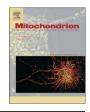
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Shedding light on molecular mechanisms and identity of mPTP



Mitochondrial ATP synthase displays features that are characteristic of the mPTP. Its activity is inhibited by the concurrent binding of the two mPTP inhibitors ADP and Mg^{2+} , whereas the mPTP inducer inorganic phosphate abolishes this block. A strategic component of the mPTP, cyclophilin D (CypD), interacts with the peripheral stalk of ATP 1synthase, reducing its catalytic activity. This activity is restored when cyclosporine A (a mPTP inhibitor) displaces CypD (Giorgio et al., 2009). Finally, Bcl-XI, which inhibits the mPTP, interacts with ATP synthase and promotes its activity (Alavian et al., 2011).

Moreover, it has been demonstrated that the c subunit of mitochondrial ATP synthase (the only transmembrane subunit of the ATP synthase with a gating capacity when oligomerized as c-ring (McGeoch and Palmer, 1999)) is a fundamental regulator of mPTP activity (Bonora et al., 2013, De Marchi et al., 2014). This idea was supported by a subsequent study describing currents that were sensitive to mPTP regulators and generated by isolated c subunits on artificial bilayers and in isolated mitochondria (Azarashvili et al., 2014).

The proposal that the c-ring forms the core of the mPTP is now supported by a recent work by Alavian et al. that demonstrates how the c-ring can generate a non-specific current ascribable to the mPTP (Alavian et al., 2014).

This fascinating study raises new questions concerning a potential mechanism that can transform an evolved enzymatic complex into a non-specific and detrimental channel. First, the precise mechanisms involved in forming this pore are unclear. Alavian et al. showed that rearrangement of the c-ring occurs during mitochondrial permeability transition. The authors suggested that through this mechanism, the c-ring diameter should increase, generating non-specific channels. It should be noted that in other species, the stoichiometry of the c-ring can vary widely, by as much as 15 monomers for one ring (Pogoryelov et al., 2007). Nevertheless, no MPT-like activity was observed in this study, suggesting that an increase in the c-ring diameter is not sufficient for inducing MPT-like activities.

Other intriguing questions are what mechanism could isolate the c-ring from the complex and what molecular factors are required for these events to occur. In the study by Alavian et al., they proposed that this event requires CypD activity, but they did not propose a molecular mechanism through which this activity could be transmitted to the c subunit.

Despite the many questions that remain unanswered, these findings add a new piece to the complicated puzzle of the mPTP structure.

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