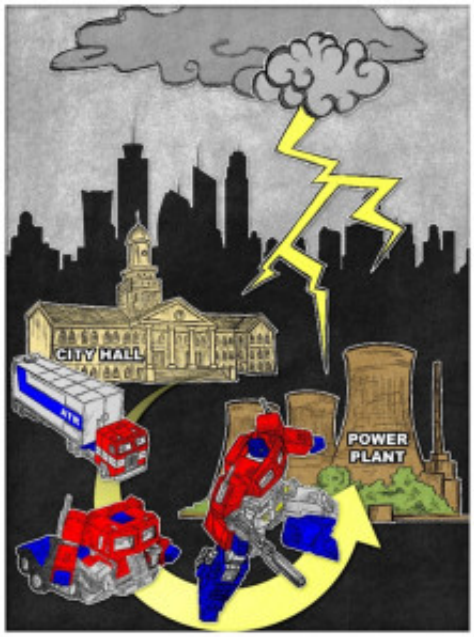
Getting time to decide about dying

Cells experience numerous challenges that jeopardize normal functions; many are routine physiologic fluctuations that require minor adaptations. However, some assaults disrupt cell metabolism so significantly that cell survival is at risk if major adjustments are not made to protect cellular integrity. Examples include gamma/ultraviolet irradiation and chemotherapeutic agents; these cause DNA damage and induce survival mechanisms called the DNA damage response (DDR). The general DDR effect is to switch from growth and cell division to a holding pattern where the damage is repaired, including stopping DNA replication and arresting the cell cycle and cell division. This arrest is critical since DNA damage must be repaired before replication can restart, thus preventing mutations in the damaged DNA which would be passed to progeny cells, perhaps leading to cancer.



An important sensor of DNA damage, especially for UV damage, is the protein ATR (*Ataxia telangiectasia* and Rad3-related). ATR passes the distress signal to downstream mediator and effector molecules by its ability to add phosphate to these proteins (a kinase activity). Essentially all reported functions of ATR occur in the nucleus, the cell's command center ("City Hall" in the figure) and an essential part of ATR's nuclear DDR function depends on ATRIP, another nuclear protein.

Hilton *et al.* describe a novel ATR function which occurs outside the nucleus and at the cell's mitochondria. They observed that UV irradiation releases nuclear ATR into the cytoplasm where a conformational change occurs due to a UV-induced transformation of ATR from the trans-isoform (ATR-L) to the cis-isoform (ATR-H).

The transformed ATR-H binds to mitochondria while the DDR tries to fix the damaged DNA to prevent cells from premature death (apoptosis). Mitochondria are the cell's "Power Plants", consuming oxygen, generating energy, and processing metabolites. Upsetting mitochondria can cause the release of death cascade protein cytochrome C into the cytosol, leading to cell death (apoptosis). This release requires tBid protein. ATR-H binds to tBid at mitochondria to sequester tBid, blocking cytochrome c release and cell death. The mitochondrial activity of ATR in form of ATR-H is independent of its activity in the nucleus in form of ATR-L, but the activities of the two different forms of ATR are coordinated during the DDR to preserve the cell integrity.

The net result of this cytoplasmic or mitochondrial ATR-H activity is to extend the period for the cell's 'do or die' decision, providing time for the DDR processes to repair the DNA for resumption of the normal cell cycle. These dual functions of ATR also allow for coordination of the nuclear DDR activities with the mitochondrial role in inducing apoptosis. If the damage is too severe for adequate DNA repair, the cells proceed to apoptotic cell death.

Publication

ATR Plays a Direct Antiapoptotic Role at Mitochondria, which Is Regulated by Prolyl Isomerase Pin1.
Hilton BA, Li Z, Musich PR, Wang H, Cartwright BM, Serrano M, Zhou XZ, Lu KP, Zou Y
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