



**HAL**  
open science

**The ATPase Inhibitory Factor 1 (IF1) regulates the expression of the mitochondrial Ca<sup>2+</sup> uniporter (MCU) via the AMPK/CREB pathway**

Danilo Faccenda, Giulia Gorini, Adam Jones, Claire Thornton, Alessandra Baracca, Giancarlo Solaini, Michelangelo Campanella

► **To cite this version:**

Danilo Faccenda, Giulia Gorini, Adam Jones, Claire Thornton, Alessandra Baracca, et al.. The ATPase Inhibitory Factor 1 (IF1) regulates the expression of the mitochondrial Ca<sup>2+</sup> uniporter (MCU) via the AMPK/CREB pathway. *Biochimica et Biophysica Acta - Molecular Cell Research*, 2021, 1868, 10.1016/j.bbamcr.2020.118860 . hal-04805761

**HAL Id: hal-04805761**

**<https://hal.science/hal-04805761v1>**

Submitted on 26 Nov 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



## BBA research letter

## The ATPase Inhibitory Factor 1 (IF<sub>1</sub>) regulates the expression of the mitochondrial Ca<sup>2+</sup> uniporter (MCU) via the AMPK/CREB pathway



Danilo Faccenda<sup>a</sup>, Giulia Gorini<sup>b</sup>, Adam Jones<sup>a,c</sup>, Claire Thornton<sup>a,c</sup>, Alessandra Baracca<sup>b</sup>, Giancarlo Solaini<sup>b</sup>, Michelangelo Campanella<sup>a,d,\*</sup>

<sup>a</sup> Department of Comparative Biomedical Sciences, The Royal Veterinary College, University of London, 4 Royal College Street, NW1 0TU London, United Kingdom

<sup>b</sup> Department of Biomedical and Neuromotor Sciences, Laboratory of Biochemistry and Mitochondrial Pathophysiology, University of Bologna, Via Irnerio 48, 40126 Bologna, Italy

<sup>c</sup> Department of Perinatal Imaging and Health, St Thomas' Campus, King's College London, 163 Lambeth Palace Road, SE1 7EH London, United Kingdom

<sup>d</sup> Department of Cell and Developmental Biology, Consortium for Mitochondrial Research (CfMR), University College London, Gower Street, WC1E 6BT London, United Kingdom.

## ARTICLE INFO

## Keywords:

Mitochondria

Calcium

IF<sub>1</sub>

AMPK and MCU

Calcium ions (Ca<sup>2+</sup>) are universal intracellular messengers that control a diverse array of cellular functions. The versatility of Ca<sup>2+</sup> signalling depends on Ca<sup>2+</sup> interaction with a wide range of sensors and transducers through varied spatiotemporal dynamics, and relies on the presence of intracellular stores enabling the functional organization of Ca<sup>2+</sup> transients in signalling microdomains [1,2]. Along with the endoplasmic reticulum (ER), mitochondria are fundamental Ca<sup>2+</sup>-sequestering organelles that act as hubs for Ca<sup>2+</sup> storage and buffering, thereby tuning the local Ca<sup>2+</sup> availability and shaping cellular Ca<sup>2+</sup> signals [3]. The tight control of mitochondrial Ca<sup>2+</sup> entry and cycling is critical to preserve intracellular Ca<sup>2+</sup> homeostasis and avoid alterations underlying the development of severe pathological conditions [2]. Hence, furthering the current understanding of the mechanisms that regulate mitochondrial Ca<sup>2+</sup> handling is crucial to the development of advanced, targeted treatment options.

Mitochondrial Ca<sup>2+</sup> storage capacity is highly correlated with the bioenergetic state of these organelles. Mitochondrial Ca<sup>2+</sup> uptake is driven by both high mitochondrial membrane potential ( $\Delta\Psi_m$ ) and low intramatrix Ca<sup>2+</sup> concentration ([Ca<sup>2+</sup>]<sub>m</sub>), while its rate is regulated by the activity of the mitochondrial Ca<sup>2+</sup> uniporter complex (MCUC), a specialized channel residing on the mitochondrial inner membrane (MIM) that fully opens at high local intracellular [Ca<sup>2+</sup>]<sub>i</sub> ([Ca<sup>2+</sup>]<sub>i</sub>) [4]. Concurrently, intramitochondrial Ca<sup>2+</sup> is a major regulator of ATP

production, promoting oxidative phosphorylation [5]. Ca<sup>2+</sup> transients are therefore crucially involved in the control of the F<sub>1</sub>F<sub>0</sub>-ATP synthase activity, in combination with its endogenous regulator, the ATPase inhibitory factor 1 (IF<sub>1</sub>) [6].

