Discovery of a Small Molecule that Induces Rapid Apoptotic Cell Death through a Non-Classical Pathway

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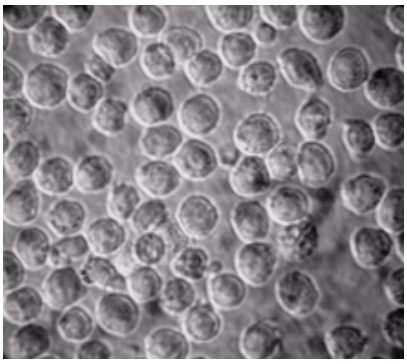
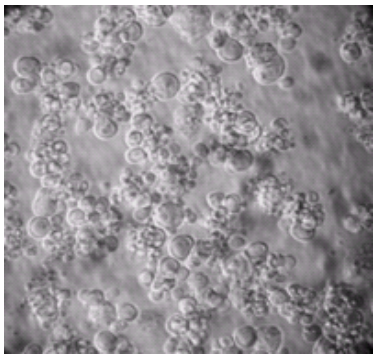
Apoptosis is a form of programmed cell death by which most clinically used anticancer agents kill cancer cells. Drugs that induce apoptosis are preferred in cancer treatment over drugs that induce other forms of non-programmed cell death (such as necrosis) because necrotic death often results in undesired inflammation. However, a drawback of apoptosis is that most anticancer agents require 6-48 hours to induce cell death. Although the field of apoptosis is over 40 years old and our knowledge of this pathway is significant, a compound that could induce apoptosis in a much more rapid manner may serve as an invaluable tool to uncover novel aspects of the apoptotic pathway and have important therapeutic consequences.

A small molecule, originally synthesized at the University of Illinois in 1960s, was discovered in a high throughput cell-based screen as a potent inducer of cell death in human leukemia HL-60 cells. Structure-activity-relationship studies identified the functional groups necessary for toxicity. Biological assays revealed that the compound has the unusual ability to fully activate the caspase-dependent apoptotic pathway within just 45 minutes of exposure. This is in contrast to the fastest classical apoptosis inducers which require at least 4-8 hours to achieve the same effect.

Further experiments revealed the compound induces apoptosis through a non-classical pathway in which the full length version of a cytosolic protein, Bid, rapidly translocates to the mitochondria, inducing cytochrome *c* release and subsequent caspase activation. In the current understanding of apoptosis however, cleavage of Bid to truncated Bid (tBid) is required to induce cytochrome *c* release. While the exact mechanism remains to be elucidated, experiments thus far have uncovered a novel role of a known apoptotic protein and demonstrated that this non-classical apoptosis pathway is significantly more rapid than the classical pathway typically induced by anticancer agents.



Untreated Cells



1 h Treated Cells