An Unexpected Ally Against Cancer: Junk DNA

“I never expected this kind of robust response,” said Qin Yan, PhD, Associate Professor of Pathology; Director of the Center for Epigenetics and Biomarkers; Scientific Co-Director of the Center for Breast Cancer; and Co-Leader of the Center for Epigenetics, Genetics, and Epigenetics Research Program at Yale Cancer Center. He was describing what he saw in a melanoma mouse model. “The whole tumor was completely gone.”

“At that point it was very clear that this would be something of interest to invest in,” added Dr. Yan’s collaborator, Marcus Bosenberg, MD, PhD, Professor of Dermatology, Pathology, and Immunobiology; Co-Leader of the Center for Cancer Immunology; Research Program; Director of the Yale Center for Immuno-Oncology; and Co-Director of the Yale SPORE in Skin Cancer. “Their research on two enzymes, KDM5 and SETDB1, has revolutionized an entire field of research. We have developed compounds that can degrade KDM5 and remove them from the cell. That would stop the enzymes from recruiting SETDB1 to silence the retroelements. “We have enough to work on for ten years to come,” said Dr. Yan. “And we’re seeing this in a melanoma mouse model. “The whole tumor was completely gone.”

“With these retroelements,” said Dr. Bosenberg, “patients treated this way are likely to have a defense system to prevent future recurrence of melanoma. “This approach to the so-called ‘immune memory response,” explained Dr. Yan. “Patients treated this way are likely to have a defense system to prevent future recurrence of melanoma. “This approach to the so-called ‘immune memory response,” explained Dr. Yan.

Both scientists are now trying to decipher the mechanism of these enzymes, and the interactions that they have with the cell. “We are working on developing drugs that will inhibit or eliminate the enzymes,” Dr. Yan said. “We are also working on developing drugs that will inhibit or eliminate the enzymes.”

“SETDB1 has the same effect, awakening the immune system to attack cancer cells. The first step was their finding that high KDM5B level is associated with poor response to immunotherapies in rare melanoma patients. Consistently, when Drs. Yan and Bosenberg’s group depleted KDM5B in the mouse model, the immune system woke up and activated type-1 interferon, which stimulated an increase in T cells, which began killing tumor cells. Dr. Yan and Bosenberg discovered that depleting SETDB1 has the same effect, awakening the immune system to attack cancer cells.

“Getting rid of KDM5B and SETDB1 somehow activates ‘retroelements’—non-coding parts of the genome that are sometimes called junk DNA. “There is a lot of folklore,” said Dr. Bosenberg, “about how tumors have this capacity to evolve over the years, and they are kind of silent. When either KDM5B or SETDB1 is removed, these retroelements can turn on. “We have shown that this process is very important for this enhanced anticancer immune response that we’re seeing in the tumors.”

In fact, he and Dr. Yan found that KDM5B recruits SETDB1 to silence retroelements and stop them from alerting the immune system. These discoveries on the researchers because the findings suggest that it might be possible to treat tumors that either don’t respond to immunotherapies or don’t develop a defense system to prevent future recurrence of melanoma. “This approach to the so-called ‘immune memory response,” explained Dr. Yan. “Patients treated this way are likely to have a defense system to prevent future recurrence of melanoma. “This approach to the so-called ‘immune memory response,” explained Dr. Yan.

But with these retroelements, the researchers also found that KDM5B and SETDB1 can work together to prevent the immune system from attacking the tumors. “We have data to show this in the mouse model.”

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