Many targeted cancer therapies suppress T cell immune responses

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José Conejo-Garcia, M.D., Ph.D., is professor and program leader of the Tumor Microenvironment and Metastasis program at The Wistar Institute. Credit: The Wistar Institute

In many cases, targeted therapies for cancer are preferred as treatments over chemotherapy and surgery because they attack and kill cancer cells

with specific tumor-promoting mutations while sparing healthy, normal cells that do not express these mutations. In clinical trials, a heavy emphasis on the effects of targeted therapies on tumor cells has been explored, but the effects they have on the immune system have not been thoroughly investigated.

However, new research from The Wistar Institute demonstrated that dozens of these targeted therapies suppressed the activity of T cells that could actually help fight tumors. While studying the FDA-approved targeted therapy trametinib, the researchers also found that pairing it with a signaling protein "superagonist" stimulated T cell activity while preserving the cancer-blocking effects of the cancer treatment. Study results are published in the journal *Cancer Research*.

"We wanted to know what the consequences to the immune system were when tumor cells were exposed to targeted therapies," said José R. Conejo-Garcia, M.D., Ph.D., professor and program leader in the Tumor Microenvironment and Metastasis program at The Wistar Institute and senior author of the study. "The effect that these drugs have on the interplay between tumor cells and leukocytes, which are essential for controlling the growth of immunogenic tumors, must be understood if we are to maximize the benefits of combination or sequential administration of targeted therapies and immunotherapies."

Conejo-Garcia and colleagues studied 41 different small molecule inhibitors and their effects on healthy human T cells, which defend the body from pathogens and cancer cells. Every targeted therapy tested in this study inhibited T cells more potently than cancer cells. In particular, they noticed that the FDA-approved drug trametinib (Mekinist) - a MEK1/2 inhibitor approved to treat metastatic melanoma with a BRAFV600E/K mutation, which affects almost half of all patients with melanoma, was a particularly powerful inhibitor of T cell activity.

The researchers speculated that if cell signaling proteins called cytokines could promote signaling on immune cells but not tumor cells, they could then rescue the T cells from the negative effects of treatment with trametinib. Cytokines that are commonly administered to patients showed protective activity. They identified interleukin-15 (IL-15) as an appropriate cytokine to study with trametinib because it promotes stronger signaling activity for effector T cells while not expanding the population regulatory T cells that could suppress the activity of effector T cells.

Conejo-Garcia and colleagues tested an IL-15 "superagonist" currently in phase I and II clinical trials called ALT-803 to determine if this drug could rescue T cells suppressed by trametinib. When they tested the effects in vivo, they found that T cell proliferation was no longer affected by trametinib. The results confirmed both the inhibitory effect of trametinib on T cells and the ability of IL-15 to overcome this suppression.

"MEK inhibitors like trametinib are being tested in a variety of tumors, and we've demonstrated an effective means of controlling the effect that these drugs have on T cells that could further help in the fight against cancer," said Michael Allegrezza, a predoctoral trainee in the Conejo-Garcia lab and first author of the study. "We plan to continue to study the effects of targeted therapies on the tumor microenvironment and see if other immune cells are impacted in the manner we observed in effector T cells."

The Wistar Institute's business development team is actively seeking a co-development partner to assist in realizing the clinical benefit of the combination of MEK inhibitors and IL-15 superagonists.

More information: M. J. Allegrezza et al. IL-15 AGONISTS OVERCOME THE IMMUNOSUPPRESSIVE EFFECTS OF MEK

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