The primary function of IF<sub>1</sub> is to inhibit the reversal of the F<sub>1</sub>F<sub>0</sub>-ATP synthase during conditions of impaired  $\Delta\Psi_m$ . Thus, IF<sub>1</sub> prevents excessive ATP loss, energy imbalance and cell death under ischaemia/hypoxia [6]. Recent studies, including work from our group, have revealed the existence of a large plethora of IF<sub>1</sub> functions, and outlined the pathological implications of its deregulation. We recently uncovered that IF<sub>1</sub> activates a pro-oncogenic mechanism of evasion of apoptosis occurring through optic atrophy 1 (OPA1)-dependent maintenance of cristae shape and preservation of redox balance [7]. We demonstrated that loss of IF<sub>1</sub> activity promotes stress-dependent OPA1 degradation, causing abnormal mitochondrial morphology and impairing cell metabolism. To further explore the impact of IF<sub>1</sub> on mitochondrial function, here we study its role in mitochondrial Ca<sup>2+</sup> homeostasis.

We previously showed that IF<sub>1</sub> over-expression counteracts typical traits of Ca<sup>2+</sup>-mediated cell death, such as mitochondrial swelling and permeability transition [8]. Moreover, there is evidence suggesting that OPA1 oligomer destabilization, which is a feature accompanying IF<sub>1</sub>-depletion [7], facilitates mitochondrial Ca<sup>2+</sup> uptake through cristae

\* Corresponding author at: Department of Comparative Biomedical Sciences, The Royal Veterinary College, University of London, Royal College Street, NW1 0TU London, United Kingdom.

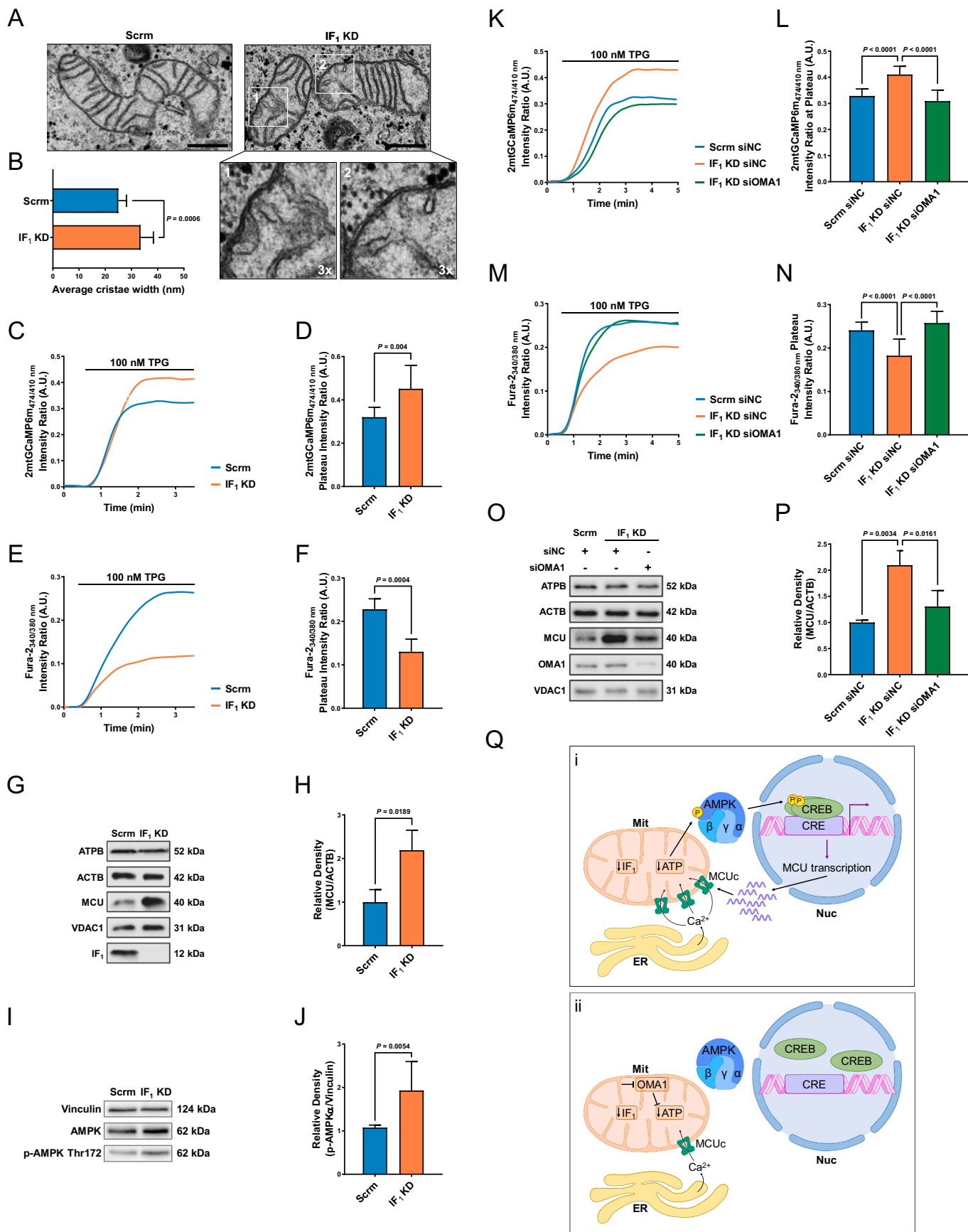
E-mail address: [mcampanella@rvc.ac.uk](mailto:mcampanella@rvc.ac.uk) (M. Campanella).

