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STINGing Antitumor Immunity into Action

Efforts to modulate STING signaling for therapeutic purposes rapidly gaining steam

How do you turn an immunologically "cold" tumor "hot"?

For some years now, researchers have been actively investigating this question and its molecular underpinnings. Lately, one signaling pathway to have attracted considerable attention is STING, which is activated not only by infection, but also when dendritic cells detect tumor-derived DNA.

The latter discovery was made in the lab of Thomas Gajewski, MD, PhD, of the University of Chicago in Illinois (Immunity 2014;41:830–42). "We knew innate immune responses against cancer could occur," he explains, "and through a series of knockout mice and other ancillary studies, we found that the STING pathway is the main bridge to this spontaneous antitumor immunity."

With STING signaling, "what you get is a boatload of type I IFNs, inflammatory cytokines, and other elements that kick off a powerful immune cascade," says Jason Baird, PhD, of Providence Cancer Institute in Portland, OR. *In vitro*, he adds, this has been shown to reprogram the immunosuppressive M2 phenotype of tumor-associated macrophages to that of M1, which encourages inflammation.

In other words, to modify a tumor's microenvironment so it's more receptive to immunotherapy, "the secret sauce may very well be STING activation," says Michael Gallatin, PhD, president of Kirkland, WA–based Mavupharma. As such, interest has soared in finding ways "to agonize this pathway, generating *de novo* antitumor responses where there were none before," Gajewski says.

WAYS AND MEANS

For now, directly targeting the STING receptor via intratumoral injections of synthetic cyclic dinucleotides (CDN)—chemically manufactured forms of natural STING ligands—is the main approach to have entered clinical trials. "Around the time we discovered STING's role in spontaneous antitumor responses, an old drug called DMXAA resurfaced," Gajewski says. "Nobody knew exactly how it worked, but it had gone all the way through phase III trials in lung cancer that were negative."

Biochemical analyses revealed that DMXAA interacted with mouse—but not human—STING, so Gajewski's team decided to probe its agonist potential in mice. "Even a single injection could completely annihilate tumors," he says. Buoyed by this proof-of-principle study, he began collaborating with Berkeley, CA–based Aduro Biotech to evaluate synthetic CDNs capable of stimulating STING in both humans and mice (Cell Rep 2015;11:1018–30).

One of these candidates, ADU-S100, is being studied in a phase I trial for patients with various tumor types—including melanoma, head and neck cancer, triple-negative breast cancer, and Merkel cell carcinoma—who have at least two cutaneously accessible lesions, says Andrea van Elsas, PhD, Aduro's chief scientific officer.

"We were the first to test a STING agonist in people, and our story is maturing," he says. "We're progressing through dose-escalation cohorts; so far, ADU-S100 appears safe and well tolerated, with no dose-limiting toxicities." Other companies have since entered the STING space, because of its compelling biology. Merck, for instance, is testing MK-1454—another intratumorally injected synthetic CDN—in a phase I trial, and Bristol-Myers Squibb has a preclinical STING program up and running.

However, "you can't inject every tumor," Gajewski notes. "Finding ways to package a STING agonist so it can be given

STIMULATING STING: TO BE DIRECT, OR INDIRECT?

Because therapeutic targeting of STING is a field in its infancy, the jury is still out regarding the best approach, if there is one—direct receptor stimulation through CDNs versus indirect small-molecule modulation of the pathway.

"All the proof-of-concept so far has been via intratumoral [CDN] injection, to really focus a STING agonist-driven immune response on the tumor itself," observes Thomas Gajewski, MD, PhD, of the University of Chicago in Illinois. However, Jason Baird, PhD, of Providence Cancer Institute in Portland, OR, notes that these ligands are "not stable by nature and don't stick around long," being prone to breakdown by phosphodiesterases in the body. Finding ways to get around this issue of rapid ligand degradation is an area of active research, he says.

Something else to take into account when engineering synthetic CDNs: single-nucleotide polymorphisms (SNP), which vary in frequency based on racial origin, within the STING receptor binding pocket. It's unlikely, then, that "one ligand will bind to different individuals with the same affinity—in some cases, it might not bind at all," Baird says.

"You have to think this means patients could well respond differently to a given STING agonist," observes Michael Gough, PhD, also of Providence Cancer Institute. The potential consequences of these SNPs are still largely unknown, but "will be very interesting to uncover," he adds.

Regarding indirect STING modulation, Gough is unsurprised that various biotechs are pursuing this strategy, "given their extraordinary small-molecule expertise, which they're now applying to immunotherapy." Emerging agents will likely have very different properties than those of CDNs, he notes. "We'll really find out then about the possibilities of longer-lasting, systemic application."

