Versipelostatin: Unfolding an Unsweetened Death

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The classical basis for successful cancer chemotherapeutic regimens has been the induction of tumor shrinkage, or response, in animal models of cancer, usually mice bearing syngeneic or xenografted human tumors. Historically, agents that had activity in a high proportion of such models had a statistically increased likelihood of demonstrating value in Phase II clinical efficacy trials in humans (1). Based on such behavior, Phase III trials could be planned to assess utility in prolonging survival. The antiproliferative mechanisms of successful conventional cytotoxic compounds in most cases ultimately involve apoptosis, or programmed cell death, with concomitant decrease in clonogenic potential of cells from treated tumors.

During the past 15 years, a number of cellular pathways leading to tumor cell apoptosis have been defined. DNA-damaging agents appear capable of activating a range of pro-apoptotic cellular responses (2). For example, in cells with an intact p53 tumor suppressor gene, DNA damage is sensed by pathways initiated by DNA-dependent protein kinase, ataxia and telangiectasia–mutated (ATM) kinase, and ataxia telangiectasia–related (ATR) kinase, depending on the nature of the damage. The p53 protein is then phosphorylated and activated, whereupon it has several proapoptotic transcriptional effects, including increases in expression of PUMA and noxa. These proteins in turn modulate the mitochondrial threshold for release of the caspase activators APAF1 and cytochrome c, which are also regulated by the bcl2-related families of pro- and antiapoptotic proteins.

Quite independent of DNA damage, stimuli arising at the cell surface through the tumor necrosis factor receptor–related family of cell death receptors can also activate caspase pathways independently through the “extrinsic” pathway, which does not primarily involve mitochondrial damage to activate caspases (3). Recent studies have emphasized additional alternative pathways for induction of apoptosis. Ceramide, a natural by-product of sphingosine metabolism, can clearly modulate the mitochondrial set-point relating to release of proapoptotic stimuli and can act in concert with the mechanisms described above (4).

A distinct alternate, non–DNA damage pathway regulating apoptosis has recently been recognized to emanate from the endoplasmic reticulum (ER). This set of organelles is responsible for the normal ordered processing of newly synthesized proteins. A highly conserved system of chaperone molecules uses energy-consuming reactions to couple proper folding of the nascent client proteins to their synthesis. In addition, the ER is also where sugars are added in proper sequence to nascent glycoproteins and where these proteins fold properly for distribution to cytosolic or other organelle compartments. If ER structure or function is disrupted by improperly folded proteins, signals emerge that can induce gene expression to mitigate the adverse effects of the unfolded protein or, alternatively, can activate an apoptotic cellular response. This cassette of signaling activities constitutes the unfolded protein response (UPR).

Prominent mediators of the UPR include the transmembrane proteins ATF6 and IRE1α (5). The former, upon proteolytic cleavage, itself becomes an activator of UPR-induced gene expression, whereas the IRE1α, upon activation, becomes an active splicing factor, mediating the appearance of the XBP1 protein, a potent UPR transcription factor whose activity is also sensitive to proteolytic cleavage. Indeed, inhibition of the proteasome by the recently introduced clinical agent bortezomib potently induces the UPR in myeloma cells and may be one reason for the striking activity of this compound in certain cases of multiple myeloma (6). Another prominent stimulus of ER dysfunction is low ambient glucose concentration. This state of nutrient depletion indirectly affects numerous functions necessary for proper ER function, including the rate of protein synthesis itself and the rate of protein folding, as well as directly altering the attachment of normal sugar residues to newly formed “glycoproteins in waiting.”

Versipelostatin is a natural product, derived from a bacterium, that was initially recognized in a cell-based screen for agents that would modulate the activation of ER chaperones such as GRP78/Bip and GRP94 (7). Park and colleagues, in this issue of the Journal, report a new activity for versipelostatin (8). They demonstrate that versipelostatin can specifically inhibit the activation of the UPR in response to glucose deprivation but not in response to other ER-disrupting stimuli, such as the glycosylation inhibitor tunicamycin. The result of versipelostatin action is enhanced sensitivity to glucose deprivation, with enhanced tumor cell death after exposure to the drug in the glucose-deprived state and much more modest antiproliferative effects in the glucose-replete state. Importantly, the authors demonstrate antitumor activity on the part of versipelostatin both alone and in combination with cisplatin in mice bearing human stomach cancer xenografts.

This work is important because we need new ways of activating cell death pathways that are selective for the tumor as opposed to the host environment. Tumors frequently have hypoxic centers because of incomplete vascularity, with consequent increases in the expression of enzymes leading to enhanced glucose uptake, and reliance on glycolysis as a prominent energy source (9). This situation underlies the basis for utility of the 18F-deoxylucose positron emission tomography scan as a diagnostic test for the presence of tumor cells (10). Therefore, just as tumor cells in their native state are living on the edge with respect to their local oxygenation, they also live in a state of avid glucose hunger and are hence in a state of relative glucose depletion compared with cells of normal organs. Thus, there may be an intrinsic basis for the selective susceptibility of tumor cells to agents such as versipelostatin that disrupt their ability to deal with the consequences of glucose deprivation. Versipelostatin is therefore a “first in class” modulator of an...
important aspect of neoplastic pathophysiology: dysregulated tumor cell glucose response pathways.

The detailed molecular mechanism for versipelostatin action is not yet known. Further studies must elucidate its intracellular binding partners and how, precisely, it alters the cellular UPR pathway in response to glucose deprivation resulting in enhanced tumor cell death. Given the unique features of the signaling systems involved, with proteolytic activation and altered mRNA processing, it is possible that the story, when completely told, will convey novel mechanistic nuances. The work reported here by Park et al. (8) will point the way toward how next to proceed in these mechanistic studies.

The current findings also serve to emphasize the importance of so-called natural products in drug discovery, with versipelostatin possessing a unique structure crafted by a lowly soil bacterium with a skill that is clearly outperforming the vast majority of human chemists and supercomputer-assisted in silico drug designers and molecular structure dockers. The studies reported by Park and colleagues (8) forcefully illustrate the boundless capacity of nature to select unique stereochemistries that allow illumination of entirely new molecular mechanisms of medicinal importance. The U.S. National Cancer Institute (NCI) maintains a collection program for extracts from the plant, marine, and microbiological worlds for general use (http://dtp.nci.nih.gov) by investigators in drug discovery. Although not derived from the NCI collection of extracts, versipelostatin again demonstrates the value of applying such extracts to smart, biologically rigorous screens that allow novel molecular phenotypes to be discerned as drug leads from such collections. Such clinically useful agents as the taxanes, camptothecins, and rapamycins, among numerous other antiproliferative or immuno-modulatory agents, got their start as crude extracts with noteworthy cell biology–directed or biochemical activities.

We await with great interest a more broad characterization of the antitumor activity of versipelostatin. It may itself be capable of entry into later stage preclinical or even clinical testing. More likely, the elucidation of its detailed molecular mechanism will allow crafting of derivatives with improved pharmacologic properties, enhanced tolerability, or intrinsically better efficacy in modulating the cellular response to glucose deprivation. But versipelostatin itself can now be recognized as a chemical tool in chipping away at the enigma of how tumors can survive in their unique nutritional milieu, and it offers a real basis for integrating a knowledge of the molecular basis for that behavior into novel treatment strategies. These approaches would provoke tumor cell death for want of the glucose that the tumor craves, a most sweet prospect indeed!

REFERENCES