Study reveals how lenalidomide fights cancer and treats blood syndrome

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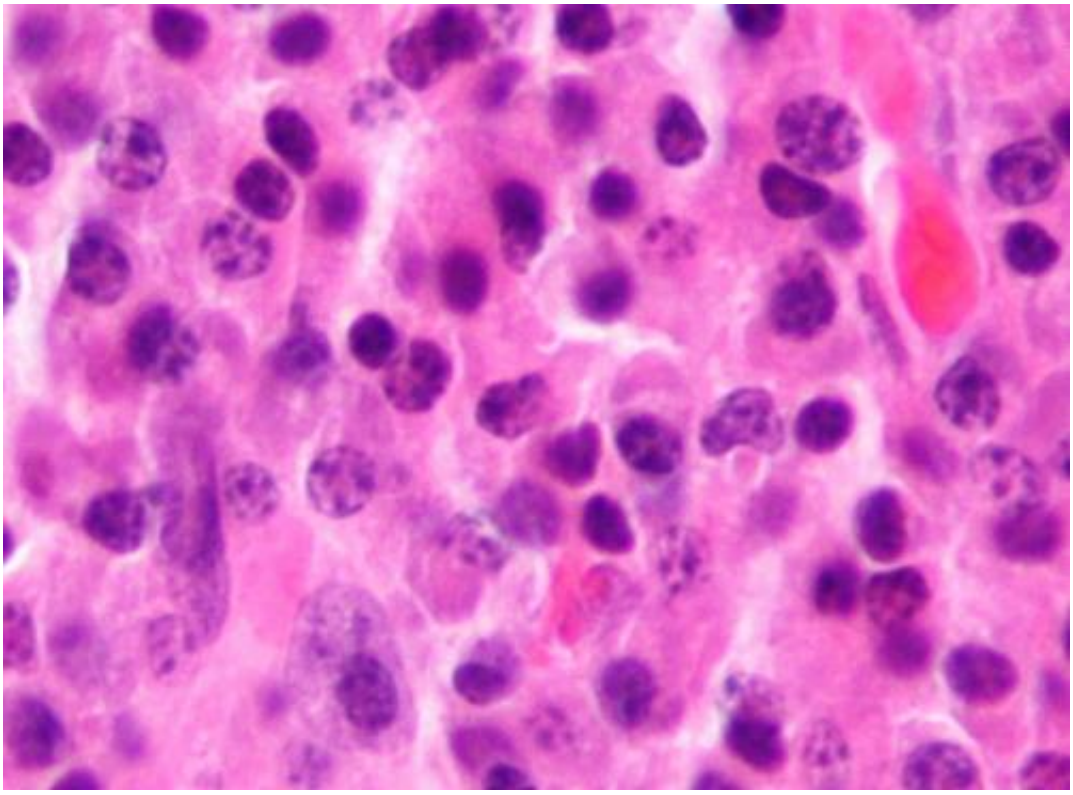

Micrograph of a plasmacytoma, the histologic correlate of multiple myeloma. H&E stain. Credit: Wikipedia/CC BY-SA 3.0

(Medical Xpress)—A team of researchers with member affiliations to institutions in the U.S. and Germany has uncovered the mechanism by which a cancer fighting drug reduces cancer cells and also helps patients with a blood disorder. They have published the details of their research

efforts in the journal *Nature*. Takumi Ito and Hiroshi Handa of Tokyo Medical University offer a News & Views piece on the work done by the researchers in the same journal edition.

Thalidomide is a well known drug because it was prescribed to pregnant women in the 50's and 60's to treat morning sickness—unfortunately, it was also found to cause serious birth defects in their children so it was subsequently banned. More recently, it has been found that derivatives of the drug, such as lenalidomide have other beneficial uses, in this case, for treating a blood cancer called multiple myeloma and for treating people with deletion-5q myelodysplastic syndrome (MDS). Up till now however, the means by which the drug helps such patients has been relatively sketchy.

MDS occurs in people who have a portion of their chromosome missing—causing some bone marrow cells to be missing which can lead to malignant cell growth—lenalidomide has been found to effectively treat the problem in roughly half of people with the syndrome. In this new effort, the researchers focused on the proteins that exist in myeloid cells, most specifically the enzyme casein kinase, to better understand what the drug causes to happen.

Prior research had found that in order for malignant cells to prosper, they needed certain proteins, such as $CRL4^{CRBN}$ E3. This new study revealed that the same is true for casein kinase, which appeared to be even more of a necessity. They also found that lenalidomide binds with the enzyme and winds up marking it for degradation—as it degrades, malignant cells essentially starve to death.

To further test the impact the drug has on cells, the researchers tested it with mice, and found the rodents were not impacted the same ways as humans—there was one slight difference in their genome, which could explain how thalidomide passed trials back in the 50's. That difference

allowed them to better see how casein kinase behaved under different scenarios.

More information: Lenalidomide induces ubiquitination and degradation of CK1α in del(5q) MDS, *Nature* (2015) DOI: 10.1038/nature14610

Abstract

Lenalidomide is a highly effective treatment for myelodysplastic syndrome (MDS) with deletion of chromosome 5q (del(5q)). Here, we demonstrate that lenalidomide induces the ubiquitination of casein kinase 1A1 (CK1α) by the E3 ubiquitin ligase CUL4–RBX1–DDB1–CRBN (known as CRL4CRBN), resulting in CK1α degradation. CK1α is encoded by a gene within the common deleted region for del(5q) MDS and haploinsufficient expression sensitizes cells to lenalidomide therapy, providing a mechanistic basis for the therapeutic window of lenalidomide in del(5q) MDS. We found that mouse cells are resistant to lenalidomide but that changing a single amino acid in mouse Crbn to the corresponding human residue enables lenalidomide-dependent degradation of CK1α. We further demonstrate that minor side chain modifications in thalidomide and a novel analogue, CC-122, can modulate the spectrum of substrates targeted by CRL4CRBN. These findings have implications for the clinical activity of lenalidomide and related compounds, and demonstrate the therapeutic potential of novel modulators of E3 ubiquitin ligases.