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Mitochondrial and cell-surface F_0F_1ATPsynthase in innate and acquired cardioprotection

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Abstract Mitochondria are central to heart function and dysfunction, and the pathways activated by different cardioprotective interventions mostly converge on mitochondria. In a context of perspectives in innate and acquired cardioprotection, we review some recent advances in F_0F_1ATPsynthase structure/function and regulation in cardiac cells. We focus on three topics regarding the mitochondrial F_0F_1ATPsynthase and the plasma membrane enzyme, i.e.: i) the crucial role of cardiac mitochondrial F_0F_1ATPsynthase regulation by the inhibitory protein IF_1 in heart preconditioning strategies; ii) the structure and function of mitochondrial F_0F_1ATPsynthase oligomers in mammalian myocardium as possible endogenous factors of mitochondria resistance to ischemic insult; iii) the external location and characterization of plasma membrane F_0F_1 ATP synthase in search for possible actors of its regulation, such as IF_1 and calmodulin, at cell surface.

Keywords Mitochondrial F_0F_1ATPsynthase · Inhibitory protein IF_1 · Supra-molecular complexes · F_0F_1ATPsynthase oligomers · Cell surface F_0F_1ATPsynthase · Calmodulin · Cardioprotection

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Introduction

Mitochondria have a central role in cardiac function and dysfunctions, as they modulate energetics, reactive radical biology, calcium homeostasis and apoptosis, as well as orchestrate nuclear regulation, metabolic pathways and cell survival programs via retrograde signalling. In normal cardiac tissue ATP produced by oxidative phosphorylation (OXPHOS) is over 90% and is used preferentially to support myocyte contractile activity. Acute pump failure in ischemia increases ATP demand in excess of ATP supply, thus some established therapeutic strategies are interventions that reduce energy demands during ischemia (Marín-García and Goldenthal 2008). F_0F_1ATPsynthase (OXPHOS complex V) in the inner mitochondrial membrane synthesizes ATP using the H^+ electrochemical gradient ($m\Delta\Psi$) generated by the respiratory chain. This is a reversible enzyme that can also hydrolyse ATP in a reaction coupled to a proton transport out of the mitochondrial matrix thus sustaining $m\Delta\Psi$. Electron microscopy studies on native mitochondrial membranes from different sources, including mammalian heart (Thomas et al. 2008; Strauss et al. 2008) have recently evidenced that F_0F_1ATPsynthase is present as dimers associated to form long row of oligomers. These structures are now considered as the physiological state of the enzyme in membrane, although F_0F_1ATPsynthase is commonly isolated as a functional monomer. This latter is composed of a soluble catalytic F_1 part connected by two stalks with a membrane-embedded F_0 part, which functions as a proton channel. The mammalian enzyme is built of at least 16 different subunits, F_1: $\alpha_3\beta_3\gamma\delta\varepsilon$+$IF_1$, F_0: *a*, *b*, c_{10}, *d*, *e*, *f*, *g*, F_6, A6L, OSCP, (factor B). (Wittig and Schagger 2008; Belogrudov 2008). Our knowledge of the enzyme membrane domain is not complete and the structures of the so-called "minor" subunits (e, f, g and A6L), as well as

those of the more loosely associated proteins DAPIT and 6.8-kDa proteolipid, are not known either. These proteins are unlikely to have a role directly in ATP synthesis, but they appear to influence variously the oligomeric state of the enzyme in the mitochondrial inner membrane (Chen et al. 2007; Meyer et al. 2007). IF_1, a basic protein of 84 amino acids in length, is a non-competitive inhibitor that reversibly binds to F_0F_1ATPsynthase with 1:1 stoichiometry in a α-β interface (Gledhill et al. 2007). Binding requires ATP hydrolysis and is favoured by low pH and $m\Delta\Psi$. The restoration of $m\Delta\Psi$ favouring ATP synthesis displaces IF_1 from its inhibitory site (Green and Grover 2000).

Many reports from several laboratories in recent years have concerned the location and function of the ATP synthase complex or its component subunits on the external surface of the plasma membrane of various mammalian cell types, including vascular endothelial cells, hepatocytes, adipocytes and tumor cells. F_0F_1 components, most usually β subunit, have been identified as cell-surface receptors for multiple ligands in studies carried out on angiogenesis, tumor proliferation/toxicity, lipid/lipoprotein metabolism, immune recognition of tumors and hypertension (Champagne et al. 2006; Chi and Pizzo 2006a, b; Mangiullo et al. 2008).

