MedicalXpress

Common cancers evade detection by silencing parts of immune system cells

March 4 2014

Johns Hopkins researchers say they have identified a set of genes that appear to predict which tumors can evade detection by the body's immune system, a step that may enable them to eventually target only the patients most likely to respond best to a new class of treatment.

Immune therapy for ovarian, breast and colorectal cancer—treatments that encourage the immune system to attack cancer cells as the foreign invaders they are—has so far had limited success, primarily because the immune system often can't destroy the cancer cells. In a report published online Feb. 16 in the journal *Oncotarget*, the Johns Hopkins team says it has identified genes that have been repressed through so-called epigenetic changes—modifications that alter the way genes function without changing their DNA sequence—which help the cells to evade the immune system. The researchers were able to reverse these epigenetic changes with the use of an FDA-approved drug, forcing the cancer cells out of hiding and potentially making them better targets for the same immune therapy that in the past may have failed.

"Chemotherapy often works, but in most cases, it eventually stops working," says one of the study leaders, Nita Ahuja, M.D., an associate professor of surgery, oncology and urology at the Johns Hopkins University School of Medicine. "What if we could get the immune system itself to fight the tumors and keep the cancer in check forever? That is the ultimate goal, and this gene panel may get us closer." The other study leader is Cynthia Zahnow, Ph.D., an associate professor of oncology at Johns Hopkins.

The researchers treated 63 cancer cell lines (26 breast, 14 colorectal and 23 ovarian) with low-dose 5-azacitidine (AZA), an FDA-approved drug for myelodysplastic syndrome, that reverses epigenetic changes by stripping off the methyl group that silences the gene. They identified a panel of 80 biological pathways commonly increased in expression by AZA in all three cancers, finding that 16 of them (20 percent) are related to the immune system. These pathways appeared to be dialed down in the cancer cells, allowing for evasion. After treatment with AZA, the epigenetic changes were reversed, rendering the cancer cells unable to evade the immune system any longer.

The researchers found that these immune system pathways were suppressed in a large number of primary tumors—roughly 50 percent of ovarian cancers studied, 40 percent of colorectal cancers and 30 percent of breast cancers. The findings may be applicable to other cancer types such as lung cancer or melanoma, they say.

After looking in cell lines, the Johns Hopkins team extended their work to human tumor samples. Again they found evidence that these immune system pathways are turned down in some patients and, that these immune genes can be turned back up in a small number of patients with breast and colorectal cancer who had been treated with epigenetic therapies.

"Most of us haven't thought of these common cancers as being immune-driven," Ahuja says. "We haven't held out much hope for immune therapy to work in them because before you can enter cancer cells to knock them down, you have to be able to get inside. They were locked and now we may have identified a key."

The hope is that clinicians could eventually pinpoint which patients with these common cancers would benefit from a dose of AZA followed by an immune therapy that stimulates the immune system to attack cancer

cells.

"This would tell us which patients' tumors are hiding from the immune system and will allow us to use all of our tools to flush that cancer out," she says.

While most of the work was done in the lab, Ahuja says her colleagues have already started to put the panel into use in a lung cancer trial. Six patients were treated first with epigenetic therapy followed by immune therapy. Though the sample is small and time has been short, four of the patients have had their cancer suppressed for many months.

"If this works—and we don't know yet if it will—this could have the potential to control someone's cancer for good," she says.

Provided by Johns Hopkins University School of Medicine