QnAs with David H. Raulet
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During a distinguished career as an immunologist and cancer researcher, David H. Raulet has studied immune sentinels, called natural killer (NK) cells and T cells, and has worked on deciphering the mechanisms underlying their anticancer activity. His research has shown how NK cells are activated and inhibited and how they recognize cancer cells. He has also attempted to harness NK cells for cancer immunotherapy, and he describes some of his recent findings in his Inaugural Article (1). Now the Schekman Chair in Cancer Biology at the University of California at Berkeley, Raulet was elected to the National Academy of Sciences in 2019.

PNAS: How did you become interested in using NK cells as part of cancer immunotherapy?

Raulet: We've been working on natural killer cells for decades. In recent years, there's been a revolution in cancer immunotherapy, and treating cancer using the immune system has become quite successful. But, of course, many cancers are still not successfully treated, and we think there's a place for NK cells in this immunotherapy revolution. They complement T cells in terms of their recognition properties, and our goal is to use the knowledge we've accumulated over all these years to develop therapeutic approaches. So our efforts over the last few years have been to make the case that NK cells can be effective immunotherapeutic agents. That's kind of what this Inaugural Article (1) is about, as it provides evidence that NK cells can be quite successful at either participating or even mediating such antitumor responses, more or less by themselves. I do want to give a shout out to the people who've led the work, including the article's first author Natalie Wolf, and a former student in the laboratory, Christopher Nicolai, who started some of this work.

PNAS: How did you investigate the antitumor responses of NK cells?

Raulet: This story builds on earlier findings, which investigated how NK cells are naturally activated in the presence of cancer. They typically will fail to eliminate tumors under natural conditions, but by understanding the signals that activate them naturally, we realized that one could supersensitize them by using the same pathways. That was the genesis of using stimulator of interferon genes (STING) agonists, and this work on STING agonists really grew out of work by a former postdoc in my laboratory, Assaf Marcus, in collaboration with my colleague Russell Vance, who's been a pioneer in that pathway (2). This led us to the finding, in an earlier paper, that STING agonists could mobilize antitumor responses mediated by NK cells in the context of some tumor models (3). But we know that some of the models we use in mice are relatively easy to treat, compared to human cancer. We've been trying to up the ante by using increasingly stringent mouse models of cancer to try and determine if NK cells can play a major role. So that's part of what we did in the Inaugural Article (1). The other part was we had been investigating the role of cytokines in altering NK function. We previously investigated the deactivation or desensitization of NK cells in cancer, and we found evidence that cytokines of the interleukin-2 (IL-2) family could either delay or maybe even reverse the desensitization process and therefore produce more effective antitumor responses. So we combined those two approaches: the STING agonist, which provides a potent initial activating signal, and then the superkine, an engineered form of IL-2 that is very potent in reactivating NK cells within the tumor microenvironment.

PNAS: What did you find?

Raulet: We found that the combination was kind of magic: it was very synergistic in its action. We used these in more stringent tumor models than in the past, and either agent alone gave some effect, but didn't cure any of the mice. But the combination was quite remarkable in mobilizing these powerful NK cell-mediated responses, and in one case, a response mediated by CD4 T cells. We also examined a spontaneous carcinogen-induced model of cancer that is difficult to cure, as an even more stringent test.

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We saw quite remarkable effects there as well, especially in combination with checkpoint therapy, a previously established cancer immunotherapy approach. What was striking here was the degree of synergy.

**PNAS:** What are of the therapeutic implications of this work?

**Raulet:** We feel that our results are substantial enough that this approach should be considered for testing in humans. These therapeutics, both the STING agonists and some of the IL-2 family cytokines, have not shown super dramatic effects in human clinical trials so far, but we think the combination should be considered because it really is synergistic and there’s a chance to actually get some potent effects. In addition, one of the issues with the existing cancer therapies that mobilize CD8 T cells is that it turns out that many tumors are resistant to CD8 T cells. This includes some really major categories of cancer that have a huge unmet need in terms of therapy, such as breast cancer, pancreatic cancer, and prostate cancer. NK cells have [a] different recognition principle than CD8 T cells, so these are alternative effector cells that we can mobilize instead. It also turns out that the approach described in the Inaugural Article (1) is very effective at mobilizing T cell responses, too. I think that’s important because you get a one–two punch that brings several different complementary effectors into the equation.

**PNAS:** What follow-up experiments do you plan to do?

**Raulet:** We still don’t have a complete understanding of the synergy here, so one project is to try look with higher resolution at what's going on with these NK cells, and really examine their expression patterns to try and understand why they’re much more potent with the combination therapy than with individual therapy. The other project is to bring other therapeutics to the table. We’ve been looking at different kinds of cancers, where there are so many different mechanisms that can impede antitumor immune responses. We’re interested in bringing approaches to bear that would prevent those kinds of inhibitory effects, and we’re testing other therapeutics with that in mind. Another process of considerable interest to clinicians is that in some fraction of patients with melanoma who respond to checkpoint therapy, the therapy eventually fails, and the tumors grow and seem to be resistant to therapy at that point. We’re interested in testing our therapeutic approach to see if it could prevent such acquired resistance in the first place, by activating both T cells and NK cells against tumors. There is growing interest in NK cells from industry and clinicians, and we will also have to show that our approach can work in clinical trials in real patients. I really believe that NK cells have a place at the table here, and it’s just a matter of getting it to a place where the right trials are done and the right agents are used, and then there [will] be an even larger groundswell to exploit this approach.

1. N. Wolf et al., Synergy of a STING agonist and an IL-2 superkine in cancer immunotherapy against MHC I–deficient and MHC I+ tumors. Proc. Natl. Acad. Sci. U.S.A., 10.1073/pnas.2200568119 (2022).
2. A. Marcus et al., Tumor-derived cGAMP triggers a STING-mediated interferon response in non-tumor cells to activate the NK cell response. Immunity 49, 754–763.e4 (2018).
3. C. J. Nicolai et al., NK cells mediate clearance of CD8+ T cell-resistant tumors in response to STING agonists. Sci. Immunol. 5, eaaz2738 (2020).