Transient inhibition of cardiac mitochondrial F_0F_1ATPsynthase in preconditioning

It is widely accepted that activation of endogenous protective responses by stimuli applied immediately before ischemia (ischemic preconditioning) or at reperfusion (postconditioning), that persist even after the initiating stimulus is removed, increases myocardial tolerance to ischemia-reperfusion injury (Gross and Auchampach 2007; Bolli 2007; Yellon and Opie 2006). Insights into mechanisms underlying these innate cardioprotective responses have resulted in the exploration of novel therapeutic avenues (Murphy and Steenbergen 2008). The pathways activated by ischemic and pharmacological preconditioning (PC), as well as by postconditioning mostly converge on mitochondria (Marin-Garcia and Goldenthal 2004; Correa et al. 2008).

It is now well known that PC induces bioenergetic tolerance and thereby remodels energy metabolism that is crucial for post-ischemic recovery of the heart. PC-hearts have less anaerobic glycolysis during the sustained period of ischemia than non-PC-hearts and the rate of ATP consumption is slower. Thus ATP levels fall more slowly, despite the fact that PC-hearts start with a lower ATP (Murry et al. 1990; Steenbergen et al. 1993; Fralix et al. 1993). An early hypothesis to account for the reduced ATP breakdown was that PC might inhibit ATP hydrolysis by a reverse mode of the mitochondrial F_0F_1ATPsynthase (mtF_0F_1), consistent with the finding that during ischemia the $m\Delta\Psi$ depolarized to a greater extent in PC-hearts (Ylitalo et al. 2000). It has been reported that as much as 35–50% of the ATP generated by glycolysis during ischemia is consumed by the reverse-mode of the mtF_0F_1 (Harris and Das 1991; Di Lisa et al. 1995; Grover et al. 2004). Several data suggest that during ischemia the mtF_0F_1 inhibitory subunit IF_1 binds to the enzyme and inhibits the ATPase activity, thus limiting ATP decline (Rouslin 1983; Rouslin and Broge 1996; Campanella et al. 2008). Then, it was proposed that PC promoted earlier binding of IF_1 to mtF_0F_1 (Ylitalo et al. 2000), but this was severely criticized (Green et al. 1998; Vander Heide et al. 1996). Other mitochondrial mechanisms were suggested including opening of the $mitoK_{ATP}$ channel that was proposed to prevent the matrix condensation caused by ischemia thereby decreasing ATP breakdown (Garlid et al. 1997). In the last few years ischemic PC (Ala-Rami et al. 2003; Penna et al. 2004; Di Pancrazio et al. 2004) and diazoxide treatment (Dzeja et al. 2003; Contessi et al. 2004; Comelli et al. 2007) have been reported to enhance IF_1 binding to mtF_0F_1, thereby renewing the emphasis of the early hypothesis of the Hassinen group that the mtF_0F_1 down-modulation by PC is one important component of energy preservation in ischemic myocardium. A review of our data supporting such hypothesis is presented below (Fig. 1b). In our opinion this hypothesis is reinforced by the recent observation that the opening probability of the $mitoK_{ATP}$ channel from cardiac mitochondria reconstituted into planar lipid bilayers is decreased by acidification (Bednarkzyk et al. 2008). As the condition used by the authors mimic ischemic acidosis, we infer that this may be the case even *in situ* diminishing the relevance of the Garlid mechanism in reducing the energy waste.

We first studied a model of *in vivo* ischemic PC on anaesthetized open-chest goat heart, able to prevent coronary reactive hyperemia (CRH). CRH is the increase in flow that follows a very brief coronary occlusion caused primarily by the release of vasoactive compounds from ischemic myocardium (Penna et al. 2004; Di Pancrazio et al. 2004). Functional and electrophoretic analyses on heart biopsies proved that mtF_0F_1 is inhibited by IF_1 during PC, whereas it is up-modulated through release of IF_1 upon CRH. Evidence that PC-elicited inhibition is slowly reversible points to an important role in ATP preservation during prolonged ischemia. Furthermore, according to our results the only significant modulator of the enzyme activity is IF_1, as we observed a close inverse correlation between enzyme activity and IF_1 content by plotting the activity *vs* electrophoretic data (obtained by detergent extraction of single heart biopsy samples and quantitative

