

MITOCHONDRIA AND CANCER CELL DEATH



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The best way to treat cancer is to kill it. Indeed, most cancer therapies work by killing tumour cells, be it directly or indirectly. Nevertheless, combined issues of toxicity and resistance limit the effectiveness of anti-cancer therapies. To address these, our research centres on understanding how mitochondria regulate cancer cell death and inflammation, with the ultimate goal of improving cancer treatment.

Mitochondria, cell death and cancer

Apoptosis requires caspase protease activity, leading to widespread substrate cleavage and rapid cell death. During apoptosis, mitochondrial outer membrane permeabilisation (MOMP) occurs, a crucial event that is required for caspase activation. Following MOMP, mitochondrial intermembrane space proteins, such as cytochrome c, are released into the cytoplasm where they cause caspase activation and apoptosis. Given its key role in controlling cell survival, mitochondrial outer membrane integrity is highly regulated, largely through interactions between pro- and anti-apoptotic Bcl-2 proteins. Cancer cells often inhibit apoptosis by preventing MOMP, often through upregulation of anti-apoptotic Bcl-2 proteins. Importantly, this can be exploited therapeutically – newly developed anti-cancer therapeutics called BH3-mimetics target these apoptotic blocks.

Mitochondria drive immunogenic cell death

Irrespective of caspase activity, widespread MOMP commits a cell to die and is therefore a point-of-no-return. As long as a cancer cell dies, should we care how it dies? Our findings argue a resounding yes. We have found that under caspase-inhibited conditions following MOMP, cells still die through caspase-independent cell death (CICD) but produce a variety of pro-inflammatory cytokines; these can stimulate an immune response towards the dying cell. As such, unlike apoptosis, CICD can be considered an immunogenic form of cell death. Importantly, we have found that CICD can elicit anti-tumour immunity. Using an in vivo model that mimics partial therapeutic responses, we have found that CICD is much more effective than apoptosis at reducing tumour growth – often CICD led to complete regression. These beneficial effects are entirely dependent on

intact immunity, consistent with CICD being an immunogenic cell death.

Investigating how CICD could be immunogenic, we focused on the role of mitochondria. Interestingly, we find that, under caspase-inhibited conditions, mitochondrial permeabilisation leads to activation of the NF- κ B transcription factor pathway. This, in turn, is required for inflammatory signalling during CICD. Mechanistically, mitochondria activate NF- κ B by releasing proteins that downregulate cIAP1/2, resulting in NIK and NF- κ B activation. As such, while mitochondrial apoptosis is largely viewed as a non-inflammatory type of cell death, the central event that initiates it – MOMP – is in itself highly pro-inflammatory.

Inner membrane permeabilisation enables mtDNA release leading to cGAS-STING signalling

Similar to others, we have found that permeabilised mitochondria, by releasing mtDNA, can also activate cGAS/STING, triggering an interferon response. mtDNA resides in the mitochondrial matrix, therefore how can it activate cytosolic cGAS-STING signalling? We investigated this key question using high-resolution light microscopy. Unexpectedly, we find that during apoptosis, the mitochondrial innermembrane becomes permeabilised, enabling mtDNA release into the cytoplasm (Fig. 1). Applying live-cell imaging, we found that prior to rupture, the innermembrane is extruded into the cytoplasm via expanding BAX/BAK pores (Fig. 2). Our data demonstrate that – contrary to prevailing dogma – the mitochondrial inner membrane permeabilises during apoptosis.

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Figure 1

Mitochondria release DNA during cell death

U2OS cells were treated with the BH3-mimetic ABT-737 in the presence of caspase inhibitor qVD-OPH to engage cell death. Cells were stained for the mitochondrial innermembrane (red – anti-AIF) and mitochondrial DNA, mtDNA (blue – anti-DNA). Images were analysed for the presence of mtDNA within the mitochondria, denoted green or outside the mitochondria, denoted blue. Specifically during cell death (right lower) mtDNA is found to exit the mitochondria.

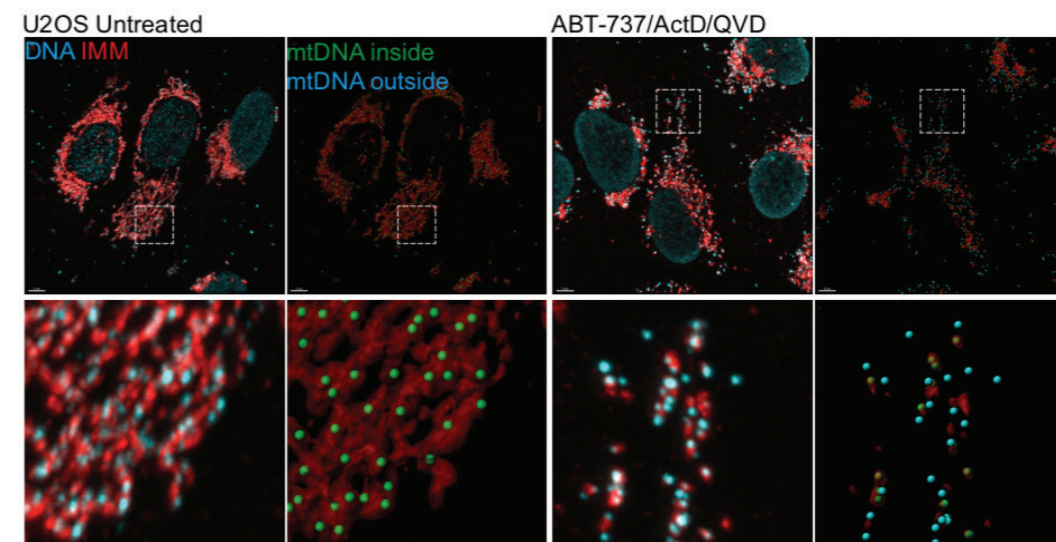


Figure 2

Innermembrane permeabilisation allows mtDNA dependent activation of cGAS-STING signaling. During mitochondrial apoptosis, following mitochondrial outer membrane permeabilisation (MOMP), pores in the outer membrane progressively widen. This allows extrusion of the mitochondrial inner membrane leading to mitochondrial inner membrane permeabilisation, mtDNA release and cGAS-STING activation. This underpins the immunogenicity of caspase independent cell death.

