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# F-ATP Synthase Inhibitory Factor 1 in Regulation of Mitochondrial Permeability Transition Pore and Metabolic Reprogramming

**Lishu Guo**[1,2,*]

[1]Center for Mitochondrial Genetics and Health, Greater Bay Area Institute of Precision Medicine (Guangzhou), Fudan University, Nansha District, Guangzhou 511400, China

[2]Tongji University Cancer Center, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai 200092, China

[*]Correspondence should be addressed to Lishu Guo, guolishu@tongji.edu.cn; guolsh15@gmail.com

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## Abstract

Mitochondrial permeability transition pore (PTP) plays an important role in mitochondrial physiology and cell fate. Emerging studies highlight PTP forms from F-ATP synthase, but whether F-ATP synthase inhibitory factor 1 (IF1) regulates the activity of PTP is basically unknown. We have recently demonstrated that IF1 interacts with p53-CyPD complex and promotes opening of the PTP, and IF1 is necessary for the formation of p53-CyPD complex. IF1, a natural inhibitor of F-ATP synthase, acts as a main driver of metabolic switch to a Warburg phenotype. In this Commentary, we intend to discuss that the PTP may act as an alternative mechanism through which IF1 regulates metabolic reprogramming. The PTP participates in physiological $Ca^{2+}$/ROS homeostasis and cell fate depending on the open state. The PTP-regulatory role of IF1 provides a clue that IF1 participates in metabolic plasticity probably involving modulation of PTP activity.

**Keywords:** Mitochondria, F-ATP synthase inhibitory factor 1, Permeability transition, Metabolic reprogramming, Cyclophilin D, ROS, p53, Transcription factors

## F-ATP Synthase Inhibitory Factor 1 Regulates the Permeability Transition Pore

Mitochondrial permeability transition is a $Ca^{2+}$-dependent increase of the inner membrane permeability mediated by the permeability transition pore (PTP) [1]. The molecular nature of PTP is a century mystery that remains contentious [2]. In the past decade, overwhelming evidences highlight that F-ATP synthase is a key component of PTP [3-14]. Cyclophilin D (CyPD) acts as the receptor for cyclosporin A (CsA), which is a well-known PTP inhibitor [15-19]. The binding of CyPD to PTP favors opening of the pore, and mitochondria devoid of CyPD or in presence of CsA become resistant to PTP inducers [19-21]. CyPD associates with F-ATP synthase through the lateral stalk of the complex including the oligomycin sensitivity conferral protein (OSCP) [4,22]. The most recent working model of PTP is that the conformational change upon $Ca^{2+}$ binding to catalytic core is transmitted to subunit e and c-ring through subunits b and g via OSCP [1,7,13,14,23-27].

The p53 tumor suppressor, a well-known transcription factor induced by DNA damage and oxidative stress, is termed as the guardian of the genome [28]. p53 regulates a variety of key processes such as cell cycle arrest, DNA repair, apoptosis, senescence, and metabolism [29]. p53, a central stress sensor to multiple insults, is translocated to mitochondria in response to oxidative stress [30]. p53 protein can promote mitochondrial membrane permeabilization by direct activation of Bax and induce apoptosis [31,32]. Mitochondrial matrix p53 interacts with OSCP subunit and promotes the assembly of F-ATP synthase [33]. The PTP-regulatory activity of p53 in response to oxidative stress is CyPD dependent, and a robust p53-CypD complex formation triggers PTP opening during necrosis [30].

F-ATP synthase inhibitory factor 1 (IF1) is a regulatory subunit of F-ATP synthase, and the binding of IF1 to the enzyme depends on the matrix pH [34-36]. IF1 dimerizes at acidic pH where it is active and forms tetramer at alkaline pH where its inhibitory region is masked [37]. The active IF1 stabilizes the dimers of F-ATP synthase through $F_1$-$F_1$ bridging [38]. Overexpression of IF1 promotes the dimerization of F-ATP synthase and increases the density of mitochondrial cristae [39,40]. We have recently reported that IF1 regulates the PTP via interaction with the p53-CyPD complex [41]. Overexpression of IF1 activated caspase 3 and sensitized the pore to $Ca^{2+}$, which was suppressed by CsA, while disruption of IF1 inhibited PTP opening and prevented cell death induced by oxidative stress [41]. The interaction of p53 with OSCP subunit via p53-CypD axis plays an important role in its tumor suppression activity, and p53-CypD complex is essential for opening of the PTP under oxidative stress [30,33]. The inducing effect of IF1 overexpression on PTP was abrogated by ablation of CyPD, and IF1 could interact with p53-CyPD complex, suggesting that IF1 facilitated PTP opening via p53-CyPD [41]. IF1 binding to p53-CyPD complex may cause a conformational change that transmitted to the inner membrane via OSCP subunit and eventually PTP formation [41]. However, the interaction between IF1 and p53-CyPD complex is direct or indirect and how they bind to each other await further studies.

