

Gene discovery links cancer cell 'recycling' system to potential new therapy

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University of Rochester scientists have discovered a gene with a critical link to pancreatic cancer, and further investigation in mice shows that by blocking the gene's most important function, researchers can slow the disease and extend survival.

Published online by *Cell Reports*, the finding offers a potential new route to intrude on a cancer that usually strikes quickly, has been stubbornly resistant to targeted therapies, and has a low survival rate. Most recent improvements in the treatment of [pancreatic cancer](#), in fact, are the result of using different combinations of older chemotherapy drugs. The research led by Hartmut "Hucky" Land, Ph.D., and Aram F. Hezel, M.D., of UR Medicine's James P. Wilmot Cancer Center, identifies a new target in the process of garbage recycling that occurs within the cancer cell called autophagy, which is critical to pancreatic [cancer progression](#) and growth.

Autophagy is derived from the Greek roots "auto" (self) and "phagein" (to eat), and is an intracellular digestive process that allows cells to survive under stress. During a cell's transformation from normal to malignant, autophagy speeds up to keep pace with rapid cellular changes and a tumor's quest to grow. The newly discovered PLAC-8 gene sustains the highly active recycling process, as it removes faulty proteins and organelles and degrades them into reusable building blocks during cancer progression.

"What makes this an exciting opportunity is that the gene we're studying

is critical to the cancer cell's machinery but it is not essential to the function of normal cells," said Land, chair of Biomedical Genetics at the University of Rochester School of Medicine and Dentistry and director of research at Wilmot. "By targeting these types of non-mutated genes that are highly specific to cancer, we are looking for more effective ways to intervene."

The *Cell Reports* study underlines Wilmot's overall unique approach to [cancer research](#). Rather than investigate single faulty genes linked to single subtypes of cancer, Rochester scientists have identified a larger network of approximately 100 non-mutated genes that cooperate and control the shared activities of many cancers. While investigating this larger gene network, Land and Hezel focused on PLAC-8.

Moreover, the team found that by inactivating PLAC-8 in mice and shutting down autophagy, they could significantly slow cancer's progression. The relevance of PLAC-8 may also extend to other tumors – lung, colon, and liver, for example—that share key genetic changes such as KRAS and p53 mutations that are present in the majority of pancreatic cancers. The breadth of these findings is an area of ongoing study in the Land and Hezel labs.

"PLAC-8 and its job within the cancer cell of accelerating recycling suggests new points of attack and what we all hope will be opportunities to identify and develop new treatments," said Hezel, vice chief of Wilmot's Division of Hematology and Oncology and a UR associate professor. "Our data showing PLAC 8's role in autophagy has great potential because while there are other drugs being evaluated to inhibit autophagy, not all of them target proteins specifically important to this process in tumors."

The role of autophagy in cancer is gaining attention. Clinical testing of new therapies is taking place at the same time that a new basic

understanding of this process and how it functions in pancreatic cancer is emerging.

The *New England Journal of Medicine* recently published a commentary on [autophagy](#)'s role in pancreatic cancer and the possible implications for clinical trials. And the Rochester paper offers explanations for some discrepancies seen in previous studies; *Cell Reports* invited Land and Hezel to write an online blog to accompany their article, describing their data in light of the scientific questions.

Provided by University of Rochester Medical Center

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