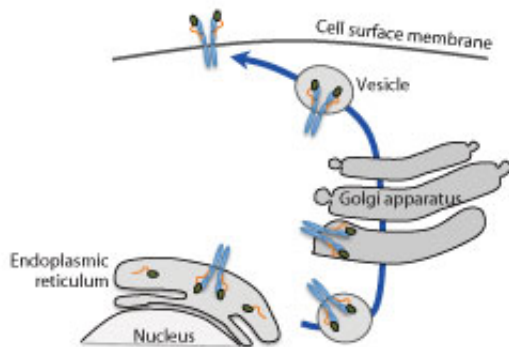


Mutant genes shown to activate a pathway that leads to overproduction of certain kinds of blood cells

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Mutant versions of the chaperone molecule calreticulin activate thrombopoietin receptor, which in turn activates the JAK2/STAT pathway. Credit: Christian Pecquet, LICR

Myeloproliferative neoplasms (MPNs) are blood cancers that cause the bone marrow to produce too many red or white blood cells, or platelets, leading to various complications. There is no known cure for most MPNs.

In 2013, scientists discovered a link between some forms of MPNs and mutations in a housekeeping gene known as CALR, which codes for calreticulin—a 'chaperone molecule' that promotes folding of proteins.

Stefan Constantinescu, of the Ludwig Institute for Cancer Research in Belgium, says the 2013 breakthrough was the first known example of a chaperone turning into an oncogenic activator of cell proliferation, but that molecular mechanisms underlying this connection were unknown.

"To learn how to treat MPNs, we first need to know what cell signaling or survival pathways are active in diseased cells," explains Choong Meng Ling of the A*STAR Experimental Therapeutics Centre.

Studies by Constantinescu, Ling and co-workers have implicated an abnormal interaction between CALR mutants and the receptor for the hormone thrombopoietin (MPL/TpoR), which regulates the production of blood platelets, in the process that drives some MPNs. The work involved an international collaboration with Robert Kralovics's group, in Vienna, Austria and William Vainchenker's group in Villejuif, France.

One of CALR's roles is the folding and processing of the thrombopoietin receptor before it is transported to the cell surface. The researchers discovered that the mutant CALRs incorrectly fold the thrombopoietin receptor into active receptors, both in the cell and at its surface. This persistently activates the JAK2/STAT pathway (see image), which the team had previously shown is activated in some MPNs.

The scientists then employed a drug combination study approach known as the Chou-Talalay method. "This approach allowed us to kill two birds with one stone: it helped us to simultaneously identify the cell survival pathways downstream of mutant CALRs and the drugs that could be used to block these pathways synergistically," says Choong.

The study has important treatment implications. "The JAK2 inhibitor, ruxolitinib, is the drug of choice for treatment of MPNs," explains Choong. "But, since JAK2 is a common signaling molecule involved in diverse functional pathways, blocking its activity would produce many side-effects. We found that MEK/ERK inhibitors could work synergistically with the JAK2 inhibitor (ruxolitinib), which would allow us to achieve the same therapeutic goal using lower quantities of the inhibitors, thus reducing side-effects."

The researchers intend to search for ways to prevent the abnormal interaction between CALR mutants and the thrombopoietin receptor. "Now we know how CALR mutants affect thrombopoietin receptor signaling, we can look for ways to block the interactions between CALR and the thrombopoietin receptor," notes Choong.

More information: I. Chachoua et al. Thrombopoietin receptor activation by myeloproliferative neoplasm associated calreticulin mutants, *Blood* (2015). DOI: [10.1182/blood-2015-11-681932](https://doi.org/10.1182/blood-2015-11-681932)

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