Study explains high platelets in ovarian cancer patients, survival reduced

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Highly elevated platelet levels fuel tumor growth and reduce the survival of ovarian cancer patients, an international team of researchers led by scientists at The University of Texas MD Anderson Cancer center reports in the *New England Journal of Medicine*.

By pinpointing a powerful cause-and-effect relationship at the heart of a clinical observation that dates back more than 100 years, the team's findings reveal a new factor in cancer progression and new potential approaches for treatment.

"We've long known that ovarian cancer patients often have markedly increased platelet counts but we haven't known why this happens or understood its relevance, if any, to disease progression," said senior author Anil Sood, M.D., professor in MD Anderson's Departments of Gynecologic Oncology and Reproductive Medicine and Cancer Biology.

"Our collaborative study not only identified a mechanism that explains platelet count elevation, but also connects this state, called thrombocytosis, to the severity of ovarian cancer," Sood said. "This suggests drugs that interfere with coagulation might be a useful addition to conventional therapies."

Tumor makes IL-6, liver produces TPO, platelets abound, tumor grows

Drawing on clinical data from ovarian cancer patients and following up with mouse model experiments and a clinical trial, Sood and colleagues discovered:

- Ovarian cancers produce the inflammatory cytokine interleukin-6 (IL-6);
- Triggering creation of the platelet-production regulating hormone thrombopoietin (TPO) in the liver;
- Causing platelet counts to soar to more than 450,000 per cubic millimeter in the blood, the threshold for thrombocytosis, and
- Stimulating tumor growth and continuation of the cycle.

"Platelets may function as a fuel depot for tumors by providing them with growth factors," Sood said. They were found not only in the blood but also in the tumor's microenvironment, in the tumor bed, and in ascites, fluid build-up in the abdominal cavity common in ovarian cancer.

In a clinical trial conducted at the Barts Cancer Institute, Queen Mary, University of London, the team also found that treatment of 18 ovarian cancer patients in a phase I/II clinical trial with siltuximab, an antibody to IL-6, sharply reduced platelet counts over a three-week period.

Clinical observation leads to survival connection

"This research comes from clinical observations," Sood said. "We have many ovarian cancer patients with thrombocytosis and decided to look into the causes for it."

A literature search revealed that the association between what was then called a "hyper-coagulable state" and cancer was noted as far back as 1867, but no relationship between the two had been established.

Of 619 ovarian cancer patients, 192 (31 percent) had thrombocytosis. Importantly, less than 2 percent of those had an iron deficiency or a non-cancerous inflammatory condition, the two most common causes of elevated platelet levels.

Patients with thrombocytosis survived for a median of 2.62 years, compared to 4.65 years for those with normal platelet counts. After accounting for age, disease stage, tumor grade and type and the extent of surgical tumor reduction, thrombocytosis remained an independent predictor of poor survival.

Tracking down cause and effect

The team found elevated platelet counts in three separate mouse models of epithelial ovarian cancer and in pancreatic and uterine cancer models, but not breast cancer.

They also found a connection between high platelet counts and higher levels of large cells called megakaryocytes, which occur in the bone marrow and fragment into platelets under the direction of thrombopoietin.

Next, in a cohort of 150 ovarian cancer patients, they analyzed plasma levels of 10 factors in the blood known to regulate creation of megakaryocytes. Again, 31 percent had thrombocytosis.

Levels of interleukin-6 and thrombopoietin in blood serum were substantially elevated in patients with thrombocytosis. A separate analysis of 310 ovarian cancer patients showed that elevated IL-6 is also associated with reduced progression-free survival.

Blocking thrombopoietin and interleukin-6 reduces

platelets, shrinks tumors

To understand the functional role TPO and IL-6 play in raising platelet levels, the researchers used short interfering RNA to shut them down separately and together in mice. In each case, platelet levels fell steeply, with thrombocytosis completely eliminated when both IL-6 and TPO were silenced.

To test IL-6 as a target, they treated two strains of mice with ovarian cancer with the IL-6 antibody siltuximab, paclitaxel chemotherapy, or both. All three treatments reduced platelet count and tumor burden. The combination was most effective, reducing tumor growth by 90 percent.

Treatment of mice with an anti-platelet antibody cut both the circulating platelet count and average tumor size in half, reduced cell proliferation by 44 percent and tumor blood vessel density by 51 percent.

More to study: precise mechanisms, potential treatments

While the researchers note that platelets are likely to promote cancer growth by strengthening tumor blood vessels, the precise mechanisms involved remain to be discovered via prospective collection and in-depth analysis of platelets from cancer patients.

The authors note their findings might explain why some blood-thinning agents improve survival in some cancer patients independent of their prevention of vascular blood clotting, and why daily use of aspirin after diagnosis of colorectal cancer also improved survival in a prospective clinical trial.

Platelet levels may also serve as biomarkers for ovarian and other

cancers, Rebecca Stone, M.D., clinical fellow in gynecologic oncology and the first author of the study, noted. "If you see high platelets, absent inflammation or iron deficiency, it would be important to look for cancer."

Provided by University of Texas M. D. Anderson Cancer Center