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Spotlight

With a little help from my T friends: T cells increase efficacy of KRAS (G12D) inhibitors

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Mutation-selective KRAS inhibitors are revolutionizing the treatment of RAS-mutant tumors but cannot achieve durable effects alone. Kemp and colleagues[1] recently showed how the KRAS-G12D-specific inhibitor MRTX1133, while impairing cancer proliferation, stimulates T cell infiltration, which is crucial for sustained disease control.

The KRAS oncogene has been found to be mutated in 30% of all human cancers, which has made of it, for more than 30 years, the most wanted, yet elusive, target for anti-cancer therapy. RAS functions as a molecular switch, transducing mitogenic signals from the membrane receptors, and activates a signaling cascade leading to proliferation. When RAS is mutated, this signaling goes out of control, resulting in unrestrained cell division, tumor initiation, and progression. The last 5 years have seen the rise of a new generation of cleverly designed KRAS inhibitors, capable of blocking the mutated oncoprotein in its inactive state. The most clinically advanced of those drugs, targeting specifically the G12C mutant, quickly made it through clinical trials, and thanks to their favorable toxicity profile and promising anti-tumor efficacy, two of them have been approved for the treatment of KRAS-G12C-mutant lung cancer.[2]

Unfortunately, KRAS-G12C mutations are very rare in the highly deadly pancreatic cancer, where G12D mutants are the most frequent (40%). Recently, a new KRAS-G12D-specific non-covalent inhibitor, MRTX1133, has been developed by Mirati Therapeutics.[3] Although not yet ready for clinical use, this drug can provide valuable information in the pre-clinical setting, especially when applied to *in vivo* models that closely mimic the human disease. This is what the Stanger lab did in their recent work in *Cancer Discovery*,[1] where they studied the efficacy of MRTX1133 in immunocompetent murine models of pancreatic cancer. Kemp and colleagues use both implantable and spontaneous mouse models expressing the KRAS-G12D oncogene (the so-called KPC mice), in the presence of an intact immune system. Importantly, this model closely reproduces the dense, stroma-rich microenvironment of human pancreatic cancer, which is thought to limit the efficacy of therapeutic interventions.[4] Kemp et al. report partial or complete tumor regression in 50%–100% of the mice treated, with variability depending on the specific model used. Nevertheless, the response is neither always complete nor durable, as tumors relapse in most of the mice after the treatment is interrupted.

If we think about what we have learned from the KRAS-G12C inhibitors, though, those results don't seem surprising. The enthusiasm elicited by the early phase clinical studies of either Amgen's compound sotorasib or Mirati's adagrasib[5,6] is primarily justified by the previous lack of any targeted therapeutic option for RAS-mutant patients. But as a matter of fact, those drugs clearly have limitations. First, less than one-third of patients with advanced G12C-mutant lung cancer and less than one-tenth with G12C-mutant colorectal cancer, respond to the treatment. Second, even in the responsive patients, G12C inhibitors can only halt tumor growth for about 6 months, after which the tumors relapse. It is thus apparent that KRAS-mutant-specific inhibitors will likely need to be used in combination with other drugs in order to achieve a more substantial clinical benefit. But which ones? Pre-clinical studies have investigated the reasons behind the limited efficacy of KRAS-mutant-specific inhibitors. Part of it, seems to reside in the capacity of cancer cells to adapt to KRAS-G12C inhibition by re-activating the inhibited signaling pathway or by switching to an alternative survival route.[2] This would suggest combinations with inhibitors of other signaling molecules within the cancer cells, which are currently being clinically explored. But another very important aspect for the efficacy of any anti-cancer therapy relies on the capacity to elicit a potent anti-tumor immune response. In this sense, the combination of G12C inhibitors with immunotherapy is also being investigated.

Luckily, KRAS inhibition seems to do more than just impair the mitogenic signaling in the mutation-bearing cancer cells. Studies have shown that KRAS-G12C-specific inhibitors also stimulate anti-tumor immunity by inducing a pro-inflammatory tumor microenvironment, enriched in tumor-suppressive M1 macrophages and cytotoxic T cells.[7,8] Now, what about KRAS-G12D inhibition? Before MRTX1133 was developed, researchers explored the effect of genetically depleting the oncogene using the siRNA tool technology. This allowed them to uncover how decreased KRAS-G12D expression also had an effect on tumor microenvironment.[9] In their *Cancer Discovery* work, the Stanger lab confirms that pharmacologic inhibition of KRAS-G12D using MRTX1133 also induces a decrease in myeloid-derived suppressor cells and an increase in pro-inflammatory M1 macrophages, thus creating an environment that favors immune response. Moreover, they add another important piece to the puzzle, by showing that the

treatment increases tumor-infiltrating cytotoxic T cells, the effectors of the anti-cancer immune response. This is particularly important in the light of two additional observations that Kemp and colleagues make in their *in vivo* experiments. On the one hand, they obtain deeper tumor regression in the T cell-inflamed KPC 2838c3 tumors, as compared to the T cell-excluded 6419c5 KPC clone. On the other hand, they experimentally deplete cytotoxic T cells from the 2838c3 KPC mice and found that this abrogates the capacity of MRTX1133 to induce complete remissions. Moreover, while 50% of the T cell-infiltrated tumors remain in remission even after the treatment is suspended, all the tumors in which T cells have been depleted inevitably relapse. Those results clearly show that while MRTX1133 has a potent tumor-intrinsic, anti-proliferative effect on KRAS-G12D-mutant pancreatic cancer cells, a complete and durable tumor eradication can only be achieved in the presence of active tumor-infiltrating cytotoxic T cells. The good news is that the drug itself seems to stimulate a tumor microenvironment that favors their expansion.

Altogether, the data from the Stanger lab build on the recent progress made in inhibiting the most potent of oncogenes, the no-more-undruggable KRAS, and shed important light on the role of T cells and tumor microenvironment in the response to anti-KRAS-G12D compounds. Their observations support the exploration of MRTX1133 in combination with immunotherapy (immune checkpoint inhibitors, tumor-infiltrating lymphocytes [TIL], or CAR T cell therapy), stimulating the patient's immune system to work together with the drug to achieve a complete and durable tumor eradication.

DECLARATION OF INTERESTS

The author declares no competing interests.

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