<https://doi.org/10.1016/j.bbamcr.2020.118860>

Received 23 July 2020; Received in revised form 10 September 2020; Accepted 16 September 2020

Available online 18 September 2020

0167-4889/ © 2020 Published by Elsevier B.V.



(caption on next page)

**Fig. 1.** IF<sub>1</sub> knock-down enhances mitochondrial Ca<sup>2+</sup> uptake in HeLa cells via AMPK- and OMA1-dependent upregulation of MCU. (A) Representative micrographs of mitochondrial ultrastructure in Scrm and IF<sub>1</sub> KD cells (scale bar: 500 nm). (B) Quantification of average cristae width (Scrm: 24.98 ± 3.11 nm; IF<sub>1</sub> KD: 33.47 ± 4.90 nm; n ≥ 15, N = 3). (C) Representative traces of TPG-induced mitochondrial Ca<sup>2+</sup> uptake in Scrm and IF<sub>1</sub> KD cells co-transfected with 2mtGCaMP6m and mtRFP, challenged with 100 nM TPG. (D) Quantification of average mitochondrial 2mtGCaMP6m fluorescence ratio at plateau (Scrm: 0.32 ± 0.05 A.U.; IF<sub>1</sub> KD: 0.45 ± 0.11 A.U.; n ≥ 15, N = 4). (E) Prototypical traces of intracellular Ca<sup>2+</sup> rise following administration of 100 nM TPG in Scrm and IF<sub>1</sub> KD cells loaded with 5 μM Fura-2 AM and 25 nM MitoTracker™ Red CMXRos. (F) Quantification of average cytosolic Fura-2 AM plateau fluorescence ratio (Scrm: 0.23 ± 0.02 A.U.; IF<sub>1</sub> KD: 0.13 ± 0.03 A.U.; n ≥ 15, N = 4). (G) Representative Western blot of MCU protein levels in Scrm and IF<sub>1</sub> KD cells; ysates were also tested for VDACL1, ATPB and IF<sub>1</sub>. GAPDH was used as loading control. (H) Bar charts reporting quantitative analysis of MCU protein levels of MCU relative to GAPDH (Scrm: 1.00 ± 0.29; IF<sub>1</sub> KD: 2.19 ± 0.46; normalized values, N = 3). (I) Western blotting analysis of cellular protein levels of AMPKα and phospho-AMPKα (Thr172) in Scrm and IF<sub>1</sub> KD cells; vinculin was used as loading control. (J) Densitometry analysis of phospho-AMPKα levels relative to vinculin (Scrm: 1.08 ± 0.06; IF<sub>1</sub> KD: 2.19 ± 0.46; N = 5). (K) Prototypical traces of changes in [Ca<sup>2+</sup>]<sub>m</sub> in Scrm and IF<sub>1</sub> KD cells co-transfected with 2mtGCaMP and either a siRNA against OMA1 (siOMA1) or a non-silencing siRNA (siNC), loaded with 25 nM MitoTracker™ Red CMXRos and treated with TPG (100 nM). (L) Quantification of average mitochondrial 2mtGCaMP6m fluorescence ratio at plateau after addition of TPG in the two cell lines (Scrm siNC = 0.33 ± 0.03 A.U.; IF<sub>1</sub> KD siNC = 0.41 ± 0.03 A.U.; IF<sub>1</sub> KD siOMA1 = 0.31 ± 0.04 A.U.; n ≥ 20, N = 3). (M) Representative traces of intracellular Ca<sup>2+</sup> dynamics following TPG treatment (100 nM) in Scrm and IF<sub>1</sub> KD cells. (N) Column diagram of average cytosolic Fura-2 AM fluorescence ratio at plateau (Scrm siNC = 0.24 ± 0.02 A.U.; IF<sub>1</sub> KD siNC = 0.18 ± 0.04 A.U.; IF<sub>1</sub> KD siOMA1 = 0.26 ± 0.03 A.U.; n ≥ 30, N = 