Study unmasks how ovarian tumors evade immune system

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Scientists at Johns Hopkins have determined how the characteristic shedding of fatty substances, or lipids, by ovarian tumors allows the cancer to evade the body's immune system, leaving the disease to spread unchecked. Ovarian cancer is considered to be one of the most aggressive malignancies, killing more than 70 percent of diagnosed women within five years, including an estimated 15,000 this year.

In a two-year series of lab experiments, a team of researchers from the Johns Hopkins University School of Medicine and its Sidney Kimmel Comprehensive Cancer Center showed that fluid secretions from tumors, called ascites, which contain lipids and collect in the space surrounding cancerous ovaries, can totally suppress the action of natural killer T cells in the immune system.

Known as NKTs for short, these special T cells must be activated to do their job of jump-starting the immune response and signaling other kinds of white blood cells to rid the body of diseases or leave healthy tissue alone.

As part of the study, researchers collected lipid-filled ascites from 25 women with ovarian cancer and then exposed the lipid samples to an immune system test to see if they blocked activation of NKT cells.

In a report set to appear in the Dec.1 issue of the journal *Clinical Cancer Research*, the research team also found this evasive blocking tactic to be virtually exclusive to a specific protein, called CD1d, needed to activate

the NKT cells.

Their experiments specifically showed that NKT activation was blocked between 10 percent and 100 percent after test cultures of cells that stimulate NKT cells were exposed to increasing concentrations of tumor-derived ascites.

Disrupted or stalled T cell action has been known to play a key role in the spread of several kinds of cancer, the scientists say. But until now, there was no firm evidence that tied a specific T cell in the body's defensive immune system to ovarian cancer.

"Our study findings lay out for the first time how ovarian cancer evades a critical check-point in the immune response, opening the door to future drug development that can halt, limit, reverse or even bypass the blockage, permitting CD1d-mediated NKT cell activation," says immunologist and study senior investigator Mathias Oelke, Ph.D.

According to Oelke, an assistant professor at Johns Hopkins, the research is believed to be the first to demonstrate the clinical effect of ascites on human NKT cells and describe the regulatory role of lipids in cancer progression. Previous studies in mice have confirmed that lipids assist in tumor evasion, he notes. But he says this is the first evidence in humans about the immune-suppressing effects of ascites on NKT cells, which are also abundant in cancers that spread to the abdomen and in other infectious diseases.

"The ultimate goal, of course, is to make sure the immune system can detect the cancer and, we hope, attack and eliminate it," says study co-investigator Jonathan Schneck, M.D., Ph.D.
Schneck, a professor of pathology, medicine and oncology, described the blocking as "rapid and prolonged," happening within four hours of ascites exposure and remaining constant for the test duration.

When ascites extracted from men and women with another disease, hepatitis C, were exposed to cells that stimulate NKT cells, only two of six ascites samples blocked its activation.

And in another experiment, immune system CD8 "killer" T cells functioned normally, even when their stimulator cells were previously treated with ascites.

Moreover, the blocking action only occurred with ascites. Matching blood serum samples from the women with cancer failed to block NKT activation.

Researchers say their next steps are to evaluate more than a dozen varieties of lipids that exist in the body to determine their specific role, if any, in modulating the blocking of the NKT cell immune response. Their goal, researchers say, is to find links to other diseases and T-cell activity gone awry.

Source: Johns Hopkins Medical Institutions