Q&A: Eileen White on Understanding Autophagy

Inhibiting cell-survival pathway may prove effective in attacking cancer

How can cancer cells, especially those stuck in the core of a tumor with limited access to oxygen, growth factors, and nutrients, survive the assaults of treatment? One response is that they turn to autophagy, chowing up old organelles and proteins, and creating what they need to survive, says Eileen White, PhD. The associate director for basic science at the Cancer Institute of New Jersey in New Brunswick, NJ, White studies how autophagy contributes to cancer metabolism and whether blocking it might make treatment more effective. She spoke with Cancer Discovery’s Suzanne Rose about her work.

What’s the normal role of autophagy?
Virtually all cells rely on autophagy. It’s a self-defense mechanism that prevents the accumulation of garbage such as damaged proteins and organelles that can be toxic to the cells. It also serves as a buffer during metabolic stress by recycling intracellular components. But cancer cells may need autophagy more than normal cells.

What’s the evidence of autophagy’s role in cancer?
We’ve blocked autophagy in cancer cells, thus sensitizing them to metabolic stress and starvation. When the stress is removed, in as little as 24 hours cells can reinstate normal metabolic behavior and begin proliferating again. We looked at tumors to find out if autophagy was occurring and, if so, when and where. We discovered that tumor cells in hypoxic regions had upregulated the autophagy pathway and required autophagy to survive the metabolic stress. We then looked at aggressive cancers and found that many had upregulated the autophagy pathway even when they were not starved. Moreover, these cancers were often dependent on autophagy for survival, suggesting that becoming a cancer cell may create stress.


Is there a way to target autophagy only in cancer cells?
That’s a key question. We’ve made a mouse model where we shut off autophagy. Then we can make a tumor in a mouse and see how the tumor is affected compared with normal tissues. That’s an important experiment that has not yet been done. We’re doing it now in non–small cell lung cancer in mice.

What happens after cancer therapies are administered?
With cytotoxic therapies, normal and cancerous cells activate autophagy to try to protect themselves and mitigate the damage. With targeted therapies, the pathways that are inhibited are the ones telling cells to grow. Those pathways also suppress autophagy. When you inhibit one of these growth-promoting pathways and autophagy is activated, that can help the cancer cell survive. The best thing to do will probably be to combine a targeted therapy with an autophagy-inhibition mechanism.

The combination would give the cancer a 1–2 punch?
That’s the hope. I don’t think that just inhibiting autophagy by itself will have a big enough effect.

What’s the status of autophagy inhibitors?
They’re in development. Many companies are interested in autophagy inhibitors, possibly to augment the activity of their targeted therapies.

A lot of people are using hydroxychloroquine as a shortcut. It interferes with lysosome function. Lysosomes are the garbage cans of the cell, and they degrade the cargo that’s delivered to them. The process of autophagy captures and delivers cargo—cellular trash, unfolded proteins, bad organelles—to the lysosome to be degraded. If you block lysosome function, you block the degradation of cargo in the autophagy pathway.

A bunch of clinical trials are using hydroxychloroquine in different cancers and in combination with different agents.

Overall, there is a lot of interest in targeting the metabolism of cancer cells, because metabolism is different in a cancer cell than it is in a normal cell. When you inhibit a metabolic pathway, one common response is the upregulation of autophagy as a compensatory mechanism. I think another use of autophagy inhibition will be to augment interference in metabolism.

Do you expect to find differences in autophagy from one cancer to another?
That’s what the evidence suggests: Autophagy is not doing one thing in all cancers. Many cancers have upregulated autophagy and depend upon it for survival, but not all of them. That raises the question: Why do some cancers, such as pancreatic cancer, as shown by Alec Kimmelman’s lab [at Dana-Farber Cancer Institute, Boston], have higher levels of autophagy and need it more than others? We don’t know.

How do you measure levels of autophagy?
In in vitro systems it’s easy because if you can transfect cells, you can introduce a fluorescent autophagy reporter, express it in transfected cells, and monitor flux in the autophagy pathway. But in human tissue, you can’t measure flux. All you can do is look at the number of autophagosomes [which hold proteins to be degraded]. The problem is that you can have a lot of autophagosomes because there’s a lot of autophagy, or because the autophagy pathway is blocked and they’ve accumulated. So there are big limitations in measuring autophagy in tissue.

One solution would be to have a panel of known autophagy substrates and use that as a secondary indication of whether or not the autophagy pathway is working.

Can you examine a patient’s tumor tissue, see if autophagy is playing a role, and then personalize treatment?
That’s the goal. The idea is that we’ll look at the number of autophagosomes and determine whether a patient will respond to autophagy inhibition.
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