3). (O) Representative Western blot of MCU protein levels in Scrm and IF<sub>1</sub> KD cells transfected with either siNC or siOMA1; ATPB, GAPDH (loading control), OMA1 and VDACL1 were also detected. (P) Quantification of MCU expression levels relative to GAPDH (Scrm siNC = 1.00 ± 0.04; IF<sub>1</sub> KD siNC = 2.10 ± 0.29; IF<sub>1</sub> KD siOMA1 = 1.30 ± 0.31; N = 3). (Q) Proposed model for IF<sub>1</sub>-dependent control of mitochondrial Ca<sup>2+</sup> uptake: in IF<sub>1</sub>-depleted cells (i), the decline in cellular ATP levels induces the AMPK-mediated, CREB-dependent transcription of genes encoding the MCU complex, causing increased mitochondrial Ca<sup>2+</sup> uptake following emptying of the ER stores; knocking-down OMA1 blocks reverts excessive mitochondrial Ca<sup>2+</sup> entry activated by IF<sub>1</sub> loss (ii).

enlargement [9]. Interestingly, stable IF<sub>1</sub> knock-down HeLa cells (IF<sub>1</sub> KD), which were prepared for transmission electron microscopy (TEM) imaging as previously described [7], showed a significant increase in cristae width, particularly at the crista junctions (Fig. 1A, B). This characteristic, which is consistent with reduced OPA1 stability in IF<sub>1</sub>-depleted cells [7], might also underlie alteration in molecular diffusion across the MIM [10]. To test the hypothesis that IF<sub>1</sub> regulates mitochondrial Ca<sup>2+</sup> handling, stable control (Scrm) and IF<sub>1</sub> KD HeLa cells were treated with the sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA) inhibitor thapsigargin (TPG, 100 nM), which causes the passive release of Ca<sup>2+</sup> from the ER and allows to study mitochondria-ER coupling. Cells were co-transfected with mitochondria-targeted GCaMP6m (2mtGCaMP6m), a green fluorescent ratiometric Ca<sup>2+</sup> indicator, and red fluorescent protein (mtRFP), to monitor mitochondrial Ca<sup>2+</sup> uptake after administration of TPG. Despite the absence of variations in the basal intramitochondrial Ca<sup>2+</sup> levels (SFig. 1A), the amplitude of TPG-elicited mitochondrial Ca<sup>2+</sup> entry was around 30% higher in IF<sub>1</sub> KD cells (Fig. 1C, D). Moreover, IF<sub>1</sub> loss disturbed whole-cell Ca<sup>2+</sup> homeostasis, as confirmed by the lower levels of Ca<sup>2+</sup> retained in the cytosol (monitored by loading cells with 5 μM Fura-2 AM, a ratiometric fluorescent Ca<sup>2+</sup> sensor, and 25 nM MitoTracker™ Red CMXRos; Fig. 1E, F). This was recapitulated in cells treated with the Ca<sup>2+</sup> mobilising agonist histamine (His, 100 μM; SFig. 1B–E). Since IF<sub>1</sub> KD cells are characterized by higher ΔΨ<sub>m</sub> and impaired ATP synthesis at resting conditions [11], the increase in mitochondrial Ca<sup>2+</sup> influx might represent an adaptive mechanism to maximize ATP production through stimulation of oxidative phosphorylation.