## F-ATP Synthase Inhibitory Factor 1 Regulates Metabolic Reprogramming

Mitochondria, known as "powerhouses of the cell", generate ATP to drive energetically dynamical life processes. Mitochondrial dysfunction results in the decline of the mitochondrial membrane potential (Δψm), such as limitation of substrate or oxygen availability, impaired oxidative phosphorylation (OXPHOS), the activation of uncoupling proteins, or a leak of protons into the matrix through the PTP [42]. The underlying mechanism of Warburg effect is proposed to be impaired mitochondria, which forces metabolic reprogramming towards aerobic glycolysis [43]. Long-lasting openings of the PTP cause rupture of the outer membrane, mitochondrial depolarization, and loss of ATP production [44]. Depending on the open state, PTP is involved in metabolic plasticity, reprogramming and cell death [43].

The compromised mitochondrial function and the decline of Δψm lead to the reverse of F-ATP synthase, hydrolyzing ATP to pump protons out from the matrix [42]. In presence of proton motive force, the bound IF1 releases from F-ATP synthase and ATP synthesis recover, thus, IF1 plays a role in preventing futile ATP hydrolysis [45]. IF1 is upregulated in a variety of carcinomas and acts as a main driver of metabolic switch to a Warburg phenotype [46]. IF1 binding to p53-CyPD complex promotes opening of the PTP, and this finding may provide an alternative mechanism through which IF1 regulates metabolic reprogramming [41]. The relative IF1 expression level to F-ATP synthase varies between tissues and cell types, which may contribute to heterogeneous metabolic phenotypes of tumors [39,43]. Therefore, to elucidate the factors that dictate IF1 expression in different cell types or tissues is a critical issue. The expression of F-ATP synthase is regulated at both the transcriptional and post-transcriptional levels [47-49]. Our unpublished data suggested that the interaction of IF1 with transcription factors c-Myc and PGC1α might be involved in IF1-regulatory metabolic reprogramming. However, whether c-Myc and PGC1α could regulate IF1 expression awaits further investigation.

## Role of the Permeability Transition Pore in Metabolic Reprogramming

Metabolic plasticity and reprogramming allow cancer cells to cope with different environments and treatments, increasing adaptability and developing chemoresistance [43]. ROS is critical to promote the tumor phenotype by regulation of oncogenic signaling and cellular metabolism, and metabolic deregulations lead to drug resistance [50]. Cytosolic $Ca^{2+}$ activates several $Ca^{2+}$-binding proteins that directly regulate many enzymes, transportome function, and gene expression [51]. Mitochondrial $Ca^{2+}$ modulates mitochondrial energy machinery by activation of mitochondrial dehydrogenase enzymes and regulation of ETC function [51]. $Ca^{2+}$ and ROS mutually influence each other, $Ca^{2+}$ signaling is crucial for the generation of ROS while ROS regulate the activity of $Ca^{2+}$ channels and transporters [52]. Transient opening of the PTP contributes to physiological $Ca^{2+}$ and ROS homeostasis, indicating the role of PTP in regulation of metabolic reprogramming [43]. The discovery that the PTP forms from F-ATP synthase and the signaling pathways affecting its transition from an energy-conserving to an energy-dissipating device provide new therapeutic perspectives for carcinomas [53].

IF1-mediated inhibition of F-ATP synthase enhances the production of mitochondrial ROS [54]. IF1 is upregulated in some phenotypes of cancer resulting in an increase of ROS level, which activates pro-survival pathways and triggers proliferative response [40]. IF1 overexpression favors opening of the PTP involving in its interaction with p53-CyPD complex [41]. The production of ROS induced by IF1 overexpression further enhances the activity of PTP. In response to metabolic stress, p53 is activated to regulate metabolic pathways and to promote cell survival [55]. Mitochondrial ROS has been found to be an important component of the stress-induced activation of p53 [55]. After activation, p53 translocation to mitochondria may promote the flickering activity of PTP and contribute to metabolic reprogramming [41,43].

The peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) synchronizes the mitochondrial and nuclear genomes and coordinates mitochondrial

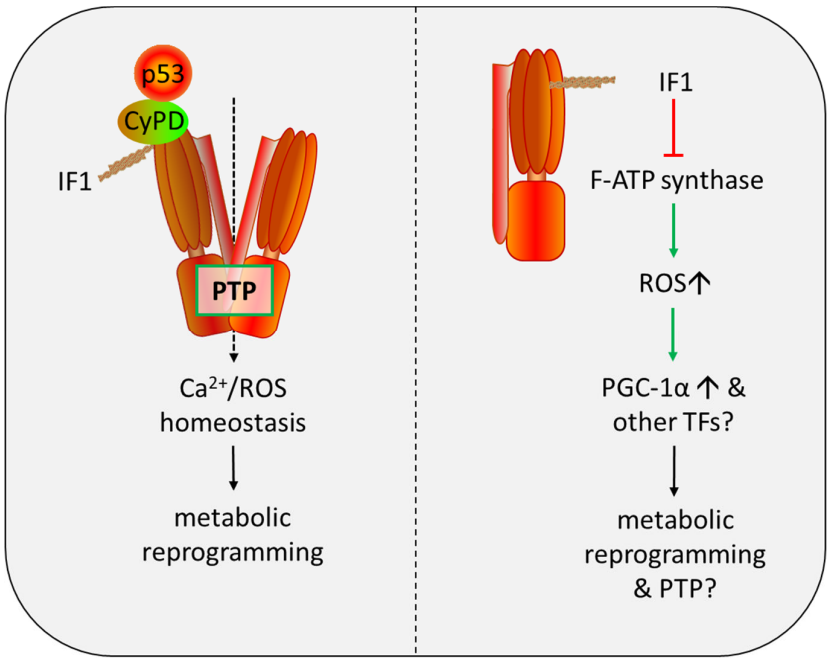


**Figure 1.** Role of IF1 in regulation of the PTP and metabolic reprogramming. IF1: F-ATP Synthase Inhibitory Factor 1; PTP: mitochondrial permeability transition pore; CyPD: Cyclophilin D; ROS: reactive oxygen species; TFs: transcription factors.

biogenesis [56,57]. Activation of PGC1α promotes OXPHOS in a transcription-dependent manner [58]. PGC1α plays a crucial role in regulating metabolic balance and chemoresistance, contributing to cancer progression [59]. The MYC/PGC1α balance acts as the main determinant for metabolic phenotype and plasticity in resistant cancer stem cells [60]. PGC1α can be translocated to mitochondria [61] and its binding to mitochondrial p53 regulates p53 transactivation of metabolic genes [62]. PGC-1α expression is induced by ROS, which in turn regulates mitochondrial biogenesis and activity [63]. PGC-1α is also co-induced with several key ROS-detoxifying enzymes under oxidative stress and acts as a broad and powerful regulator of ROS metabolism [64]. Whether PGC-1α regulates PTP activity and its role in metabolic reprogramming await further investigations.

## Conclusions and Perspectives

We have recently reported that IF1 interacts with p53-CyPD complex and facilitates opening of the PTP, and IF1 is required for the formation of p53-CyPD complex. We propose that IF1 binding to p53-CyPD complex induces a conformational change transmitted to the inner membrane subunits via OSCP subunit and eventually PTP formation. As an intrinsic inhibitor of F-ATP synthase, IF1 has been well characterized to be a main driver of metabolic switch to a Warburg phenotype. The PTP-regulatory activity of IF1 provides a clue that IF1 may participate in maintenance of $Ca^{2+}$/ROS homeostasis by regulating PTP opening, contributing to metabolic reprogramming (**Figure 1**). IF1-mediated inhibition of F-ATP synthase enhances the production of mitochondrial ROS, and ROS mediates the expressions of oncogenes and transcription factors like MYC/PGC1α mediating metabolic plasticity (**Figure 1**). The function of IF1 extends beyond that envisaged in literature, and we still have a great deal to learn about this fascinating little protein.

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## Conflicts of Interest

The author declares no conflict of interest.

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