Melanoma ranks among the most lethal cancers, causing about 90 percent of all skin cancer deaths. Scientists have traced most melanomas—to mutations in the BRAF and NRAS genes. But what happens in the interval between the onset of these mutations and the proliferation of melanoma cells? What signals and mechanisms set off the cascade of responses that ends in skin cancer?

The answers to these questions, once unclear, have recently been answered by findings at Yale Cancer Center. Narendra Wajapeyee, PhD, Assistant Professor of Pathology, and his team have traced the connections. BRAF and NRAS cannot form tumors without the crucial contribution of a microRNA called miR-146a.

The discovery, noted Dr. Wajapeyee, reveals one of melanoma’s vulnerabilities and gives drug developers an obvious target. “They can test approaches against miR-146a,” he said, “to see whether we can effectively cure metastatic melanoma.”

Previous research has established that microRNAs (miRNAs) regulate gene expression and play a part in tumorigenesis and metastasis, but the miRNA activator in melanoma was unknown. Dr. Wajapeyee and his team worked for almost five years to reach their breakthrough. They began by analyzing melanomas to find the most common miRNAs upregulated by the BRAF and NRAS oncogenes. They identified the miRNA with the most elevated levels: miR-146a. But their work was just beginning.

They began studying miR-146a’s downstream effects on signaling pathways that lead to melanoma. They learned that miR-146a targets a protein called NUMB and suppresses it. NUMB ordinarily regulates Notch, a receptor pathway favored by cancer. So when NUMB is suppressed and miR-146a begins overexpressing, the signals from Notch, now unregulated, get amplified. This prompts even heavier production of miR-146a, inducing skin cancer cells to proliferate and grow faster. Result: melanoma.

Next Dr. Wajapeyee and his team theorized that suppressing miR-146a would interfere with Notch signaling and disrupt the progression toward melanoma. Without help from miR-146a, Notch signaling was silenced and the melanoma cells stopped growing. “We found that miR-146a is required for BRAF and NRAS transformation,” explained Dr. Wajapeyee, “and that they cannot form tumors without it.”

The findings suggest a clear method of fighting melanoma: knock down production of miR-146a to stop it from blocking NUMB and activating Notch signaling, or target the Notch pathway itself. Dr. Wajapeyee noted that pharmacological antibodies that specifically inhibit Notch already exist, and these can be targeted against melanoma cells. Unfortunately these older Notch inhibitors have strong gastrointestinal side effects.

“But the new Notch antibodies are highly specific,” said Dr. Wajapeyee, “blocking only specific forms of Notch that are pro-oncogenic. They are highly effective and do not produce any GI side effects.” He and his team, in initial testing on cell lines, found that the most effective treatment against melanoma was a combination of drugs that inhibited both the production of miR-146a and the Notch signaling pathway. He also foresees possibilities in combining these targeted therapies with immunotherapies.

Among all cancer types, he noted, melanoma has the highest number of mutations on its genome. “For that reason, the melanoma cells will find ways to escape most therapies. So it may be best to combine two or three approaches and kill them early on before they evolve. Dr. Wajapeyee and his team are now using genomics and screening to identify a new target: the genes that allow melanoma cells to survive while circulating in the bloodstream after the primary tumor metastasizes. “If we can intercept those cells,” said Dr. Wajapeyee, “we can make them die in the bloodstream and prevent metastasis.”