We then investigated the molecular determinants driving enhanced mitochondrial Ca<sup>2+</sup> uptake in IF<sub>1</sub>-depleted cells, starting from MCU. Quite unexpectedly, IF<sub>1</sub> KD induced a significant upregulation of the pore forming subunit of the complex, MCU (Fig. 1G, H), without affecting mitochondrial mass (SFig. 1F, G). To dissect a potential MCU-dependent mechanism augmenting mitochondrial Ca<sup>2+</sup> entry in IF<sub>1</sub> KD cells, we looked at changes in mRNA levels of the different MCU components. Likewise, IF<sub>1</sub> KD cells showed a nearly 1.6-fold increase in MCU transcript levels, which was matched by a similar increase in the expression of all other subunits (SFig. 1H). Additional analysis of the expression ratio of each MCU subunits to MCU revealed no alterations in the stoichiometry of the complex between Scrm and IF<sub>1</sub> KD cells (SFig. 1I), which suggests that the latter have a higher content of fully functional, non-constitutively active MCU. To further examine the mechanism leading to MCU upregulation in IF<sub>1</sub> KD cells, we then monitor the expression levels and activation state of cAMP response element-binding protein (CREB), which is a known transcriptional regulator of MCU transcription [12], and its upstream regulator 5'

AMP-activated protein kinase (AMPK), the increased activity of which has recently been shown in the heart of IF<sub>1</sub> KO mice [13]. Western blotting analysis revealed a remarkable increase in the degree of both AMPKα and CREB phosphorylation when IF<sub>1</sub> is down-regulated (2- and 1.5-fold increase, respectively; Fig. 1I, J + SFig. 2D, F), confirming the involvement of an AMPK-mediated, CREB-dependent mechanism of MCU expression. Of notice, while the total levels of CREB were unchanged between the two cell lines (SFig. 2E), AMPKα expression was significantly higher in IF<sub>1</sub> KD cells (SFig. 2A). This indicates that IF<sub>1</sub> depletion promotes AMPK activity via upregulation of the protein rather than by augmenting the rate of its phosphorylation, which is not affected by changes in IF<sub>1</sub> expression (SFig. 2B). Collectively, our data suggest that IF<sub>1</sub> controls MCU expression in resting cells by limiting AMPK-mediated CREB activation, which is enhanced when IF<sub>1</sub> expression is down-regulated (SFig. 2G). Considering that AMPK is rapidly activated when ATP production decreases, we compared the total cellular ATP levels between the two cell lines. As expected, IF<sub>1</sub> KD cells showed a nearly 40% decrease in cellular ATP levels (SFig. 2C), pointing to ATP depletion as the driving mechanism for increased AMPK activity.

Mitochondrial Ca<sup>2+</sup> uptake appears to be facilitated by unfolding of the cristae through alteration of the membrane diffusion barrier [9,10]. This event is prevented by OPA1, the loss of which impairs both cristae structure and Ca<sup>2+</sup> homeostasis [14]. Under stress conditions, OPA1 degradation occurs rapidly following activation of the mitochondrial zinc metalloproteinase OMA1, which is prevented by IF<sub>1</sub> [7]. Furthermore, a recent study showed that OMA1 KO is protective against MCU upregulation in a murine model of heart failure, with concurrent preservation of cristae integrity and energy metabolism [15]. Considering the increase in cristae width that accompanies IF<sub>1</sub> KD, we speculated that the lack of IF<sub>1</sub> might also favour mitochondrial Ca<sup>2+</sup> accumulation through OMA1-dependent destabilization of OPA1 oligomers. Therefore, we measured intracellular Ca<sup>2+</sup> mobilization following TPG administration in cells down-regulated for OMA1 (SFig. 3A). Interestingly, OMA1 KD reduced mitochondrial Ca<sup>2+</sup> uptake in IF<sub>1</sub> KD cells to levels comparable to control cells (Fig. 1K, L), thus restoring the normal TPG-induced cytosolic Ca<sup>2+</sup> response (Fig. 1M, N). Moreover, knocking down OMA1 inhibited the increase in MCU protein levels induced by IF<sub>1</sub> loss (Fig. 1O, P) without affecting mitochondrial content (SFig. 3B,C). OMA1 KD also significantly reduced ATP loss in cells depleted of IF<sub>1</sub> (SFig. 3D), further confirming that OMA1 activation critically promotes mitochondrial dysfunction in IF<sub>1</sub> KD cells.