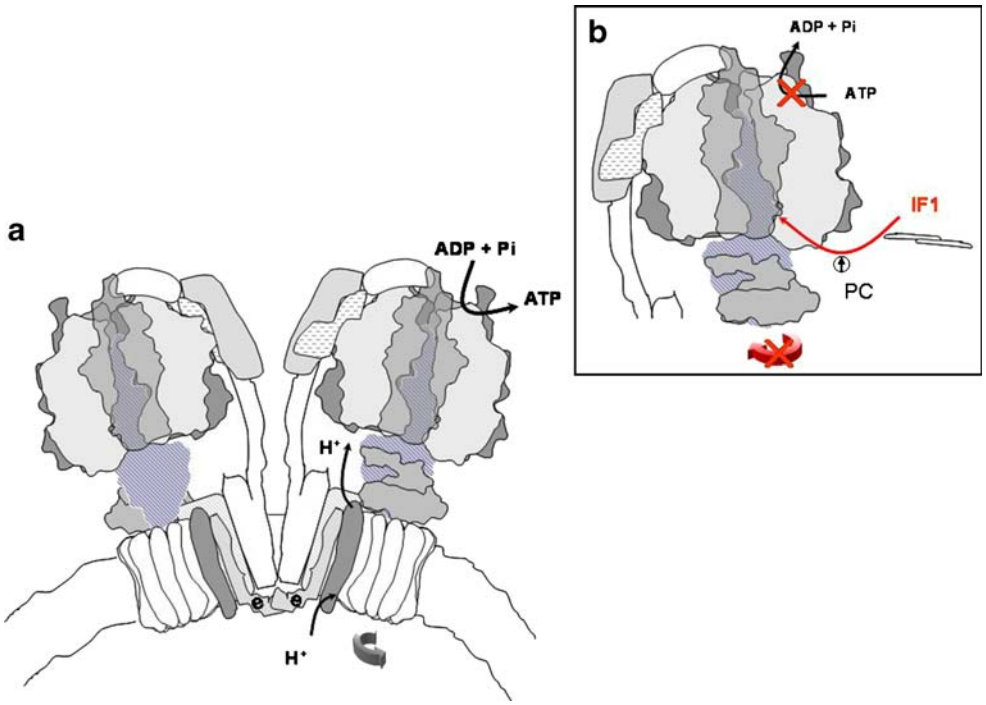

Fig. 1 Cartoons of mtATPsynthase structure and operations in heart mitochondria under physiological and pathological conditions. **a** The figure schematically represents a model of mtF_0F_1 oligomers interface focusing on the single subunits e present in each F_0 sector of two vicinal monomers by the interaction of the C-terminal regions protruding into the intermembrane space (Bisetto et al. 2008). This does not exclude the involvement of other F_0 subunits in oligomer stabilization not yet identified in mammalian heart mitochondria. The dimerization interface is not shown. The enzyme operation is here towards ATP synthesis. **b** The figure represents the binding of IF_1 dimeric in solution (Cabezon et al. 2000), to the F_1 catalytic sector of mtF_0F_1 which switches from synthesis to hydrolysis in ischemia. IF_1 binding results in the down-modulation of ATP hydrolysis and is favored (upward arrow) by ischemic preconditioning and diazoxide treatment (PC). The enzyme operation is here towards ATP hydrolysis

analysis of IF_1 bound in mtF_0F_1 by blue-native gel electrophoresis and 2-D immunoblotting).

