Collagen Receptor Implicated in Immune Exclusion

Tumors shield themselves from immune attack by constructing protective barriers of collagen. But this defense mechanism can be circumvented through blockade of the collagen receptor DDR1, allowing for cancer-killing T cells to flood in and slow tumor progression.

The findings, from a mouse model of breast cancer, suggest that therapeutically targeting DDR1 could help overcome a key mechanism of immune exclusion, a trait common to many solid tumors that has been linked to poor survival (Nature 2021 Nov 3 [Epub ahead of print]).

In the new study, a team co-led by Rong Li, PhD, of George Washington University in Washington, DC, and Zhiqiang An, PhD, of the University of Texas Health Science Center at Houston, showed that the outer segment of DDR1 helps to align collagen fibers in the extracellular matrix surrounding cancers. This creates fencing akin to barbed wire around tumors that keeps T cells at bay.

In mice, genetic removal of DDR1 from tumors disrupted the patterning of collagen, leading to enhanced immune infiltration and reduced tumor growth. Antibody drugs directed at DDR1's outer domain had the same effect.

The researchers focused their efforts on models of triple-negative breast cancer—and they have human data to suggest the findings should have clinical relevance. In women with this aggressive malignancy, the researchers showed that higher expression of DDR1 in tumor samples correlated with greater exclusion of anticancer T cells.

However, Li anticipates that DDR1 blockade should be an effective way of modulating the immune milieu in a variety of different tumors. "Immune exclusion is a pan-cancer phenotype," he says, so "the same strategy could be applied to other cancer types."

Shaan Gandhi, MD, DPhil, director of Northpond Ventures in Cambridge, MA, agrees, which is why his firm has backed Parthenon Therapeutics, a new startup focused on targeting immune exclusion in tumors. When his team saw Li and An's data, "we were astounded by how much of a role the extracellular matrix actually plays in promoting a tumor microenvironment that can either exclude T cells or, in the case of developing an anti-DDR1 antibody, can allow T cells to infiltrate the tumor," Gandhi says.

Parthenon launched on November 3 with $65 million in initial funding and a plan to advance a DDR1-directed therapeutic into clinical trials. Both Li and An are scientific advisors to the company.

Finding the right disease and patient population, however, could be a challenge. As Rafael Fridman, PhD, of Wayne State University in Detroit, MI, points out, "not all tumors have this rich collagen environment."

Some research from other tumor models also indicates that targeting collagen assembly could have negative consequences. Earlier this year, for example, Raghu Kalluri, MD, PhD, and his colleagues at The University of Texas MD Anderson Cancer Center in Houston, reported that depleting collagen around pancreatic tumors in mice resulted in more immune suppression, not less (Cancer Cell 2021;39:548-65.E6).

Given the known antitumor and protumor functions of collagen, Li notes, it's possible that altering the higher-order structure of the protein might be a more favorable therapeutic approach than simply eliminating it. More research, however, is needed to clarify the issue. As Kalluri puts it, "the stromal regulation of cancer needs a bit of a revisit." *–Elie Dolgin* ■

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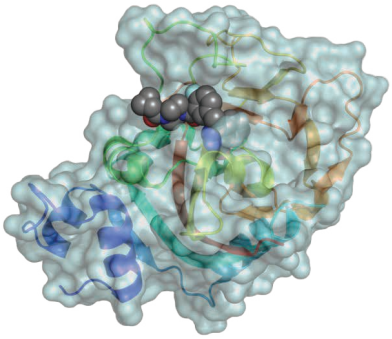
As Maintenance Therapy, Olaparib's Benefits Continue

The PARP inhibitor olaparib was approved in 2018 by the FDA as a first-line maintenance therapy for women with advanced *BRCA*-mutated ovarian cancer following completion of platinum-based chemotherapy. The decision was based on the randomized phase III SOLO1 trial, which found that the risk



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The PARP inhibitor olaparib (shown as a space-filling model) prevents DNA repair, causing the death of cancer cells.

of disease progression or death was 70% lower with olaparib than with placebo after a median of 41 months (N Engl J Med 2018;379:2495–505).

Now, a 5-year analysis of the data shows that patients treated with olaparib for 2 years had a median progression-free survival (PFS) 3.5 years longer (56 months versus 13.8 months) than those who received placebo (Lancet Oncol 2021 Oct 26 [Epub ahead of print]). The most common grade 3 and 4 adverse events among the 260 patients in the olaparib arm were anemia (22%) and neutropenia (8%). Serious adverse events—but no deaths—occurred in 21% of the olaparib group and 13% of the placebo group.

"The [initial] results of the SOLO1 study set a new standard of care for women with *BRCA*-mutated newly diagnosed advanced ovarian cancer," says Susana Banerjee, PhD, of The Royal Marsden National Health Service Foundation Trust and The Institute of Cancer Research in London, UK. Nonetheless, "it is important to check that effectiveness is maintained over time with longer patient follow-up. We have [now] shown that the effectiveness is maintained beyond the point at which treatment was stopped, which is an important point.

"This 5-year follow-up shows the long-term benefit of 2 years of maintenance olaparib, and that there was no increase in toxicities," Banerjee continues, adding that no new toxicities emerged since the initial report. Importantly, PFS was extended regardless of whether patients were considered high- or low-risk, or which *BRCA* mutation they carried.