and timing of immunotherapy in patients with either cancer or persistent severe infection is essential.

In two recent studies, investigators made potential advances in identifying appropriate patient populations.^{4,5} Using a model of chronic viral infection in mice, Crawford et al.⁴ analyzed immune effector cells at the level of the transcriptome. They identified unique gene-expression patterns involving inhibitory receptors and transcription factors that are present in dys-

functional CD4+ and CD8+ T cells. These findings provide a foundation for further development of a quantitative nucleic acid–based method of identifying and targeting patient-specific immunologic defects.

Another method to gauge host immunity uses the patient as a “test tube.” Most healthy persons harbor numerous latent viruses (e.g., cytomegalovirus, herpes simplex virus type 1, and Epstein–Barr virus), which can reactivate, replicate, and enter the circulation during impaired host immunity. De Vlaminck et al. performed serial sequencing of the virome in patients undergoing organ transplantation.⁵ Results showed a correlation between the total viral load and the intensity and dose of medications used to suppress immunity and prevent organ rejection. They also observed a correlation between the types of virus that were detected and the intensity and dose of medications. Tapering of immunosuppressive drugs led to changes in specific viruses and a reduction in viral loads. If replicated, tests that quantitate the human virome may be useful in predicting immunocompetence in hospitalized patients.

A revolution in immunotherapy is under way in oncology, and its turbulence is beginning to affect the experimental treatment of infectious diseases. Granulocyte–macrophage colony-stimulating factor (GM-CSF) is in clinical trials involving patients with cancer and sepsis. Anti-PD-1 and anti-PD-L1 drugs have been effective in several clinical trials to treat melanoma, non–small-cell lung cancer, and renal-cell cancer, and they are being tested in the treatment of human immunodeficiency virus infection. Interleukin-7, one of the most promising and broadly active immunomodulators, was efficacious in early trials involving pediatric patients with sarcoma and was found to reverse gut pathology in patients with HIV infection or JC virus–induced progressive multifocal leukoencephalopathy.⁶

What next? An experimental test of these approaches to treat sepsis could be considered. On a more general level, greater collaboration is required between oncologists, infectious-disease specialists, translational immunologists, and pharmaceutical companies in developing clinically relevant tests that identify patient-specific

defects in innate or adaptive immunity. The recently announced and unprecedented collaboration among four major pharmaceutical companies in developing combination immunotherapeutic drugs for cancer⁷ underscores the perceived importance of immunotherapy and the recognition that teamwork is critical to success. Rapid tests of the overall health of a patient's immune system would enable clinicians to guide immunotherapy and follow its efficacy. Nucleic acid–based detection of mechanisms of immunosuppression and of reactivated latent viruses might identify candidates for immunotherapy and enable therapeutic monitoring.^{4,5} Coordination of clinical trials with sharing of data and patient samples would expedite drug development. A change in clinical outcomes — in both cancer and infectious disease — will occur more quickly if investigators in these specialties pull together.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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