As cardioprotection is afforded by treatments with various drugs including the K_{ATP} channel opener diazoxide (Costa et al. 2006), we also focused on its effect on mtF_0F_1. We first documented (Contessi et al. 2004) that *in vitro* diazoxide interacts with the beef heart F_1 sector, strengthening IF_1 binding to F_1 and inhibits ATP hydrolysis by mtF_0F_1. On the basis of kinetic analyses we demonstrated that diazoxide exerts a stabilising role on Mg-ADP bound in the catalytic site of one β subunit and favours a F_1 conformation suitable for IF_1 binding. Then, the diazoxide binding region in mtF_0F_1 is located within a nucleotide binding domain, as in the K_{ATP} channel (Dzeja et al. 2003). Diazoxide effect was further investigated using the embryonic heart-derived myoblasts H9c2 as an *in vivo* model (Comelli et al. 2007). We observed that in normoxic intact cells, diazoxide has a transient dual effect on the enzyme, resulting in enhancement of IF_1 binding and down-modulation of ATPase activity. Diazoxide-triggered mild mitochondrial uncoupling and depolarisation (as detected by confocal microscopy and flow cytometry analyses) inhibit ATPase activity by promoting binding with the $m\Delta\Psi$-sensitive IF_1. Concomitantly diazoxide interferes with the IF_1 interaction with the enzyme further enhancing the inhibition. An interesting study by (Arrell et al. 2006) documented that adenosine-PC results in extensive serine/threonine phosphorylation of the mtF_0F_1 β subunit as a specific and targeted effect. This effect was fully characterized with the identification of 5 novel phosphorylation sites, each conserved across many mammalian species. Thus, considering also the finding that the phosphorylation status of mtF_0F_1 β subunit seems to modulate the enzyme activity (Mei J. et al. 2007), it may be inferred that phosphorylation of the β subunit can be an attractive mechanism of pharmacological PC by inhibiting the mtF_0F_1 ATPase activity per se and/or by favouring IF_1 binding.

Mitochondrial F_0F_1ATPsynthase oligomers in mammalian myocardium

Supra-molecular assembly can be considered as one additional regulatory mechanism acting on OXPHOS and resulting in functional advantages. There is strong evidence that mtF_0F_1 oligomers are involved in the formation of mitochondrial cristae, serving as a kind of backbone stabilizing tubular cristae structures. This may

favour efficient ATP synthesis under aerobic conditions (Paumard et al. 2002; Strauss et al. 2008). Pathological ischemia produces abnormal mitochondria characterized by broken and non-uniform cristae, eventually leading to mitochondrial rupture (Mc Lachlan et al. 2007). On these bases, we focused on structural/functional properties of mtF_0F_1 oligomers in mammalian heart, in order to define factors able to positively influence their stability and activity. Our working hypothesis is that the presence of more stable and active oligomers might be associated with minor vulnerability of mitochondria to hypoxic injury as well as to better recovery during reperfusion. A powerful approach for studying mtF_0F_1 oligomers consists in one-step mild detergent extraction from membranes followed by blue native PAGE (BN-PAGE), which separates monomers, dimers and higher oligomeric forms into abundant, clearly identifiable bands. Single bands can be analysed by proteomics approaches including iterative SDS-PAGEs, immunoblotting and mass spectrometry. Using this strategy combined with *in situ* limited proteolysis of mitochondrial membranes, we have analysed the distribution of the mtF_0F_1 oligomeric forms on BN-PAGE before and after selective tryptic degradation of the subunit e in bovine heart mitoplasts without affecting membrane integrity or ATPase capacity. The data document that the integral subunit e of the F_0 sector contributes to the enzyme's ability of maintaining the dimeric and especially the higher oligomeric forms in bovine heart (Bisetto et al. 2008) (Fig. 1a). Our results are in accordance with the observations that in yeast two monomers interact in dimers through the membrane domain of the peripheral stalks, and dimers associate themselves through interactions involving the vicinal subunits e and g of F_0 (Fronzes et al. 2006). Moreover, electron microscopy studies showed that dimers/oligomers interfaces include the membranous F_0 domain also in the bovine enzyme (Strauss et al. 2008), although a great variability in the shape of these supra-molecular assemblies was also observed. Considering that under our conditions (Bisetto et al. 2008) a single copy of subunit e (whose stoichiometry was determined using an MS-based quantitative proteomics approach) is sufficient to strengthen the interaction through dimers, and that a variable stoichiometry of e was described depending on dietary and stress conditions (Hong and Pedersen 2003), it is tempting to propose that a higher e stoichiometry may favour mtF_0F_1 oligomers stabilization and, eventually, diminish mitochondrial susceptibility to ischemic insult. An intriguing aspect of mtF_0F_1 oligomers relates to the molecular mechanisms responsible for their higher catalytic activity with respect to the monomers. By combining BN-PAGE with in-gel enzyme activity staining, we confirmed that at physiological temperatures mtF_0F_1 dimers have greater specific ATPase activity than monomers (Bisetto et al. 2007). Moreover, as the higher ATPase activity of the dimers was lost due to membrane remodelling by sonication, we suggest that selective interactions of dimers with unknown components are able to modulate the enzyme activity. A set of proteins that can be considered as candidates are the Pi (PIC) and ADP/ATP (ANT) carriers, that form in rat liver mitochondria a supra-molecular complex with mtF_0F_1 named ATPsynthasome (Chen et al. 2004) thereby allowing efficient delivery and removal of substrates and products of ATP synthesis. In this respect, a structural association between mtF_0F_1 oligomers and ANT has been recently seen in bovine heart mitochondria, suggesting the assembly of ATPsynthasome units in oligomeric forms (Wittig and Schagger 2008). Conversely, based on the identical IF_1 content observed we excluded that the functional difference between monomers and dimers is related to a different IF_1 binding (Bisetto et al. 2007). This conclusion is in accordance with our previous demonstration that in bovine heart, like in yeast (Dienhart et al. 2002), mtF_0F_1 self-association did not require IF_1 (Tomasetig et al. 2002). Nevertheless, a recent study shows that in different cell lines IF_1 overexpression can stabilize mtF_0F_1 dimers in respiring mitochondria and that such stabilization promotes ATP synthesis (Campanella et al. 2008). These observations raise two questions: i) how is the hydrophilic IF_1 able to stabilize the mtF_0F_1 dimers which interact through their membrane domain (Strauss et al. 2008)?; ii) how does IF_1 function in respiring mitochondria? Although the authors do not answer these questions, they interestingly document that IF_1 overexpression is significantly protective against ischemic injury as a consequence of ATP preservation at the expense of $m\Delta\Psi$.

