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Juntendo University Corporate Communications

Juntendo University research: Mutant chaperone molecule triggers cancer

(Tokyo, 27 June) Researchers at Juntendo University report in the journal Leukemia how mutants of the protein calreticulin lead to molecular mechanisms triggering myeloproliferative neoplasms, which can cause cancer. The findings may lead to the development of novel therapies for certain types of blood cancer.

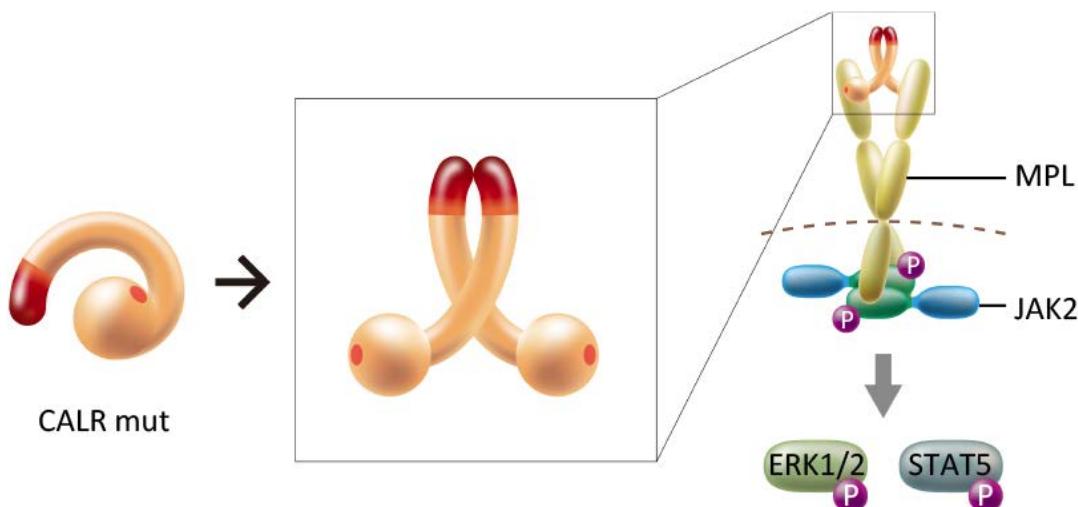


Fig 1.

The formation of multimers of mutant CALR is found to play a key role in the pathogenesis of CALR-mutant myeloproliferative neoplasms. The structural change induced by the homomultimerization makes MPL bind to the multimer complex, which in turn activates a particular signaling pathway. Taken from **Fig. 5 of the paper**.

Myeloproliferative neoplasms (MPNs) are a class of diseases in which the body produces too many blood cells or platelets (thrombocytes) in the bone marrow. MPNs can lead to cancers, including acute myeloid leukemia. It has been established that in some patients with MPNs, mutation of calreticulin (CALR) occurs; CALR is a protein capable of binding to other, misfolded proteins, triggering their degradation. Mutant CALR, in turn, is known to promote the activation of another protein, thrombopoietin receptor, associated with the development of cancers. Now, a team of researchers led by Marito Araki from Juntendo University has understood the mechanism behind the activation of thrombopoietin receptor through mutant CALR. Their findings have important consequences for developing new therapies against tumors induced by mutant CALR.

The researchers started from the hypothesis that the interaction between mutant CALRs mediates a particular association between two thrombopoietin receptor molecules (also known as MPL molecules, the abbreviation referring to myeloproliferative leukemia). This assumption was based on earlier work by the research team establishing that mutant CALR indeed activates MPL and a set of signaling molecules, one of which is known as JAK2, triggering cancer.

Marito Araki et al., *Blood* 127:1307-1316, (2016)

<http://www.bloodjournal.org/content/127/10/1307?ssq-checked=true>

A key observation made by the scientists is that mutant CALR molecules form homomultimeric complexes (clusters of identical proteins), whereas non-mutant ('wild-type') CALRs do not. Araki and colleagues could attribute the multimerization to particular chemical motifs in the mutant molecules. The researchers then confirmed that the formation of homomultimeric complexes indeed leads to the activation of MPL, by comparing with experiments performed on wild-type CALR.

Based on their observations, the scientists propose that the actual activation happens through homomultimeric mutant CALR interacting simultaneously with two MPL molecules, which in turn triggers the formation of JAK2 and subsequent biochemical signalling pathways during MPN development. The researchers conclude that their insights show that inhibiting the intermolecular interaction provides a way to prevent tumor formation, but point out that further studies are needed: "Although more detailed molecular and structural analyses are required to understand the mechanism behind MPL activation by mutant CALR proteins, our findings shed light on MPN pathogenesis and provide support for the development of novel therapeutic strategies against MPNs with mutant CALR proteins."

Background

Mutant calreticulin

Calreticulin (CALR) is a protein that binds Ca²⁺ ions, is encoded by the CALR gene, and is typically located in the cell's endoplasmic reticulum. Its function is to bind to misfolded proteins; such molecular 'chaperoning' enables disposing of the misfolded proteins.

Recently, Marito Araki from Juntendo University and colleagues have revealed that mutant CALR triggers a signalling pathway and the pathogenesis of myeloproliferative neoplasms (MPNs). Now Araki and colleagues have provided more insights into the molecular mechanisms at play: a particular clustering of the mutant CALR molecules, absent for non-mutant molecules, leads to interactions with thrombopoietin receptor molecules, which in turn triggers the pathogenesis of MPNs.

Reference

Marito Araki, Yinjie Yang, Misa Imai, Yoshihisa Mizukami, Yoshihiko Kihara, Yoshitaka Sunami, Nami Masubuchi, Yoko Edahiro, Yumi Hironaka, Satoshi Osaga, Akimichi Ohsaka & Norio Komatsu. "Homomultimerization of mutant calreticulin is a prerequisite for MPL2 binding and activation", *Leukemia* (2018), Published online 26 June 2018.

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Mission Statement

The mission of Juntendo University is to strive for advances in society through education, research, and healthcare, guided by the motto "Jin – I exist as you exist" and the principle of "Fudan Zenshin - Continuously Moving Forward". The spirit of "Jin", which is the ideal of all those who gather at Juntendo University, entails being kind and considerate of others. The principle of "Fudan Zenshin" conveys the belief of the founders that education and research activities will only flourish in an environment of free competition. Our academic environment enables us to educate outstanding students to become healthcare professionals patients can believe in, scientists capable of innovative discoveries and inventions, and global citizens ready to serve society.

About Juntendo

Juntendo was originally founded in 1838 as a Dutch School of Medicine at a time when Western medical education was not yet embedded as a normal part of Japanese society. With the creation of Juntendo, the founders hoped to create a place where people could come together with the shared goal of helping society through the powers of medical education and practices. Their aspirations led to the establishment of Juntendo Hospital, the first private hospital in Japan. Through the years the institution's experience and perspective as an institution of higher education and a place of clinical practice has enabled Juntendo University to play an integral role in the shaping of Japanese medical education and practices. Along the way the focus of the institution has also expanded, now consisting of four undergraduate programs and three graduate programs, the university specializes in the fields of health and sports science and nursing health care and sciences, as well as medicine. Today, Juntendo University continues to pursue innovative approaches to international level education and research with the goal of applying the results to society.