With this work, we demonstrate that IF<sub>1</sub> is required for maintaining mitochondrial Ca<sup>2+</sup> homeostasis. Our data prove that IF<sub>1</sub> down-regulation triggers an AMPK-mediated mitochondrial signalling response

that results in the CREB-dependent over-expression of MCU, leading to increased mitochondrial  $\text{Ca}^{2+}$  accumulation following emptying of the ER stores (Fig. 1Qi). We also found that silencing of the mitochondrial protease OMA1 restores normal MCU levels and mitochondrial  $\text{Ca}^{2+}$  uptake (Fig. 1Qii), indicating that OMA1 is involved in the pathway activated by  $\text{IF}_1$  loss and suggesting that the mitochondrial ultrastructure regulates the  $\text{Ca}^{2+}$  buffering capacity of these organelles. In view of previous observations ascertaining the protective effect of OMA1 loss against cristae aberrations [15], OMA1 inhibition in  $\text{IF}_1$  KD cells might favour OPA1-mediated cristae folding and respiratory chain supercomplex assembly, improving both mitochondrial bioenergetics and function.

Collectively, our data confirm that loss of  $\text{IF}_1$  impairs mitochondrial  $\text{Ca}^{2+}$  import with consequences in both cell physiology and pathology.  $\text{IF}_1$  loss may facilitate mitochondrial  $\text{Ca}^{2+}$  overload through alteration of cristae morphology and MCUC activity, contributing to cristae remodelling and mitochondrial swelling. Conclusive evidence confirming that cristae enlargement has a direct effect on mitochondrial  $\text{Ca}^{2+}$  dynamics is still missing, and the relationship between mitochondrial  $\text{Ca}^{2+}$  handling and structure is poorly understood. Nevertheless, this work proposes  $\text{IF}_1$  as a key player in this pathway, as well as a molecular mediator of the retrograde response that links impaired mitochondrial bioenergetics and structure to alterations in intracellular signalling.

#### CRedit authorship contribution statement

M.C. and D.F. conceived the idea for the study and designed the experiments. D.F. conducted the experiments and data analysis and wrote the manuscript. G.G. assisted with  $\text{Ca}^{2+}$  imaging and Western blotting analysis of MCU levels. A.J. and C.T. helped with Western blotting analysis of CREB and AMPK. C.T., A.B and G.S were involved in discussions and commented on the final manuscript.

#### Declaration of competing interest

There are no competing interests of any nature to report.

#### Acknowledgments

The research activities led by M.C. are supported by the following funding agencies, which are gratefully acknowledged: European Research Council Consolidator Grant [COG 2018 - 819600\_FIRM]; Biotechnology and Biological Sciences Research Council [BB/M010384/1 and BB/N007042/1]; Petplan Charitable Trust; LAM-Bighi Grant Initiative; FIRB-Research Grant Consolidator Grant 2

[RBFR13P392], Italian Ministry of Health [IFO14/01/R/52]. A.J. is supported by the UK Medical Research Council [MR/N013700/1] and King's College London, MRC Doctoral Training Partnership in Biomedical Sciences.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbamcr.2020.118860>.

