Can Molecular Imaging Measure T-cell Activation?

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Successful immunotherapy usually depends on activation of T cells in the tumor microenvironment. However, ascertaining whether T-cell activation has occurred in vivo is difficult without invasive tissue sampling. Inducible T-cell costimulator (ICOS) is a specific marker of T-cell activation that can be imaged by radiolabeling an anti-ICOS antibody and performing PET scanning. Hopefully, this agent will be the first of many molecular imaging constructs that can determine whether T-cell activation has occurred and could be used in drug development and clinical trials of cancer immunotherapy.

See related article by Xiao et al., p. 3023

Cancer immunotherapy, comprising an array of drug- and cell-based methods has transformed cancer management. Among the various forms of immunotherapy, immune checkpoint inhibitors have had the greatest clinical impact with the approval of multiple mAbs against such targets as CTLA-4, PD-1, and PD-L1. Checkpoint inhibitors have produced impressive responses in some patients especially in such cancers as melanoma, bladder, and lung, but overall, only a minority of patients respond. The tantalizing results in a few patients contrasted with the disappointing results in the majority have prompted interest in predictive markers including assessments of the tumor microenvironment, mutational burden, gene expression profiling, T-cell repertoire sequencing, and IHC. In contrast to these serum or tissue assays, molecular imaging offers advantages as a predictive marker (1). For instance, there is evidence that in vitro and in vivo expression of immune checkpoints may differ so that in vivo molecular imaging may be more predictive (2). Imaging also offers a whole-body perspective rather than a single sample, thus, revealing the predictable heterogeneity of expression among different sites. Moreover, it localizes and quantifies the volume of disease, potentially enabling focal therapy for nonresponsive sites. Thus, there has been interest in developing molecular imaging agents for immunotherapy.

One limitation of such agents as a predictive marker is that there are a plethora of antibodies and cell therapies now deployed in the clinic that would require an equal number of labeled agents as companion diagnostics. Given the epitope specificity of checkpoint inhibitors, for instance, no one imaging probe could predict for the entire class (1). Nor is it likely that the needed number of agents would be sustainable by the medical market. Finally, it will be hard for clinicians to deny an agent with curative potential to a dying patient based on a molecular imaging agent development. However, from a clinical perspective one could predict that such an agent might be extremely useful (8, 9). While not predictive of response per se, it could quantitate response after each administration. The phenomenon of pseudoprogression, wherein exuberant immune reactions lead to early enlargement of the tumors simulating tumor progression, is one potential application of such an agent.

Resting T cells can be identified by their characteristic-specific cell surface markers such as CD4, CD8, and FOXP3, which is the basis for several targeted imaging agents (3), however, these markers are present whether or not the T cell is activated. Thus, accumulation of radioactivity could represent a nonspecific inflammatory response instead of a specific antitumor response. Markers uniquely associated with T-cell activation are unusual (4). Activated T cells express granzyme beta, IFNγ, and CXCL9/10, which are potential targets but they tend to be transient, diffusible, and are located in the extracellular matrix rather than on the T cell.OX40, a T-cell surface co-stimulatory receptor, is a promising marker because it is only expressed upon antigen-specific recognition (5). It can reveal T-cell activation in tumor draining lymph nodes but is generally limited to CD4 cells, although it is found on other cell types as well. In their article, Xiao and colleagues in this issue present yet another target of activated T cells, inducible T-cell costimulator (ICOS), also known as CD278 (6). ICOS mediates immune response across multiple therapy strategies and is primarily expressed on activated cytotoxic T cells, both CD4 and CD8 T cells, memory T cells, and regulatory T cells. Ligation of ICOS and its ligand, ICOS-L, expressed on B cells, macrophages, and dendritic cells, initiates the ICOS pathway and triggers a series of intermediates, which regulate T-cell proliferation and survival, as well as secretion of IFN and cytokines.

In their article, Xiao and colleagues radiolabeled an anti-ICOS antibody with Zirconium-89 (89Zr), a positron-emitting radioisotope with a 3-day half-life. The relatively slow clearance of the antibody is therefore matched with a positron emitter of comparable physical half-life. This compound, 89Zr-DFO-ICOS mAb, can noninvasively quantify activated CD4 and CD8 T-cell responses in the rodent Lewis lung cancer model. This agent proved successful in monitoring T-cell activation after several immune therapies.

Because it is based on PET, this method is inherently more quantitative than most imaging methods. In fact, in their study, the authors compared the effectiveness of two different treatments (antiPD-1 and STING) with regard to the uptake of 89Zr-DFO-ICOS mAb, reflecting differing levels of T-cell activation. From a drug development perspective, being able to compare the degree of T-cell activation in two different treatments in vivo might be helpful in choosing drug candidates. Of course, the normal caveats apply that there are only a limited number of syngeneic mouse models in which immunotherapy can be tested and this is limiting both for drug and imaging agent development. However, from a clinical perspective one could predict that such an agent might be extremely useful (8, 9). While not predictive of response per se, it could quantitate response after each
targeting ligands due to emerging platform technologies. Such an agent could enable imaging on the same day of injection, making the agent much more practical.

Another potential limitation of ICOS-based imaging is that the nature of immune responses is transient and somewhat unpredictable so timing of the scan may be critical. To compare cycles or different therapies where quantitation will be important, each of the various parameters affecting uptake must be controlled including the timing of the scan with reference to the time of administration of therapy, the time from injection to scanning (uptake time), and scanning conditions (vendor and technology used), which may introduce variables into the ability to measure and compare activity. History tells us that such consistency is difficult to achieve in clinical practice.

Even though ICOS PET is not envisioned primarily as a predictive agent, it is possible that an ICOS-based imaging agent could ultimately be predictive if it were combined with a test dose of therapy. Although this would be paradigm bending to use imaging as an initial pharmacodynamic marker of drug activity, given the expense of immunotherapy treatments, such an approach might be considered.

Thus, ICOS-based immune imaging could provide clinicians with an important parameter of effectiveness of immunotherapy. Rather than developing numerous imaging agents custom designed to predict the outcomes of each drug, an approach that measures T-cell response is apt to be more universal. Of course, superiority over conventional imaging including FDG PET would have to be proven, but this should not be hard. This could justify the sustainable commercial development of this or similar lower molecular weight ICOS-targeted agent. While there are improvements to be made, ICOS PET imaging is a good start in the right direction.

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