Can Molecular Imaging Measure T-cell Activation?

Peter L. Choyke

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
drug cycle to detect early signs of drug resistance. An immediate application could be in distinguishing tumor progression from pseudoprogression. One could also imagine an imaging method that reads out immune activation as highly useful in guiding a patient through the increasing complex drug landscape of combinatorial immunotherapies wherein each combination could be compared for its ability to activate T cells in each patient. If used early enough, such information could lead to treatment modifications before completion of a templated treatment course. Although there is not yet validation, it is reasonable that where there is low or no activation of ICOS, the likelihood of success is similarly low and another line of treatment might be considered. ICOS imaging could improve clinical patient management by allowing earlier decisions regarding drug dosing or switching drug regimens. ICOS imaging, thus, may lead to improved patient outcomes by enabling the selection of optimal therapy prior to tumor progression and potentially decrease costs associated with unnecessary therapies of no benefit, yet still posing risks to patients.

While highly encouraging, enthusiasm has to be tempered by the formulation of this agent, a radiolabeled antibody. Antibodies accumulate in the liver and the long circulation time allows for \( ^{89}\text{Zr} \) to be released by the antibody and find its way to bone, causing nonspecific uptake. Antibody-based imaging necessarily means that there is prolonged background activity due to slow clearance reducing sensitivity. In addition, antibody imaging usually takes place over several days to reduce background activity sufficiently to detect the target. This is time consuming and inconvenient for the patient and delays treatment decisions. Moreover, larger molecules such as antibodies do not diffuse freely in tumors, resulting in incomplete penetration. These problems could be overcome if a smaller molecule—targeting ICOS with equal or higher affinity could be found. Single-domain antibodies or nanobodies, peptides, and other antibody fragments are examples of such agents. There has never been a better time to discover suitable low molecular weight 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 it 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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No potential conflicts of interest were disclosed.

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References

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