Insights from a rare genetic disease may help treat multiple myeloma

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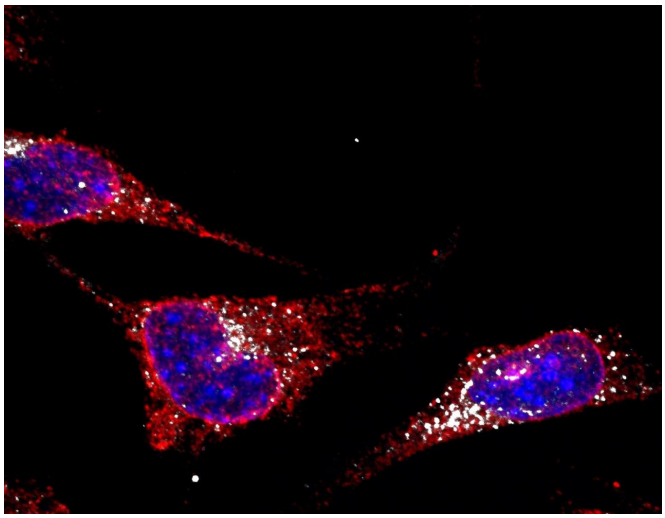

A protein called Nrf1 (shown in white in these mouse cells) can hamper promising drugs for blood cancers, but now researchers have found a possible workaround to shut Nrf1 down. Credit: The American Chemical Society

A new class of drugs for blood cancers such as leukemia and multiple myeloma is showing promise. But it is hobbled by a problem that also plagues other cancer drugs: targeted cells can develop resistance. Now scientists, reporting in *ACS Central Science*, have found that insights into a rare genetic disease known as NGLY1 deficiency could help scientists understand how that resistance works—and potentially how drugs can outsmart it.

A class of compounds called proteasome inhibitors that include bortezomib and carfilzomib—both approved by the U.S. Food and Drug Administration—have been effective at treating certain types of blood cancers. The drugs work by jamming some of cancer cells' machinery to induce cell death. But the drugs have been limited by cancer cells ability to development resistance, as well as the inhibitors inability to fight solid tumors effectively. Studies have suggested that resistance could be linked to a protein called Nrf1. When proteasome inhibitors go into action, Nrf1 is spurred into overdrive to restore the cells' normal activities and keep them alive. If researchers could figure out how to block Nrf1, they might be able to address the resistance problem. Carolyn Bertozzi and colleagues, through studying NGLY1 deficiency, a seemingly unrelated condition, may have hit upon an approach to do this.

The researchers were investigating how lacking the enzyme NGLY1 causes a host of debilitating symptoms. They found that NGLY1 is responsible for activating Nrf1, the protein that is suspected of weakening proteasome inhibitors' effectiveness against cancer. Further testing showed that dampening NGLY1 allowed a proteasome inhibitor to continue doing its work killing cancer cells without interference from Nrf1. This finding, the authors note, holds great promise for the development of combination therapeutics for blood cancers in the future.

More information: Frederick M. Tomlin et al. Inhibition of NGLY1 Inactivates the Transcription Factor Nrf1 and Potentiates Proteasome Inhibitor Cytotoxicity, *ACS Central Science* (2017). DOI: 10.1021/acscentsci.7b00224

Provided by American Chemical Society

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