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 Genomics, 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 work on," added Dr. Yan's collaborator, Marcus Bosenberg, MD, PhD, Professor of Dermatology, Pathology, and Immunobiology; Co-Leader of the 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, KDM5B and SETDB1, has revealed epigenetic keys that could open the door to powerful new treatments for melanoma and other cancers, including cancers resistant to immunotherapies. The results of their research, which was supported by the Yale SPORE in Skin Cancer, were published in October 2021 in the prestigious journal *Nature*.

Drs. Yan and Bosenberg's moment of surprise sounds sudden but was decades in the making. Dr. Yan began studying the KDM5 family of proteins more than 15 years ago during his postdoctoral training at the Dana-Farber Cancer Institute in the lab of William Kaelin, MD, who recently won the Nobel Prize in medicine. He has continued to research KDM5 in his lab at Yale. Dr. Bosenberg runs one of the nation's leading labs on melanoma research. He has developed numerous mouse models used by scientists around the world to test melanoma therapies. The two researchers came together about a decade ago over their mutual interest in epigenetics and began exploring KDM5B's role in melanoma. The new paper is the culmination of five years of collaborative effort.

The first step was their finding that high KDM5B level is associated with poor response to immunotherapy in human 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. Drs. 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 are a lot of these things," said Dr. Bosenberg, "almost like barnacles on a ship, that have evolved over the years, and they are kind of silent. When either KDM5B or SETDB1 is removed, these retroelements can then be expressed or seen, and we've shown that that 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 excite the researchers because the findings suggest that it might be possible to treat tumors that either don't respond to immune therapies or that develop resistance to them. Such therapies usually target genes expressing a specific protein or showing lots of mutations, and they have been highly effective in some cancers for some patients. Yet too often the cancer cells defeat the strategies behind such immunotherapies or eventually find ways to overcome them.

"But with these retroelements," said Dr. Bosenberg, "the tumors are carrying all the things that the immune system might need to recognize them, and they could be turned on to generate effective responses against hard-to-treat tumors and tumors that don't have a lot of mutations, like pediatric tumors. It's not clear that's going to be the case, but it was true for the tumors in our study."

There is more promising news in this research. When these retroelements are released to express themselves and trigger the immune system, the effect seems to be long-lasting. "This approach might establish 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 these tumors. We have data to show this in the mouse model."

Both scientists are now trying to decipher the mechanism or mechanisms behind the responses they have documented. They are also working to develop drugs that deplete or inhibit the enzymes, with Dr. Yan focusing on KDM5B and Dr. Bosenberg on SETDB1. Dr. Yan is working with a new class of drugs called degraders that destroy specific proteins such as KDM5B and remove them from the cell. That would stop KDM5B from recruiting SETDB1 to silence the retroelements. He is confident this can be done. "We have found some compounds that can degrade KDM5B," he said. Dr. Bosenberg is equally confident about finding inhibitors that are effective on SETDB1. "We have enough to work on for ten years to come," said Dr. Yan.