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.

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 could trigger caspase-dependent DNA-damage having oncogenic effects. This occured through limited MOMP in a few mitochondria – what we termed minority MOMP. Nonetheless, why some mitochondria selectively permeabilised remained enigmatic. Kai Cao and Joel Riley set out to address this question finding that mitochondrial dynamics and function regulated minority MOMP. Mitochondrial fusion protected cells from sub-lethal apoptotic stress, whereas fission had the opposing effect. Moreover, we found that loss of mitochondrial function served as an intrinsic priming signal, sensitising mitochondria to permeabilization. By targeting mitochondrial dynamics and/or function these findings offered new strategies to both prevent oncogenic sub-lethal stress as well as enhance the tumour killing capacity of anti-cancer therapies.

Targeting cell death to better treat glioblastoma

Glioblastoma is an extremely aggressive type of brain tumour with limited treatment options. Anna Koessinger, Cat Cloix and others investigated whether targeting anti-apoptotic BCL-2 proteins may be an effective way to treat glioblastoma. We found genetic inhibition or drug targeting of MCL-1 and BCL-xL with BH3-mimetics could effectively kill glioblastoma cells *in vitro* and improve survival in mouse models of glioblastoma. Importantly, alternating treatment with drugs targeting BCL-xL or MCL-1 maintained potency on tumour tissue without observable toxicity in healthy brain tissue. This paved the way for further investigation of BH3-mimetics in glioblastoma treatment.

Publications listed on page 114

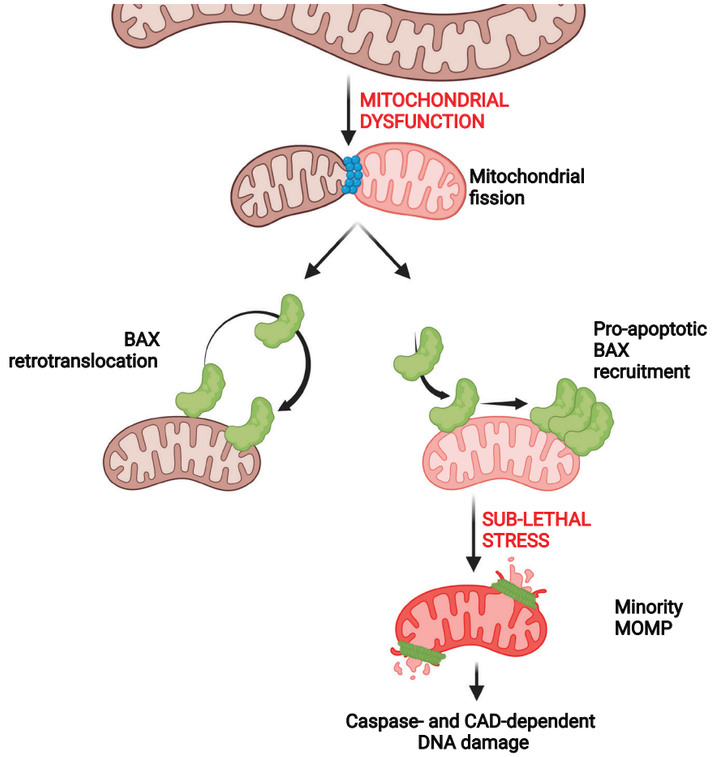

Figure 1
Mitochondrial function and dynamics regulate caspase dependent DNA-damage
Summary model: Mitochondrial dysfunction promotes mitochondrial fission and mitochondrial pro-apoptotic BAX. This facilitates mitochondrial outer membrane permeabilisation leading to caspase-dependent DNA-damage.

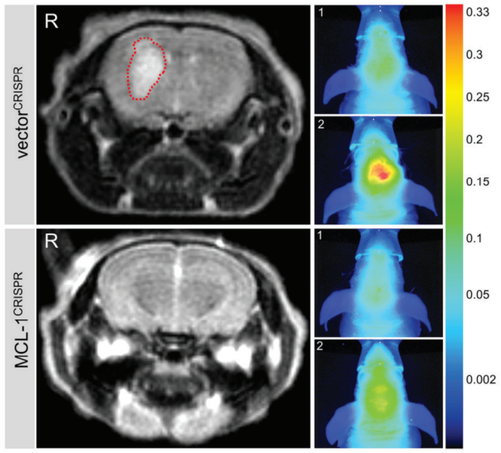

Figure 2
Anti-apoptotic MCL-1 is required for growth of glioblastoma
Glioblastoma cells expressing iRFP with or without anti-apoptotic MCL-1 (MCL-1 CRISPR) were assessed for their ability to grow in an orthotopic brain tumour model. MRI (left) or infrared imaging, demonstrated that only cells expressing MCL-1 led to tumour growth.