August 28, 2007

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New Details about How Cancer Spreads by Aggregating Platelets

BETHESDA, Md. – Scientists have provided new details about how cancer cells spread by surrounding themselves with platelets – the blood cells needed for blood clotting. Katsue Suzuki-Inoue, Associate Professor of Medicine at the University of Yamanashi, Japan, and colleagues have identified for the first time a protein on the surface of platelets that plays a key role in cancer-induced platelet aggregation. These results could help design new drugs that prevent cancer cells from metastasizing, or spreading throughout the body.

"In order to spread, cancer cells release chemicals that make neighboring platelets aggregate and surround the cancer cells, helping them evade the immune system and allowing them to bind to the blood vessels' inner linings," Suzuki-Inoue says. "We have discovered how one of these chemicals, called podoplanin, binds to the platelet cells and stimulate their aggregation. Although podoplanin has been known since 1990, how it induces platelet cell aggregation has been a mystery – until now."

The new study, to be published in the September 7 issue of the *Journal of Biological Chemistry*, was selected as a "Paper of the Week" by the journal's editors, meaning that it belongs to the top one percent of papers reviewed in significance and overall importance.

Suzuki-Inoue and colleagues had previously discovered that the snake venom rhodocytin stimulates platelet aggregation by binding to a protein called C-type lectin-like receptor 2 (CLEC-2) located on the surface of the platelets in a way similar to a key (rhodocytin) binding to a lock (CLEC-2).

By studying the details of what happens inside these platelets before and during aggregation, the scientists noticed many similarities with the way platelets aggregate when they are induced by podoplanin from cancer cells. Whether stimulated by rhodocytin or podoplanin, the platelets are slow to aggregate at first and, after they start aggregating, the proteins that are activated inside the platelets are similar in both cases.

Suzuki-Inoue and her team reasoned that maybe CLEC-2 binds not only to rhodocytin but also to podoplanin. The scientists tested this hypothesis by first growing CLEC-2 in culture and then by adding them to cultured cells expressing podoplanin. The hypothesis was confirmed: CLEC-2 and podoplanin bound to each other in the same lock-and-key mechanism displayed by CLEC-2 and rhodocytin.

"We were pleasantly surprised," Suzuki-Inuoue says. "After all these years, we finally found the long-missing protein to which podoplanin binds to promote platelet

aggregation."

The scientists confirmed their findings by mixing podoplanin-expressing cells with platelet cells genetically altered so that the CLEC-2 on their surface could not bind to podoplanin. Platelet aggregation was completely inhibited, confirming that CLEC-2 was the protein necessary for podoplanin-induced platelet aggregation.

This result also suggested that it may be possible to prevent cancer cells from stimulating platelet aggregation – and thus allow the cancer cells to metastasize – by blocking the interaction between CLEC-2 and podoplanin.

"Our study clearly shows that podoplanin on the surface of tumor cells induces platelet aggregation by interacting with CLEC-2 on the surface of platelet cells," Suzuki-Inuoue says. "Preventing CLEC-2 and podoplanin from binding to each other may be a good therapeutic way of preventing tumor metastasis."

The role of podoplanin-CLEC-2 interaction may not be limited to tumor metastasis, the scientists note. When podoplanin and CLEC-2 bind to each other, not only do platelets aggregate, but they also release chemicals that may form new blood vessels which, in turn, provide the tumor with the nutrients and oxygen it needs to grow. As a result, locking the podoplanin-CLEC-2 interaction may not only prevent cancer metastasis but also limit the growth of cancer cells, Suzuki-Inuoue says.

The researchers also found that podoplanin present within lymphatic vessels – which carry plasma and white blood cells – also induces platelet aggregation, showing that a better understanding of how podoplanin and CLEC-2 bind together may provide information on how lymphatic vessels form and work.

Suzuki-Inuoue and colleagues are now trying to develop antibodies that look like CLEC-2 and that can bind to podoplanin, preventing it from attaching to platelet cells. The scientists are also investigating the role of the podoplanin-CLEC-2 interaction in the formation of blood clots and the development of lymphatic vessels.

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ARTICLE: "Involvement of the snake toxin receptor CLEC-2 in podoplanin-mediated platelet activation by cancer cells," by Katsue Suzuki-Inoue**,** Yukinari Kato, Osamu Inoue, Mika Kato Kaneko, Kazuhiko Mishima, Yutaka Yatomi, Yasuo Yamazaki, Hisashi Narimatsu, and Yukio Ozaki

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