It is now evident (Huttemann et al. 2008) that reversible phosphorylation through cell signalling is a main regulatory mechanism acting on OXPHOS complexes including mtF_0F_1 (Ko et al. 2002) in higher organisms to fine-tune their function. In this context, we have explored the hypothesis that phosphorylation may have a role in mtF_0F_1 oligomers formation and in the resulting gain of function. We analysed by a structural proteomic approach the pattern of steady-state phosphotyrosine residues in monomers and dimers from bovine heart under physiological conditions (Di Pancrazio et al. 2006). Interestingly, we found that only γ subunit was phosphorylated, most probably in Try52 (detected by LC-ESI/MS analysis after iterative BN-, SDS-PAGEs), which is located in a solvent-accessible loop at the foot of the F_1 central stalk. Phosphorylation of the γ subunit was observed selectively in the monomers. Nevertheless, only a small fraction of monomers was phosphorylated, limiting the possibility that this phosphorylation has a key role in dimer formation. The possibility that serine

phosphorylation regulates cardiac mtF_0F_1 dimerization is attractive and remains to be verified, as in yeast a recent study demonstrates a role in dimer formation of serine phosphorylation of F_0 subunit g, which is conserved in mammals, (Reinders et al. 2007).

Cell-surface F_0F_1ATP-synthase and IF_1 as a putative target of calmodulin

It has emerged that an enrichment of F_0F_1 components occurs in caveole/lipid rafts on plasma membrane of different cell types (Kim et al. 2004; Kim et al. 2006; Wang et al. 2006; Yamamoto et al. 2007), sometimes together with some other mitochondrial proteins suggesting intracellular traffic connections between mitochondria and other membrane compartments (Yonally and Capaldi 2006). The subunit composition and arrangement of the plasma membrane complex (ecto–F_0F_1) remain to be established and requires definitive experiments. Only few F_0 subunits were observed in rat liver lipid rafts proteome (Bae et al. 2004), and the subunits d and OSCP were shown on plasma membrane of an osteosarcoma cell line by an immunocytochemical study based on an elegant co-labelling approach (Yonally and Capaldi 2006). Furthermore, ecto–F_0F_1 structure and subunit composition may differ between cell types and conditions and might possibly be related to different specific functions. Unfortunately, an exhaustive survey of cell types and tissues for evidence of ecto–F_0F_1 components has not yet been made, and data about cardiomyocyte are still lacking. Noteworthy preliminary data obtained by our group (unpublished) show that some F_0F_1 subunits, including β, OSCP and IF_1, are located at the cell surface of cardiomyoblasts (H9c2 cell line) as monitored by flow cytometry. Moreover, enzyme activity measurements on intact and viable cells, based on oligomycin sensitivity, show ATPase and ATP-synthase activity. This prompts us to suggest that even in cardiac cells ecto–F_0F_1 may have the bifunctional ability to synthesize and hydrolyse ATP and the potential to regulate pH_e/pH_i and the extracellular ATP/ADP ratio, as in endothelial, tumoral and hepatic cells (Chi and Pizzo 2006b; Mangiullo et al. 2008). As the decline of ATP concentrations