Immune system 'escape hatch' gives cancer cells traction

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Scientists at Johns Hopkins and elsewhere say they have mapped out an escape route that cancers use to evade the body's immune system, allowing the disease to spread unchecked.

In a report published in the July 1 issue of the journal *Nature Medicine*, the Hopkins team, along with researchers from Florida and Nebraska, describe how myeloid-derived suppressor cells (MDSCs), which normally keep the immune system in check and prevent it from attacking otherwise healthy tissue, can suppress the anti-tumor response to cancer.

These suppressor cells block other immune system cells, CD8 "killer" T cells, from binding with proteins that identify the foreign antigens on the surface of unhealthy cancer cells, marking them for destruction, the team reports.

The good news, they say, is that their experiments also suggest that the chain reactions in T-cell tolerance are reversible, raising the possibility of vaccine and drug therapies that break through the blocked immune system.

Previous research had confirmed that MDSCs, produced in the bone marrow, were attracted to tumors, but until now, scientists had not identified exactly how the cells inhibit the immune system's ability to mount an attack.

By explaining some of the precise biological workings of MDSCs in cancer the team's findings suggest why experimental cancer vaccines have to date been plagued by T-cell tolerance, a weakened rather than strengthened immune response, says Jonathan Schneck, M.D., Ph.D., one of the study's authors.

"Our findings also open up a new door in drug and vaccine development that we never knew existed and provide another opportunity for drug development into autoimmune diseases, where the immune system is in overdrive and needs to be slowed down," says Schneck, a professor of medicine, pathology and oncology at The Johns Hopkins University School of Medicine and its Kimmel Cancer Center.

The team's latest report built on research initially conducted at the University of South Florida, where researchers analyzed blood samples and lymph tissue from healthy mice injected with MDSCs and found that T-cell levels remained the same, indicating that MDSCs did not destroy the immune response but apparently altered how the T cells behaved.

Using chemical tests in which individual tumor cells can be tagged with a fluorescent dye that allows them to glow when they are not bound to T cells, Florida researchers measured the immune response in mice to various foreign proteins, with and without injections of MDSCs. They found an 80 percent suppression of the immune response in the presence of MDSCs, confirming that the suppressor cells were inactivating the T cells.

The Florida team then turned to Schneck, who in 1993 developed several novel proteins to test how various antigens, such as those on cancer cells, specifically latch on to T cells.

Researchers then began experiments to determine if the MDSC T-cell

interference was simply genetic or had some biochemical explanation, testing a half-dozen major reactions known to occur during infection to see if any set path was particularly active during interference.

In tissue tests from tumor-filled mice bred to lack a biochemical reaction, the scientists found that one specific pathway, the reactive-oxygen species, or ROS pathway, stood out, because when inactivated, T-cell tolerance did not develop. Researchers were surprised when subsequent tests showed that ROS actually modified the T cells, altering their structure so they could no longer bind to tumor-cell antigens.

When a known byproduct of ROS, the chemical peroxynitriate, was neutralized, T-cell tolerance failed to develop in test tube studies, pinning down peroxynitrate as the culprit prohibiting immune cell binding to and marking of “foreign” tumor cells.

“Peroxynitrate activity is the escape hatch, and now that we have identified it, we can try to cut it off before T-cell tolerance develops, or you can reverse it,” says Schneck.

Plans are underway to investigate the binding receptors of MDCSs and different anticancer drugs for their ability to lower levels of MDSCs and to explore the role of MDSCs in suppressing the immune response to stress, bacterial and viral infections, organ transplantation and autoimmune diseases. Their goal, researchers say, is to find some means of accelerating or slowing down T-cell activity gone awry.

Source: Johns Hopkins Medical Institutions

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