

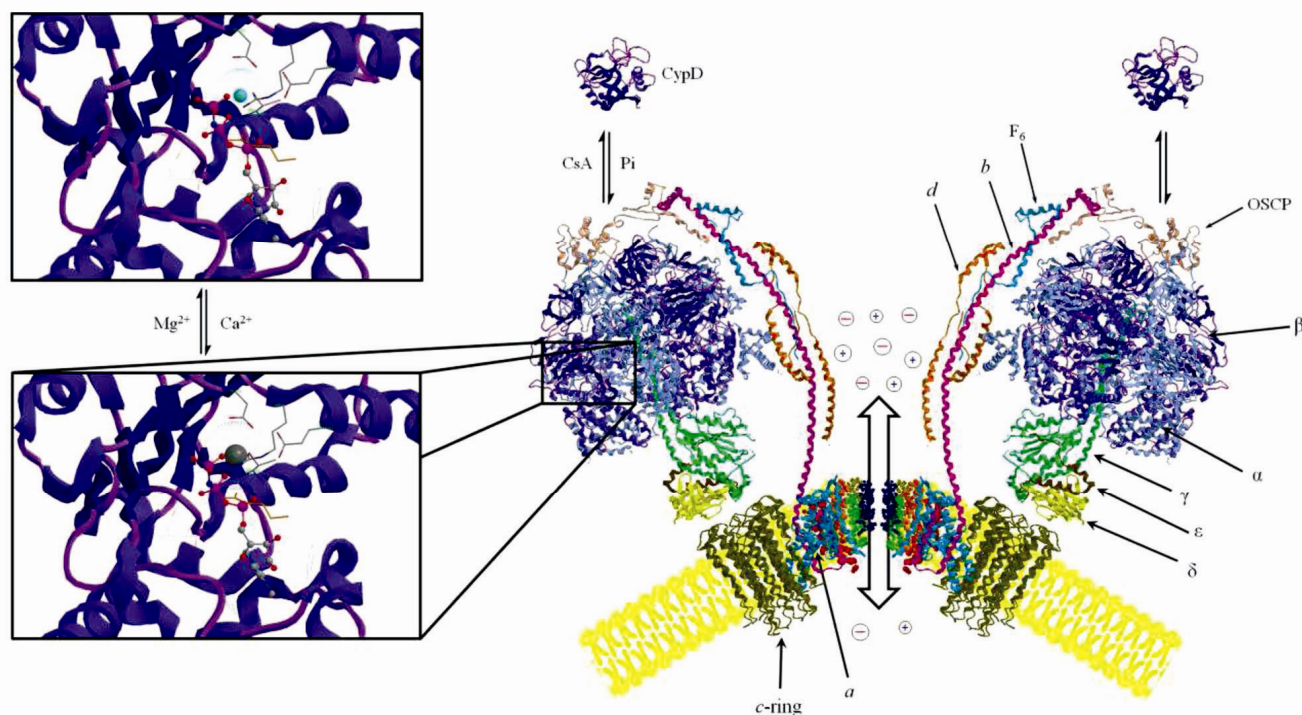
## The mitochondrial permeability transition and the connection between $F_1F_0$ -ATPase and calcium

Recently, He *et al.*<sup>1</sup> asserted that their new data 'definitively' disprove the *c*-ring of the mitochondrial  $F_1F_0$ -ATPase as molecular identity of the permeability transition pore (PTP). The authors' conclusion is also confirmed by the results of the calculated ionic conductance of *c*-ring lumen, which would be incompatible with the PTP channel properties<sup>2</sup>. However, in my opinion, the role of calcium-activated  $F_1F_0$ -ATPase as an alternative functioning mode of the  $F_1F_0$  complex should also be considered in events that trigger the PTP opening.

The PTP dramatically changes the permeability features of the mitochondrial membrane to ions and solutes, and it can lead to mitochondrial swelling and cell death. Recent advances assume that the  $F_1F_0$ -ATPase constitutes the mysterious PTP and two mechanisms for channel

formation within the  $F_1F_0$ -ATPase are accepted: the channel forms within the *c*-ring of enzyme<sup>3</sup>; the pore forms in  $F_1F_0$ -ATPase dimers<sup>4</sup>. In general, when the PTP opens, in response to high  $Ca^{2+}$  concentrations, the mitochondrial ATP is hydrolysed by the  $F_1F_0$  ATPase<sup>1,5</sup>. This event has been related to different pathways of cell death. Indeed, in physiopathological conditions, if the  $F_1F_0$ -ATP synthase works in reverse, it hydrolyses ATP and reenergizes the membrane<sup>6</sup>. Another event linked to the PTP opening is the inner mitochondrial membrane depolarization by dissipation of proton motive force ( $\Delta p$ ) (ref. 5). He *et al.*<sup>1</sup> argue that in cells the PTP is formed even in the absence of the *c*-ring; this structurally defective or vestigial  $F_1F_0$ -ATPase lacks the *a* and A6L subunits and the PTP opens independently of the enzyme

$H^+$  translocation pathways. Therefore, any or all the membrane subunits of the ATP synthase, *b*, *e*, *f* and *g*, could be involved in PTP formation. However, when the mitochondrial  $Ca^{2+}$  concentration increases,  $Ca^{2+}$  can replace the natural cofactor  $Mg^{2+}$  in the catalytic site of the  $F_1F_0$  complex<sup>7</sup>. Interestingly, the Ca-activated  $F_1F_0$ -ATPase supports ATP hydrolysis but not ATP synthesis and the  $Ca^{2+}$ -dependent ATP hydrolysis, which drives the  $H^+$  translocation<sup>8</sup>, does not build the  $\Delta p$ . Therefore, the inner mitochondria membrane is not polarized by the Ca-activated  $F_1F_0$ -ATPase, while the ATP pool is depleted by the enzyme hydrolytic activity. The  $Ca^{2+}$  binding to catalytic subunits of  $F_1F_0$ -ATPase has a major steric hindrance than  $Mg^{2+}$ , which changes the coordination geometry of the cofactor binding site from hexacoordinated



