



The kiss of death

Cellular suicide is a grave matter, motivating researchers to a thorough exploration of the genetic pathways involved. Of the three main means by which cells die, most in the scientific community are quite familiar with the genetically regulated apoptotic pathway (1). Autophagy, in which the cell literally digests itself, is likewise now also recognized as a form of regulated cell death (2). However, the third member of the cellular death triad, necrosis, has generally been considered merely an unregulated — accidental — form of cellular death. But there has been increasing evidence that cells may in fact choose, in a programmed genetic fashion, to take their lives via necrosis as well (3).

Now Zong et al. provide solid data making it clear that the idea that necrosis can be a regulated pathway is, indeed, “dead to rights” (4). Here, the researchers show a necrotic form of cellular death that is completely independent of the main apoptotic effectors but that has an absolute requirement for activation of the DNA repair protein poly(ADP-ribose) polymerase (PARP). Activation of PARP is not, however, sufficient for this suicidal pathway; for necrosis to be instigated, the cell must also rely primarily on glycolysis for energy production.

Craig Thompson, a University of Pennsylvania researcher and senior author of the article by Zong et al., additionally noted that this work may provide potential insight into some paradoxical aspects of how cancer therapies work and create novel directions for cancer therapy.

“During carcinogenesis there is a drive in the cancer cells to acquire mutations that render them resistant to apoptosis,” Thompson told the *JCI*. “Despite that, there has also been a lot of evidence, mostly by studying normal cells, that one way that cells deal with chemotherapeutic agents is by initiating apoptosis.”

Thus, the paradox is as follows: if cancer cells are more resistant to apoptosis than are normal cells, how is it that a purportedly apoptosis-inducing drug can be an effective anticancer agent? “That suggested to us that chemotherapy must have some mechanism to initiate cell death even in cells that were resistant to apoptosis,” Thompson said.

Testing several chemotherapeutic agents on laboratory-generated apoptosis-resistant cells, they found that alkylating agents,

one of the chemotherapeutic agents with historically the longest use, killed these cells just as effectively as normal cells and did it through this regulated necrotic pathway.

“This doesn’t give you a therapeutic window,” Thompson said, “but it explains how you can be apoptosis resistant and still be killed by an effective and widely used group of chemotherapeutic agents.”

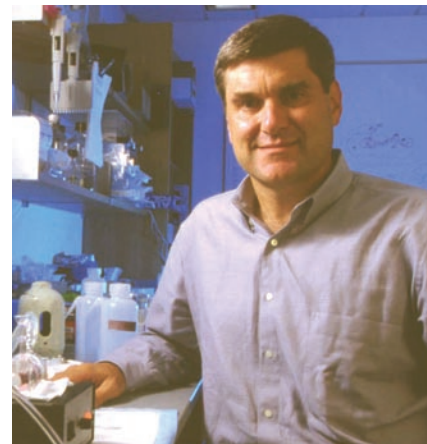
Thompson went on to describe an additional puzzle about how chemotherapy works. “We are always taught that chemotherapy kills by killing cells that are actively in the cell cycle. Except when you look in most human tumors, less than 10% of the cells are ever in the active cell cycle. Most of them are not proliferating.” As Thompson put it, “there is a big disconnect in how we imagine chemotherapy works.”

Early studies of the metabolism of cancer cells had indicated that cancer cells rely preferentially on glycolysis for ATP production, a phenomenon initially called the Warburg effect because it was first described by Nobel Laureate Otto Warburg.

In their studies, Thompson and colleagues found that when PARP was activated by the alkylating agent, it depleted the cytosolic pool of NAD within hours of drug treatment. NAD is a cofactor required for glycolysis. “The minute a cell that is dependent on glycolysis consumes all of its cytoplasmic NAD, it can no longer produce ATP,” Thompson stated, “and it has to die.” Thus, chemotherapy can kill even the tumor cells that are not actively cycling.

“There is a third big puzzle that has existed in the oncology literature,” Thompson said, going on to explain how in each round of chemotherapy, only a certain percentage of the cancer cells are killed. “If you carefully measure how many cells are killed in each round of chemotherapy then extrapolate that out for the four to six rounds of chemotherapy that most patients get that are cured, the chemotherapy isn’t sufficient to kill all the cancer cells.” Theoretically, approximately 10^5 – 10^6 cancer cells remain. The argument has been that the body’s own immune system deals with the remaining cells.

“When cells die apoptotically,” Thompson noted, however, “they specifically block immune responses. In contrast, necrotic cell death is very proinflammatory.” So when cancer cells die from necrosis in response to the chemotherapy, this would activate



Craig Thompson contemplates paradoxes in oncology research.

the innate immune response and possibly, if there are cancer-specific antigens, activate a response against the remaining cancer cells, providing a potential way for the immune system to actively deal with the remaining cancer cells.

This aspect has particularly intrigued Thompson. “One of the things we would like to think is that this form of cell death may be a particularly good adjuvant to initiating cancer immunovaccines, as we begin to understand and regulate the process.” He and his colleagues have set up a collaboration to investigate this possibility further.

All speculation aside, Thompson sums up the work. “What I think our paper helps to establish is that there are advantages to having cell deaths be necrotic. That it can protect the organism as whole. And that necrotic cell death can be regulated in a way to serve the purposes of the host.”

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