JBC: SNAKE VENOM STUDIES YIELD INSIGHTS FOR DEVELOPMENT OF THERAPIES FOR HEART DISEASE AND CANCER

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Aug. 2, 2010 -- Researchers seeking to learn more about stroke by studying how the body responds to toxins in snake venom are this week releasing new findings that they hope will aid in the development of therapies for heart disease and, surprisingly, cancer.

The Japanese team is reporting in a Journal of Biological Chemistry "Paper of the Week" that they are optimistic that inhibiting a protein found on the surface of blood cells known as platelets may combat both irregular blood clotting and the spread of certain cancers throughout the body.

"The finding that platelets not only play a role in blood clotting but also in the development of vessels that allow tumors to flourish was quite unexpected and paves the way for new research on the role or roles of platelets," says Katsue Suzuki-Inoue, the associate professor at the University of Yamanashi who oversaw the 13-person team's work in professor Yukio Ozaki's laboratory.

ABOUT PLATELETS, BLOOD CLOTS AND STROKE

Under normal conditions, platelets are activated to become sticky when blood vessels are injured, and their clumping together (aggregation or clotting) naturally stops bleeding. But, irregular platelet aggregation caused by disease can lead to dangerous clots or even stroke if a clot clogs or bursts in a vessel that carries oxygen and nutrients to the brain.

"When a blood clot, or thrombus, forms during the body's normal repair process, it's doing its job," says Suzuki-Inoue. "But, thrombotic diseases, such as heart attack and stroke, are leading causes of death in developed countries. Understanding and manipulating the underlying chemical reactions could help us save many lives."

But what does this have to do with snake venom? It's sort of a long story.

HOW VENOM CAN PREVENT OR CAUSE CLOTTING

"Snake venom contains a vast number of toxins that target proteins in platelets," says Yonchol Shin, an associate professor at Kogakuin University who specializes in snake toxins. "Some of those toxins prevent platelets from clotting, which can lead to profuse bleeding in snake bite victims. Others, like the one we've focused this research on, potently activate platelets, which results in blood clots. Identification of the molecular targets of many of these toxins has made an enormous contribution to our understanding of platelet activation and related diseases."

Intrigued by the then-recent discovery that elements in snake venom can promote irregular aggregation of platelets – the kind that leads to clots and stroke – Inoue's and Ozaki's team set out in 1997 to understand better the molecular underpinnings of those chemical reactions. They hoped that whatever they learned could be applied to the search for new therapies for irregular blood clotting caused by disease.

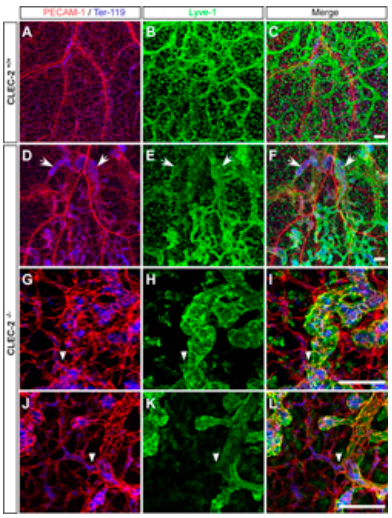
In 2000, another set of investigators came across a protein on the surface of platelets and dubbed it C-type lectin-like receptor 2, or CLEC-2. At the time, it remained unclear how CLEC-2 was produced or what its job was, but the team suspected it was worth further study.

After six years of research and collaborations with British investigators, the team in 2006 discovered how rhodocytin -- a molecule purified from the venom of the Southeast Asia pit viper *Calloselasma rhodastoma* -- binds to the CLEC-2 receptor protein on the platelet surface, spurring the platelet to clot with others like it.

Then, in another JBC "Paper of the Week" in 2007, Suzuki-Inoue and her colleagues reported how a separate molecule, called podoplanin, binds to the CLEC-2 platelet receptor protein very much like the venom molecule does. Discovered in 1990, podoplanin is a protein expressed on the surface of cancer cells, and, when bound to the CLEC-2 receptor on platelets, it spurs blood clotting, too.

"To shield themselves from the immune system, cancer cells send out a chemical, podoplanin, which binds to the CLEC-2 receptor protein on platelets, telling the platelets to get together and form a protective barrier around the cancer cells. Once enveloped, the cancer cells are not detected by the immune system and are able to bind to blood vessels' inner linings and spread, or metastasize, throughout the body," she explained.

Using a mouse model, the team in 2008 showed that blocking the tumor protein podoplanin from binding with the platelet receptor protein CLEC-2 could prevent tumors from metastasizing to the lung.



