Blocking cellular quality control mechanism gives cancer chemotherapy a boost

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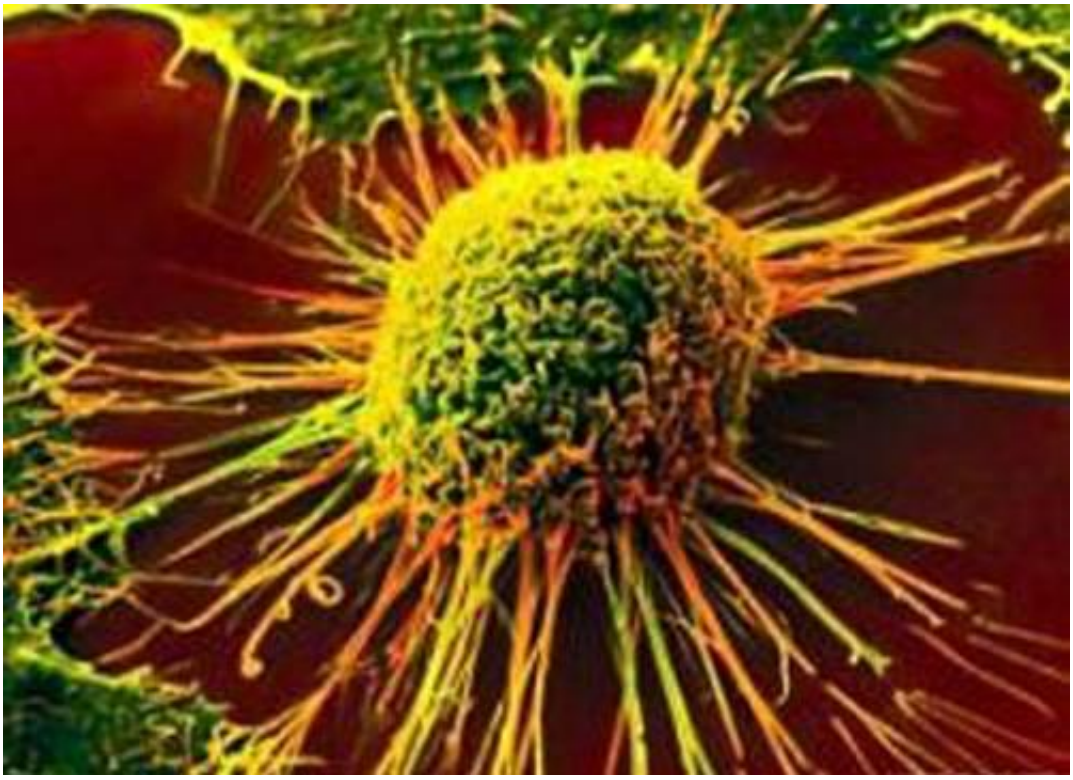

A University of Rochester team found a way to make chemotherapy more effective, by stopping a cellular quality-control mechanism, according to a study published today in *Nature Communications*.

The mechanism is known as NMD (nonsense-mediated mRNA decay),

and scientists found that exposing breast cancer cells to a molecule that inhibits NMD prior to treatment with doxorubicin, a drug used to treat leukemia, breast, bone, lung and other cancers, hastens cell death.

The research team, led by Lynne E. Maquat, Ph.D., director of the Center for RNA Biology at the University of Rochester, acknowledges that the work is in the early stages and a long way from being applied in humans. But, they believe their data provide insights that could lead to new treatment strategies for cancer patients in the future.

"The work from Lynne Maquat's lab is critical because it demonstrates the role for NMD in cancer cell survival and shows us how the NDM pathway might be connected to chemotherapy response," said Hartmut "Hucky" Land, Ph.D., director of research at the Wilmot Cancer Institute.

Maximilian Popp, study author and a post-doctoral fellow in Maquat's laboratory, describes NMD as the body's way of proof reading messenger RNA or mRNA, which takes genetic instructions from DNA and uses it to create proteins that carry out our body's functions. NMD flags and derails the production of unwanted proteins that can disrupt normal processes and initiate disease, like an inspector flags and removes faulty products from an assembly line.

In the last several years, Maquat's team and others have discovered that NMD is a more dynamic pathway than they thought; it also helps our cells adjust to changes in their environment and more rapidly respond to certain stimuli.

In the new study, Popp exposed breast cancer cells to doxorubicin alone and measured their viability following treatment. Next, he simultaneously treated cells with doxorubicin and a compound that inhibits NMD. Finally, he treated cells with the compound that inhibits

NMD, removed the compound after several hours, and then treated cells with doxorubicin.

The third treatment regimen - NMD-inhibiting compound followed by doxorubicin - was the most effective: cells were two-and-a-half times more likely to die compared to doxorubicin alone. Why this strategy works is not entirely clear, but Maquat and Popp speculate that blocking NMD primes cells for apoptosis (cell death) by boosting the activity of genes that respond to the cellular stress caused by chemotherapy. They note that blocking NMD alone isn't enough to kill breast cancer cells; they need the second stimulus - the doxorubicin - to tip the scale towards apoptosis.

"The idea of combining a drug that inhibits NMD with chemotherapy that is already used to treat a wide range of cancers has the potential to impact patient care," said Popp, a Howard Hughes Medical Institute fellow supported by the Damon Runyon Cancer Research Foundation. "We don't completely understand the detailed mechanisms by which NMD operates, so there is still a lot of work to do, but this study gives us a path forward."

"This research highlights the importance of basic research and its relevance to human disease and therapies," said Maquat, the J. Lowell Orbison Endowed Chair and Professor in the Department of Biochemistry and Biophysics at the University of Rochester School of Medicine and Dentistry. Her lab has spent more than 30 years working to understand the molecular mechanisms of NMD and in 2011 she was elected to the National Academy of Sciences for her research in the field. She is also a recipient of the 2015 Gairdner International Award, Canada's major international science prize for medical researchers whose work contributes significantly to improving the quality of human life.

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