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 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.

How do cells engage oncogenic sub-lethal apoptotic stress?

While apoptosis has potent anti-tumour activity, we have previously shown that sub-lethal apoptotic stress can trigger caspase-dependent DNA-damage having oncogenic effects. This occurs through limited MOMP in a few mitochondria – what we termed minority MOMP. Nonetheless why some mitochondria selectively permeabilised remained enigmatic. Mitochondrial fusion protects cells from sub-lethal apoptotic stress, whereas fission has the opposing effect. Moreover, we found that loss of mitochondrial function serves as an intrinsic priming signal, sensitising mitochondria to permeabilization.

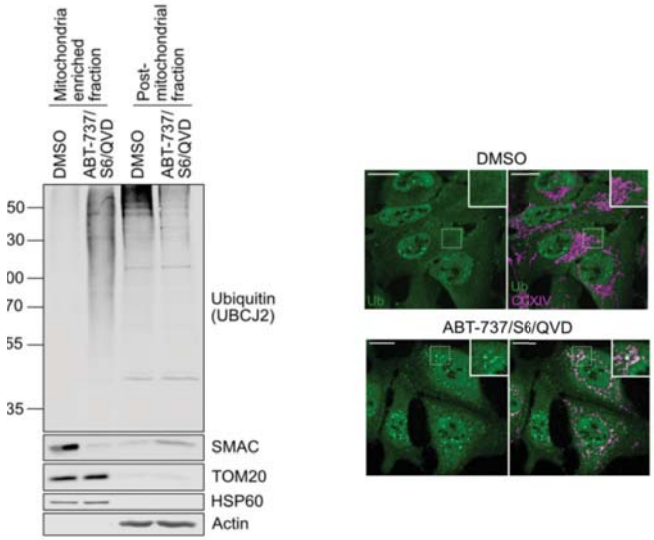

Figure 1. Mitochondria are ubiquitinated following outer membrane permeabilization
SVEC cells were treated to undergo mitochondrial apoptosis (ABT737/S6) and mitochondria were probed for ubiquitin by western blot (left) or imaging (right, ubiquitin: green, mitochondria: cyan). Following MOMP, extensive mitochondrial ubiquitination is observed.

By targeting mitochondrial dynamics and/or function these findings offer new strategies to both prevent oncogenic sub-lethal stress as well as enhance the tumour killing capacity of anti-cancer therapies.

Mitochondrial permeabilization promotes inflammation that engages anti-tumour immunity

Mitochondrial apoptosis is a silent form of cell death. Importantly, even in the absence of caspase activity, MOMP leads to cell death through progressive mitochondrial dysfunction. Our previous research has shown that such caspase-independent cell death (CICD) is immunogenic and can be harnessed to trigger anti-tumour immunity. Underpinning this immunogenicity is that permeabilised mitochondria activate myriad inflammatory pathways. We have investigated how MOMP engages inflammation. Our recent data shows that upon permeabilization mitochondria are extensively decorated with ubiquitin (Figure 1). Ubiquitination occurs in a promiscuous manner targeting many mitochondrial inner and outer membrane proteins. While traditionally considered a degradative post-translational modification, ubiquitination can also serve non-degradative signalling functions. Indeed, we find that mitochondrial ubiquitination serves to recruit the NF-κB adaptor molecule NEMO leading to activation of pro-inflammatory NF-κB signalling (Figure 2). Perhaps stemming from the bacterial ancestry of mitochondria, this process displays striking analogy to how our cells cope with intracellular bacteria, where invading bacteria are ubiquitinated leading to a protective NF-κB inflammatory response. We are currently investigating how mitochondrial-ubiquitination driven-inflammation contributes to the immunogenicity of tumour cell death.

Publications listed on page 128

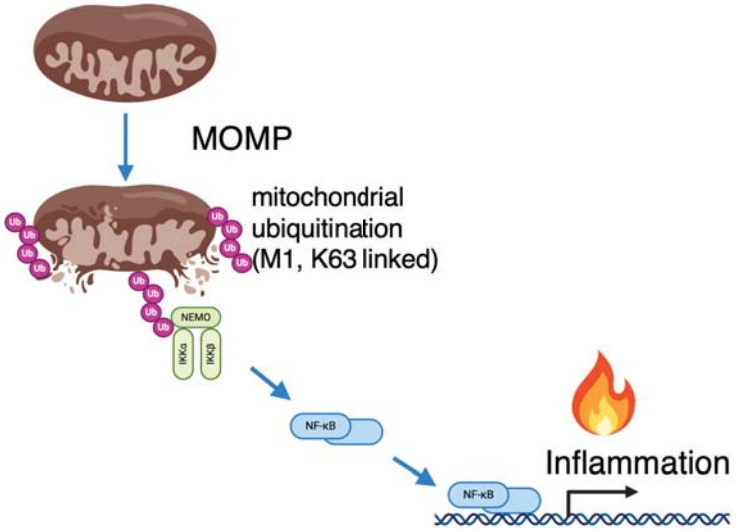

Figure 2. Mitochondrial ubiquitination drives inflammation following MOMP
Upon MOMP, mitochondria are extensively ubiquitinated. Ubiquitination serves to recruit the NF-κB adaptor molecule NEMO to mitochondria, promoting NF-κB driven-inflammation.