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Editorial

Introduction to a review series on therapeutic antibodies

The success of antibodies in fighting infection is clear, but directing this power against cancer cells has been a challenge. For cancer, antibodies are usually made externally and injected into patients, where they act against established or residual tumors. The initial goal of this form of cancer immunotherapy was to develop antibodies able to bind relatively specifically to cancer cells and thereby activate various Fcγ-receptor-mediated effector pathways to kill the target cells. This approach has achieved impressive results for hematologic malignancies, with anti-CD20 and anti-CD38 as examples of clinical efficacy in follicular lymphoma and multiple myeloma, respectively. Although there is clinical success, understanding the mechanism of killing the target cells and of the various effector cells involved in vivo remains uncertain. However, improvement of performance by various structural modifications such as humanization, modification of Fc regions, conjugation to toxins/drugs, or addition of a second specificity to create bispecific antibodies, has followed, and antibodies, usually in combination with chemotherapy, are now part of treatment protocols for a range of hematologic cancers.

Two of the reviews in this series address aspects of this direct or modified antibody therapy: "CD38 antibodies in multiple myeloma: back to the future" by van de Donk et al and "Redirecting T cells to hematological malignancies with bispecific antibodies" by Velasquez et al.

In the 1990s, another role for antibodies emerged. It developed from the question as to why tumors, which often carry mutations and potentially immunogenic molecules, fail to induce spontaneous protective immunity. There may be two answers to this puzzle: one operates at the induction phase at which there could be inadequate T-cell priming. This is perhaps expected because, apart from some virus-associated tumors, most cancer cells do not provide the second signal required for full T-cell activation. A major mediator of this signal is CD28, but other coreceptors of the tumor necrosis factor receptor superfamily, such as CD27, OX40, and 4-1BB, contribute to activation. Opportunities to replace priming by cautiously using agonistic "accelerator" antibodies against these coreceptors now exist.

Two of the reviews in this series describe the potential and clinical testing of these "accelerator" antibodies: "The immunobiology of CD27 and OX40 and their potential as targets for cancer immunotherapy" by Buchan et al and "Immunotherapy targeting 4-1BB: mechanistic rationale, clinical results, and future strategies" by Chester et al.

The second reason for the apparent failure of the immune system to control cancer operates at a postpriming stage. Natural immune responses against infection have to be regulated to control inflammation and to maintain immune tolerance. Significant players in this regulation are $CD4^+CD25^+FoxP3^+$ regulatory T cells, which inhibit T-cell responses, and these, together with other microenvironmental factors, can create an immunosuppressive environment. During chronic low-level immune stimulation, such as might occur with immunogenic cancers, the balance can therefore shift from activation to suppression, the latter operating via a range of "check points." Reversing these pathways looks like an attractive strategy to release antitumor immunity from regulation, although a general release has a theoretical, and in some cases actual, danger of inducing autoimmunity. Targets to reverse regulatory T-cell activity include CTLA-4, which interacts with CD80/CD86 expressed on antigen-presenting cells, and programmed cell death protein 1 (PD-1), which engages programmed death-ligand 1 (PD-L1) and PD-L2 on tumor cells. Blockade of CTLA-4 and PD-1, either alone or in combination, can release the "brake" on the antitumor immune response, with clinical benefit. Interestingly, a similar approach is being tested for treating chronic infections in which immune regulation may again operate.

Although much of the exciting clinical potential of check-point blockade has emerged from solid cancers, promising results with anti-PD-1 and anti-PDL1 are being reported in classical Hodgkin lymphoma, in some subtypes of non-Hodgkin lymphoma, and, in combination with immunomodulatory drugs, in multiple myeloma.

Two reviews in this series describe the biology and blockade of CTLA-4 and PD-1: "CTLA-4: a moving target in immunotherapy" by Rowshanravan et al and "PD-1 expression and clinical PD-1 blockade in B-cell lymphomas" by Xu-Monette et al.

Manipulation of the immune system against cancer is now a billion-dollar industry. The exciting clinical effects are clearly helping patients, and although there is further to go, the responses induced are leading to a new understanding of how immune pathways can be activated to control cancer cells. Once again, linkage between biology and therapy is seen to be revelatory, and this review series aims to describe this for the hematologic community.

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