Blood-filled disorganized lymphatic vessels and abnormal connection between blood and lymphatic vessels in Clec-2−/− embryos. Whole-mount triple fluorescence confocal microscopy of embryonic back skin was performed with antibodies to PECAM-1 (red), LYVE-1 (green), and TER-119 (blue) at E14.5 (A–I) and E17.5 (J–L). A–F, whereas blood vessels visualized by PECAM-1 staining appear unaffected in Clec-2−/− embryos, lymphatic vessels visualized by LYVE-1 staining are disorganized and distended in Clec-2−/− embryos. Lymphatic vessels are filled with TER-119+ erythrocytes (arrows) in Clec-2−/− embryos. G–L, abnormal connection sites (arrowheads) between blood and lymphatic vessels were detected in Clec-2−/− embryos. Scale bars = 100 μm.

FROM SNAKE VENOM TO PLATELETS TO TUMORS

The recent investigations by the team, published in the JBC online July 4, hinged on the generation and study of genetically engineered mouse embryos that lacked the platelet receptor protein CLEC-2. In the end, the experiments showed that CLEC-2 is not only necessary for blood clotting but also necessary for the development of a different type of vessel, specifically lymphatic vessels that carry fluid away from tissues and prevent swelling, or edema.

"During fetal development, the CLEC-2 deficiency disturbed the normal process of blood clotting and, in fact, the normal development and differentiation of blood and lymphatic vessels," says Masanori Hirashima, an associate professor at Kobe University. "They had disorganized and blood-filled lymphatic vessels and severe swelling."

Podoplanin, Hirashima explains, is also expressed on the surface of certain types of lymphatic cells and is known to play a role in the development of lymphatic vessels: "These findings suggest that the interaction between CLEC-2 and podoplanin in lymphatic vessels is necessary for the separation between blood vessels and lymphatic vessels."

It has been known that tumors generate blood vessels to promote their growth, and it's possible that the formation of lymphatic vessels also may contribute to the spread of cancer throughout the body, says Osamu Inoue, an assistant professor at the University of Yamanashi.

"We speculate that the interaction between the platelet's CLEC-2 protein and the podoplanin molecule in lymphatic cells plays an essential role in the creation of lymphatic vessels,

thereby facilitating tumor growth. If this is the case, a drug that blocks that interaction would prevent the spread of tumors through lymphatic vessels," Inoue said.

By being deemed a "Paper of the Week," the team's work is categorized in the top 1 percent of papers reviewed by the JBC editorial board in terms of significance and overall importance. Other contributors included Guo Ding, Satoshi Nishimura, Kazuya Hokamura, Koji Eto, Hirokazu Kashiwagi, Yoshiaki Tomiyama, Yutaka Yatomi and Kazuo Umemura.

Citation

Essential in Vivo Roles of the C-type Lectin Receptor CLEC-2. EMBRYONIC/NEONATAL LETHALITY OF CLEC-2-DEFICIENT MICE BY BLOOD/LYMPHATIC MISCONNECTIONS AND IMPAIRED THROMBUS FORMATION OF CLEC-2-DEFICIENT PLATELETS. Katsue Suzuki-Inouea, Osamu Inouea, Guo Ding, Satoshi Nishimura, Kazuya Hokamura, Koji Eto, Hirokazu Kashiwagi, Yoshiaki Tomiyama, Yutaka Yatomi, Kazuo Umemura, Yonchol Shin, Masanori Hirashima and Yukio Ozaki. August 6, 2010 The Journal of Biological Chemistry, 285, 24494-24507.

Involvement of the Snake Toxin Receptor CLEC-2, in Podoplanin-mediated Platelet Activation, by Cancer Cells. Katsue Suzuki-Inoue, Yukinari Kato, Osamu Inoue, Mika Kato Kaneko, Kazuhiko Mishima, Yutaka Yatomi, Yasuo Yamazaki, Hisashi Narimatsu and Yukio Ozaki. September 7, 2007 The Journal of Biological Chemistry, 282, 25993-26001.

More from these authors

Evidence That Integrin αIIbβ3-dependent Interaction of Mast Cells with Fibrinogen Exacerbates Chronic Inflammation. Toshihiko Oki, Koji Eto, Kumi Izawa, Yoshinori Yamanishi, Naoki Inagaki, Jon Frampton, Toshio Kitamura and Jiro Kitaura. November 6, 2009 The Journal of Biological Chemistry, 284, 31463-31472.

The Death Effector Domain-containing DEDD Supports S6K1 Activity via Preventing Cdk1-dependent Inhibitory Phosphorylation. Nobuya Kurabe, Satoko Arai, Akemi Nishijima, Naoto Kubota, Futoshi Suizu, Mayumi Mori, Jun Kurokawa, Miki Kondo-Miyazaki, Tomohiro Ide, Kouji Murakami, Katsuhisa Miyake, Kohjiro Ueki, Hisashi Koga, Yutaka Yatomi, Fumio Tashiro, Masayuki Noguchi, Takashi Kadowaki and Toru Miyazaki. February 20, 2009 The Journal of Biological Chemistry, 284, 5050-5055.

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