Researcher lights the way to better drug delivery

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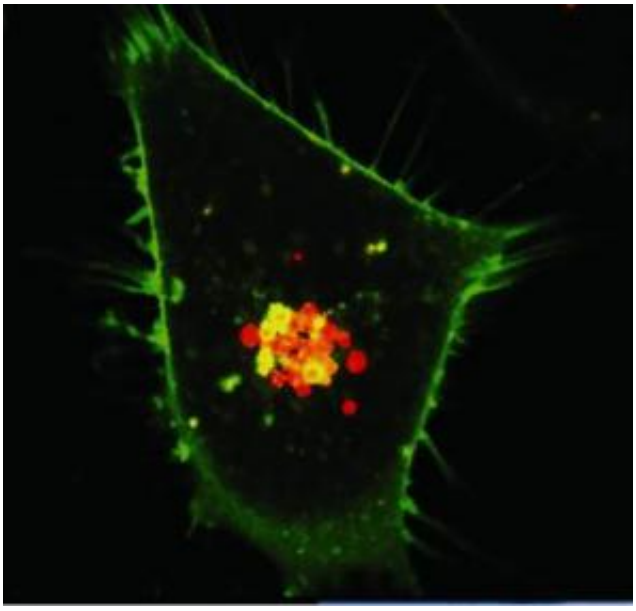

This image depicts drug release within a treated cancer cell. Once inside the cell, the drug turns from red to green as receptor endocytosis releases it from its folate-linker. By linking to the vitamin, toxic drugs are transported directly to the cancer cell and do not harm healthy cells. Credit: Image courtesy of Proceedings of the National Academy of Sciences

A Purdue University researcher has explained for the first time the details of how drugs are released within a cancer cell, improving the ability to deliver drugs to a specific target without affecting surrounding cells.

"As a general strategy, the indiscriminate delivery of drugs into every cell of the body for the treatment of a few specific pathologic cells, such as cancer cells, is a thing of the past," said Philip Low, the Ralph C. Corley Distinguished Professor of Chemistry. "Most new drugs under development will be targeted directly to the pathologic, disease-causing cells, and we have shed light on the details of one mechanism by which this is achieved."

An understanding of the cellular process that leads to the release of targeted drugs is a major advancement for the field, he said.

"This will help others interested in targeted drug therapy," said Low, who also is founder and chief science officer of Endocyte Inc., a Purdue Research Park-based company. "The knowledge applies not only to the treatment of cancer. The understanding of how to deliver and unload a cancer drug can be extrapolated to all sorts of other diseased cells. The uptake pathways are similar in cells involved in arthritis, multiple sclerosis, psoriasis and Crohn's disease."

Interest in how drugs are released after they enter their targeted cell led Low and his team to develop a color-coded method to visualize the cellular mechanisms. Jun Yang, a postdoctoral research associate in Low's research group, together with Ji-Xin Cheng, an assistant professor in the Department of Biomedical Engineering, and his graduate student Hongtao Cheng, developed this method using a technique called fluorescence resonance energy transfer imaging.

"The drug turns from red to green when it is released inside the cell, clearly illuminating the process," Yang said. "This is the first optical method to be developed to monitor this release. The main promise of this method is that it does not damage the cells being studied. Therefore, we are able to observe the process under true physiological conditions and watch it right as it is happening."

This research, funded by Endocyte, will be detailed in a paper in Tuesday's (Sept. 12) issue of the *Proceedings of the National Academy of Sciences* and is currently available online.

In targeted drug therapy, drugs are linked to molecules that are used in excess by pathologic cells, for example a required nutrient, in order to transport drugs directly to the targeted cells while avoiding significant delivery of the toxic drug to normal cells. A commonly used agent, referred to as a ligand, is the vitamin folic acid. Cancer cells need folic acid to grow and divide and, therefore, have developed abundant receptors to capture it. These receptors are largely absent in normal cells. This means folic acid, and the drug linked to it, are attracted to the pathologic cells and are harmless to healthy cells, Low said.

Low led the team that discovered this folate-targeted treatment method in 1991 and the receptor-targeted technology is proprietary to Endocyte.

"It is desirable to have the drug released from the ligand, folic acid, once the folate-linked complex enters the cell," Yang said. "This 'conditional drug release' is usually realized by attaching folate to the drug through a linker that falls apart inside the cell. There were several linkers in common use, but with mixed efficiency. In this study we undertook to interrogate the full details of this breakdown process."

Yang examined receptor endocytosis, the process by which cells absorb materials - such as a drug attached to folic acid - that have been captured at special sites, called receptors, on the cell surface. The compound is then broken down and processed, releasing the drug.

One of the key mechanisms of this breakdown is disulfide reduction, which involves the breaking of chemical bonds. It was thought that disulfide reduction relied on the movement of the material along microtubules, hollow tubelike structures, and fusion with special

digestive-enzyme containing compartments within the cell called lysosomes. However, the research showed that disulfide reduction occurred even when such components were removed from the process.

By inactivating different cellular components, Yang discovered which components are essential to the disulfide reduction process.

"It was surprising to learn that many other components of the cell, aside from those previously assumed to be responsible, were capable of releasing the drug from folic acid," Yang said. "This significantly increases the opportunity for the drug to be released. For instance, we used to believe it had to get to a specific location to be released, and now we know it can happen almost anywhere during endocytosis."

The mechanisms, locations and cellular components involved in the release of drugs within a cell had been under debate for several years, Low said.

"This is the definitive statement on how drugs are released within a cell," he said. "We will use this knowledge to develop better receptor-targeted drug therapies to treat cancer and other diseases."

Source: Purdue University