"You might not have to touch STING itself to modulate signaling," Gajewski agrees. "Exploring broadly—looking to target positive or negative pathway regulators, for instance—is generally wise in drug development."

"There's still an awful lot to tease apart," Gough adds. "As is often true with cancer therapeutics, we tend to use a pathway rather than understand it. Exactly which critical targets you can hit will become clearer, I think, as more publications appear on STING-related molecules and how they work." –*AP*

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systemically, yet still mostly accumulate in tumors, will be an important next step."

Mavupharma has set its sights on this route, with plans to develop non-nucleotide small molecules that, delivered orally, modulate the STING pathway indirectly rather than target the receptor itself. "We're focusing on conditional agonists," Gallatin explains, "by which I mean even though they're systemically available—we can achieve high levels in the blood—their impact is manifest only where other conditions are met, as would be the case in the tumor microenvironment."

"We think this offers an advantage," Gallatin adds, "especially if one looks at the experience with TLR agonists," which target another pathogen-sensing innate immune pathway. For instance, topically applied imiquimod, an FDA-approved treatment for superficial basal cell carcinoma, induces significant local and systemic toxicities, including skin ulcers and flu-like symptoms.

Mavupharma is a young company; its STING-focused efforts "started in earnest just about a year ago," says Bob Baltera, the executive chairman. Even so, "we've already evolved some very unique and potent compounds, and we're tracking toward an IND [investigational new drug application] in 2019."

TOWARD COMBINATIONS

To Michael Gough, PhD, also of Providence Cancer Institute, the strong innate immune activation that STING signaling triggers "is a great way to transition to T cell–mediated adaptive responses, which will likely be what finishes the job" in terms of tumor eradication.

This points to synergy between STING modulation and immune checkpoint inhibition: Although the former's production of IFNβ helps recruit cytotoxic T cells, these in turn generate IFNγ, which upregulates PD-L1 and IDO "to throw some water on the fire and cool off the immune response," Gajewski explains. "A logical combination to evaluate, then, would be a STING agonist followed by blocking PD-1 plus IDO."

Aduro is already headed in this direction, van Elsas notes, having recently started a collaboration with Novartis to evaluate the latter's investigational PD-1 inhibitor, PDR001, alongside ADU-S100 in a phase I study.

"I'd also expect STING agonists to expand the efficacy of CAR T-cell therapy," Gajewski adds. "We've had this rate-limiting problem of adoptively transferred T cells not infiltrating solid tumors, for instance, because there's no innate immune pathway activated to give them direction."

All told, when it comes to determining the full therapeutic utility of modulating STING, it's still early days. As pathways go, however, "I think STING has the right breadth of impact," Gallatin says. "It stands out as having the potential to be a central integration point between innate and adaptive immunity, triggering a whole program by which both these systems synergize to eliminate tumors."
–Alissa Poh ■

STING AGONISTS: A SAMPLING

COMPANY	STING AGONIST	PIPELINE STATUS
Aduro Biotech (Berkeley, CA)	ADU-S100, a synthetic cyclic dinucleotide	Phase I clinical trials in solid tumors and lymphomas: monotherapy or in combination with PD-1 blockade (Novartis)
Bristol-Myers Squibb	Small-molecule pathway modulator(s)	Preclinical; portfolio acquired from IFM Therapeutics (Boston, MA) in August 2017
Curadev (India)	Small-molecule pathway modulator(s)	Preclinical
iTeos Therapeutics (Belgium)	Small-molecule pathway modulator(s)	Preclinical; partnering with Cristal Therapeutics (Netherlands) on nanoparticle-based targeted delivery strategy
Mavupharma (Kirkland, WA)	Small-molecule conditional pathway modulators; orally bioavailable	Preclinical; completed a $20 million Series A financing in December 2017
Merck	MK-1454, a synthetic cyclic dinucleotide	Phase I clinical trials in solid tumors and lymphomas: monotherapy or in combination with pembrolizumab (Keytruda)
Nimbus Therapeutics (Cambridge, MA)	Small-molecule pathway modulator(s)	Preclinical
Selvita (Poland)	Small-molecule pathway modulator(s)	Preclinical
Spring Bank Pharmaceuticals (Hopkinton, MA)	SB 11285, designed for intravenous delivery as an antibody–drug conjugate	Aims to start phase Ib/II trials in liver cancer in 2018

Several of the STING-focused efforts currently under way. Other companies may be developing similar agents.

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