**Figure 1.** Ca-activated  $F_1F_0$ -ATPase dimer in permeability transition pore (PTP) formation. (Right) The subunits of the enzymes are depicted in ribbon representation (PDB ID code: 5ARA). OSCP subunit that has been identified the binding partner of cyclophilin D (CypD)<sup>4</sup>, with the subunits  $F_6$ , *d*, *b*, *a* form the integral stator of the enzyme. The factors promoting binding/release of interactors are Pi (inorganic phosphate) and CsA (cyclosporin A) respectively. The putative region of open PTP is designated by bidirectional arrow and the membrane subunits *e*, *f*, *g*, A6L, DAPIT (diabetes-associated protein in insulin sensitive tissues), 6.8 kDa proteolipid, whose structures have not been defined yet, are drawn as space-filling model. (Left) Boxes showing the ground-state structure of catalytic site of enzyme (PDB ID code: 2JDI) binding  $Mg^{2+}$  (above) or  $Ca^{2+}$  (below), which has a larger steric hindrance than  $Mg^{2+}$  in the  $\beta_{DP}$ -subunit.

octahedral complex up to form eight bonds<sup>9</sup>. As a result, Ca<sup>2+</sup> would cause a conformational change within the enzyme which would be transmitted to the membrane subunits of the dimeric F<sub>1</sub>F<sub>0</sub>-ATPase super-complexes. These conformational events may pull the stalk modifying the stalk-to-stalk distance between dimers<sup>10</sup> leading to PTP opening (Figure 1) and consequent mitochondrial swelling and burst.

To sum up, the vestigial F<sub>1</sub>F<sub>0</sub>-ATPase, lacking the *c*-ring, *a* subunit and A6L subunit, cannot translocate protons but allows PTP opening; at the same time the Ca-activated F<sub>1</sub>F<sub>0</sub>-ATPase hydrolyses ATP without building the  $\Delta p$ . Both ATP depletion and  $\Delta p$  dissipation are linked to the PTP opening.

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## MEETING REPORT

### Medical ethics\*

The symposium on medical ethics began with a talk on the history and evolution of ethics by A. T. K. Rau (Department of Paediatrics, M.S. Ramaiah Medical College, Bengaluru) who defined medical ethics as a self-regulatory system based on moral principles that apply values and judgements to the practice of medicine. He also mentioned that the pillars of modern medical ethics rest on autonomy, beneficence, non-maleficence, justice, dignity, truthfulness and honesty. Commenting upon the evolution of medical ethics during the pre-Hippocratic, Hippocratic and post-Hippocratic era, he revealed that the oath of Charaka was the first ever record of medical ethics as early as in 250 BC, which was followed in other parts of the world as well as in Mesopotamia, the Middle East and ancient Korea. The Hippocratic era saw the origin of the Hippocratic Oath, which shifted the focus from class-based medicine to selfless service of individual patients. In the post-Hippocratic era, the first book on medical ethics was written

by Ishaq ibn Ali al-Ruhawi in AD 671 and was followed by Thomas Percival's dictum on medical ethics in 1847, which was later modified by Joseph Fletcher. The Nuremberg code of conduct emerged in 1947 after the holocaust of the Second World War. The Hippocratic Oath and Nuremberg code of conduct were combined to form the Geneva declaration in 1948 which is now, after modification, the international code of medical ethics. Further refinement in the ethics came in the form of the Helsinki Declaration in 1964. Newer concepts of bio-ethics which handle ethical issues from the relatively recent aspects of medicine such as CT scans, MRIs, etc. have also come up. All of these have now been amalgamated to form a huge volume of work called medical ethics with the Institutional Review Board (IRB), Data and Safety Monitoring Board (DSMB), Drug Controller General of India (DCGI) and Indian Council of Medical Research (ICMR) acting as the monitors in India. The general principle of medical ethics is 'Do unto others as you would them do unto you'.

The keynote lecture on ethical issues in medical research was delivered by Soumya Swaminathan (ICMR and Department of Health Research, Govern-

ment of India). She began her address indicating that good and high-quality research is the key for India to be at the cutting edge of any endeavour. She also stressed the need to introduce research methods in the UG and PG medical curriculum and pointed out that ICMR could convince the Medical Council of India (MCI) to introduce research methods into the curriculum for furthering research and also interpreting information correctly in medical publications. She mentioned that ICMR also sponsors various research schemes for medical students.

Soumya talked about the formation of research clusters to facilitate medical research and gave the example of the Indian Statistical Institute, New Delhi, and All India Institute of Medical Sciences, New Delhi, which came together to form a scientific cluster to conduct research. She also mentioned Bengaluru's strength in engineering and technology, computational engineering, bioinformatics and genomics, and indicated that organizations such as the Indian Institute of Science, National Institute of Mental Health and Neurosciences, etc. must come together to form such a cluster.

She also touched upon the need to have registries in medical research and

\*A report on the one-day symposium on Medical Ethics conducted at the M.S. Ramaiah Medical College, Bengaluru, on 9 September 2017.