#### References

- [1] D.E. Clapham, Calcium signaling, *Cell* 131 (2007) 1047–1058.
- [2] C. Giorgi, A. Danese, S. Missiroli, S. Patergnani, P. Pinton, Calcium dynamics as a machine for decoding signals, *Trends Cell Biol.* 28 (2018) 258–273.
- [3] R. Rizzuto, D. De Stefani, A. Raffaello, C. Mammucari, Mitochondria as sensors and regulators of calcium signalling, *Nat. Rev. Mol. Cell Biol.* 13 (2012) 566–578.
- [4] S. Marchi, P. Pinton, The mitochondrial calcium uniporter complex: molecular components, structure and physiopathological implications, *J. Physiol.* 592 (2014) 829–839.
- [5] A.I. Tarasov, E.J. Griffiths, G.A. Rutter, Regulation of ATP production by mitochondrial  $\text{Ca}^{2+}$ , *Cell Calcium* 52 (2012) 28–35.
- [6] D. Faccenda, M. Campanella, Molecular regulation of the mitochondrial F<sub>1</sub>F<sub>0</sub>-ATP synthase: physiological and pathological significance of the inhibitory factor 1 (IF<sub>1</sub>), *Int. J. Cell Biol.* 2012 (2012) 367934.
- [7] D. Faccenda, J. Nakamura, G. Gorini, G.K. Dhoot, M. Piacentini, M. Yoshida, M. Campanella, Control of mitochondrial remodeling by the ATPase inhibitory factor 1 unveils a pro-survival relay via OPA1, *Cell Rep.* 18 (2017) 1869–1883.
- [8] D. Faccenda, C.H. Tan, A. Seraphim, M.R. Duchon, M. Campanella, IF<sub>1</sub> limits the apoptotic-signalling cascade by preventing mitochondrial remodelling, *Cell Death Differ.* 20 (2013) 686–697.
- [9] L. Fulop, G. Szanda, B. Enyedi, P. Varnai, A. Spat, The effect of OPA1 on mitochondrial  $\text{Ca}^{2+}$  signaling, *PLoS One* 6 (2011) e25199.
- [10] C.A. Mannella, The relevance of mitochondrial membrane topology to mitochondrial function, *Biochim. Biophys. Acta* 1762 (2006) 140–147.
- [11] M. Fujikawa, H. Imamura, J. Nakamura, M. Yoshida, Assessing actual contribution of IF<sub>1</sub>, inhibitor of mitochondrial FoF<sub>1</sub>, to ATP homeostasis, cell growth, mitochondrial morphology, and cell viability, *J. Biol. Chem.* 287 (2012) 18781–18787.
- [12] S. Shanmughapriya, S. Rajan, N.E. Hoffman, X. Zhang, S. Guo, J.E. Kolesar, K.J. Hines, J. Ragheb, N.R. Jog, R. Caricchio, Y. Baba, Y. Zhou, B.A. Kaufman, J.Y. Cheung, T. Kurosaki, D.L. Gill, M. Madesh,  $\text{Ca}^{2+}$  signals regulate mitochondrial metabolism by stimulating CREB-mediated expression of the mitochondrial  $\text{Ca}^{2+}$  uniporter gene MCU, *Sci. Signal.* 8 (2015) ra23.
- [13] K. Yang, Q. Long, K. Saja, F. Huang, S.M. Pogwizd, L. Zhou, M. Yoshida, Q. Yang, Knockout of the ATPase inhibitory factor 1 protects the heart from pressure overload-induced cardiac hypertrophy, *Sci. Rep.* 7 (2017) 10501.
- [14] Y.E. Kushnareva, A.A. Gerencser, B. Bossy, W.K. Ju, A.D. White, J. Waggoner, M.H. Ellisman, G. Perkins, E. Bossy-Wetzel, Loss of OPA1 disturbs cellular calcium homeostasis and sensitizes for excitotoxicity, *Cell Death Differ.* 20 (2013) 353–365.
- [15] R. Acin-Perez, A.V. Lechuga-Vieco, M. Del Mar Munoz, R. Nieto-Arellano, C. Torroja, F. Sanchez-Cabo, C. Jimenez, A. Gonzalez-Guerra, I. Carrascoso, C. Beninca, P.M. Quiros, C. Lopez-Otin, J.M. Castellano, J. Ruiz-Cabello, L.J. Jimenez-Borreguero, J.A. Enriquez, Ablation of the stress protease OMA1 protects against heart failure in mice, *Sci. Transl. Med.* 10 (2018).