during ischemia impairs the membrane ion transport, ecto–F_0F_1 involvement in regulating pH_e/pH_i in cells challenged by ischemic acidosis is intriguing. A very important aspect in this topic is to investigate the inhibitory activity of endogenous IF_1 on ecto–F_0F_1 and factors that may regulate it on the cell surface, if any. Interestingly, recent analyses on the hepatic cell line HepG2 lead us to hypothesize that IF_1 interacts with calmodulin (CaM) at the cell surface (Contessi et al. 2007), in accordance with our previous data showing that IF_1–Ca^{2+}–CaM interaction *in vitro* is characterized by a rather high affinity (Contessi et al. 2005). Until now, the inhibitory action of IF_1 on ecto–F_0F_1 has been assessed using exogenous IF_1 (Martinez et al. 2003; Burwick et al. 2005) and agrees with the known function of IF_1 in mitochondria (see above). On the other hand the presence of endogenous ecto–IF_1 is documented only for vascular endothelial (Burwick et al. 2005; Cortes-Hernandez et al. 2005) and for hepatic cells (Contessi et al. 2007; Mangiullo et al. 2008). Our immunofluorescence and Western blotting analyses documented that a relevant amount of total cellular IF_1 is localized on the plasma membrane where we also found Ca^{2+}–CaM, OSCP and β. Confocal microscopy showed that IF_1 co-localizes with Ca^{2+}–CaM on the plasma membrane indicating that the two proteins likely interact. This suggests a possible role of such interaction in modulating the cell surface availability of IF_1 for ecto–F_0F_1 (Fig. 2). It should be considered that the IF_1–Ca^{2+}–CaM interaction may trigger some additional function of IF_1, in accordance with the hypothesis of Cortes-Hernandez et al. (2005) which showed that the ratio of IF_1 to subunit β exhibited significant variation in endothelial cells upon stimulation

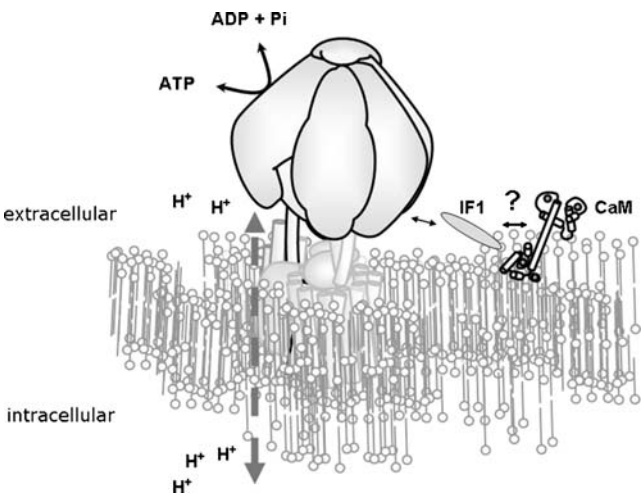

Fig. 2 Schematic representation of ecto-F_0F_1 together with IF_1 and CaM, two candidates for its regulation on the cell surface. The figure represents ecto-F_0F_1 on the cell surface as previously proposed by (Chi and Pizzo 2006b). The subunit composition and organization is still uncertain, particularly for the F_0 sector. Hydrophobic F_0 sector functions as a proton channel while hydrophilic F_1 synthesizes or hydrolyzes ATP in the extracellular space. Thus the enzyme contributes to regulation of pH_e/pH_i and extracellular ATP/ADP ratio. IF_1 and CaM have been depicted as present on the cell surface where they have been shown to co-localize (Contessi et al. 2007). As indicated by the question mark, an *in vivo* evidence of IF_1-CaM complex formation is lacking, although the two proteins are known to interact *in vitro* (Contessi et al. 2005). The question mark also emphasizes that the chemical interactions with the plasma membrane of the two proteins remain to be established. Other evidences are required to sustain the intriguing hypothesis that the IF_1-CaM complex takes part in ecto-F_0F_1 regulation

with TNF-α and suggested that the IF_1 function on the plasma membrane may not be limited to regulation of ATP hydrolysis catalysis. Further experiments are needed to ascertain such intriguing hypotheses.

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