

Review

Redox Control of Metabolism: How Fgr Kinase Shapes Mitochondrial Function and Cellular Adaptation

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Abstract

Mitochondria coordinate cellular energy production, metabolism, and signalling through the organization of the electron transport chain (ETC) and formation of respiratory super-complexes. These structures facilitate efficient electron transfer and enable coenzyme Q (CoQ) channelling, allowing differential regulation of NADH- and succinate-driven respiration while modulating reactive oxygen species (ROS) production. Beyond their damaging potential, ROS act as key signalling molecules that regulate mitochondrial function through redox-sensitive modifications. Mitochondrial protein kinases add an additional layer of control, with Src-family kinases playing a central role. In particular, the mitochondrial tyrosine-kinase Fgr is activated by H₂O₂ and promotes phosphorylation of succinate dehydrogenase, boosting complex II activity, delivering more electrons to CoQ and inducing reverse electron transfer (RET) through CI, in a ROS-induced ROS generation amplification cycle. This induces a metabolic rewiring aimed at supporting stress adaptation, immune cell activation, and macrophage polarization. Overall, the interplay between supercomplex organization, ROS signalling, and kinase activity is critical for metabolic flexibility and represents a promising target for therapeutic intervention.

Keywords: mitochondria; Fgr kinase; ROS; Src kinase family; complex II

1. Introduction

Mitochondria are central hubs for metabolism, signalling, cation homeostasis and energy production. For that, the structure of mitochondria is essential. An outer mitochondrial membrane (OMM) allows the entry of small molecules and atoms into the intermembrane space (IMS). The osmolality, pH and ion concentration of the IMS is equal or very similar to that of the cytosol, as the OMM does not represent a barrier for their diffusion [1]. However, the inner mitochondrial membrane (IMM) represents a highly impermeable barrier to the diffusion of even small cations such as H⁺, in this way isolating the interior of the mitochondria, the matrix, from the exterior. In the IMM are located the five mitochondrial complexes in charge of energy production in the cell, the oxidative phosphorylation system (OXPHOS). Complex I (CI), complex III (CIII) and complex IV (CIV) couple the transfer of electrons to H⁺ pumping, creating an electrochemical potential gradient across the IMM which is then used by the complex V (CV) to phosphorylate adenosine diphosphate (ADP) into adenosine triphosphate (ATP). Such electrochemical



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potential gradient, or proton-motive force, is composed of the mitochondrial membrane potential ($\Delta\psi_{mt}$) and the difference in mitochondrial pH (ΔpH).

CI accepts electrons from reduced nicotinamide adenine dinucleotide (NADH) and reduces ubiquinone (CoQ) into ubiquinol. Similarly, complex II (CII) oxidizes succinate into fumarate and reduces ubiquinone into ubiquinol. CIII, always found as a dimer (III₂), uses ubiquinol to reduce cytochrome c (cyt c), a heme protein attached to the outer side of the IMM, which, in turn, donates its electrons to CIV. Ultimately, CIV reduces oxygen and produces water. These complexes comprise the mitochondrial electron transport chain (mETC). However, leakage may occur during electron transfer, anticipating the reaction of electrons with oxygen and producing reactive oxygen species (ROS).

CI, CIII and CIV can assemble into quaternary structures called supercomplexes. CI assembles with CIII to form the supercomplex I+III₂ [2–5], and with CIII and CIV to form the supercomplex I+III₂+IV or N-respirasome [3–9]. CI can also interact with CIV to form the supercomplex I+IV and I+IV₂ [10,11]. CIII interacts with CIV to form the supercomplex III₂+IV or Q-respirasome, and CIV can interact with other CIV to form dimers and oligomers [10,11].

The assembly between CIII and CIV to form the Q-respirasome in mammals is mediated by the supercomplex assembly factor 1 (SCAF1) [10,12,13]. The Q-respirasome can then interact with CI, forming the N-respirasome [14]. A second, structurally distinct N-respirasome can be formed by the independent interaction of CI with CIII and CIV [15,16]. Disassembly of the Q-respirasome by SCAF1 deletion in mammals or by targeted mutagenesis in the interaction interface in yeast demonstrated metabolic channelling of cyt c between CIII and CIV [12,13,17,18]. These results closed a long-lasting discussion on the role of the III₂+IV supercomplex, validating the hypothesis of the existence of cyt c channelling [12,19].

On the other hand, there are no known protein assembly factors required to mediate the interaction between CI and CIII. Rather, it has been shown that phospholipids [20] and the interaction between defined structural subunits of both complexes mediate its formation. Thus, given that phospholipids are integral parts in the IMM, there have been several approaches to ascertain whether CoQ is also subjected to substrate channelling. Flux control analysis revealed that there exists a functional relevant association between CI and CIII but not between CII and CIII [21]. Later, amphipol-purified I+III₂ showed limited access of CoQ into the superstructure and clear kinetic interdependency [2]. Nevertheless, the definitive evidence has come from the use of alternative oxidases (AOXs) [22]. By using wild-type and mutant cell lines overexpressing AOXs, it was possible to dissect the kinetic behaviour of CI in the presence and absence of CIII. If CI was assembled into supercomplexes with CIII, CI-dependent NADH oxidation was not affected by succinate; however, as CIII was absent and CI was alone, CI-dependent NADH oxidation decreased to half, indicating that as CI operates in isolation, ubiquinol from CII is able to establish competition with that generated by CI for the downstream ubiquinol-oxidizing enzyme (CIII/AOX) [10]. Analogous approaches using wild-type mitochondria have revealed similar results [19,23]. This partial segregation of CoQ into functionally segmented pools allows the differential management of respiratory substrates, which consumption can be modulated only by modifying the activity of the respective complex (CI or CII). Further evidence has come from the fact that intramitochondrial Na⁺ can diminish CII-based respiration and CII+CIII activity by decreasing IMM fluidity, but not NADH-based respiration or I+III₂ activity; this, in turn, is related to hypoxic adaptation through the production of ROS [24].

Indeed, another major role of CoQ metabolic channelling involves ROS production. The first evidence came from in vitro experiments showing that CI and CIII produced larger amount of ROS when reconstituted as individual complexes and lower levels when

assembled as supercomplex I+III₂ [25]. This was in agreement with physiological observations that correlate the higher proportion of CI assembled into supercomplexes with lower mitochondrial ROS production in neurons vs. astrocytes [26]. Lately, it has been shown that ROS production by CIII during hypoxia depends on intramitochondrial Na⁺, which drives superoxide production only if ubiquinol comes from CII, but not from CI, indicating that I+III₂ is insensitive to the Na⁺-dependent decrease in IMM fluidity [24,27].

Thus, CoQ metabolic channelling enables the differential modulation of substrate utilization and ROS production by the mETC. Alteration in the levels of activity of individual CI or CII can modulate the utilization of NADH or succinate, opening a panoply of possibilities for metabolic homeostasis and signalling.

2. ROS as Second Messengers

Reactive oxygen species (ROS) are generated as by-products of electron transfer reactions, with mitochondria representing a major intracellular source. Under physiological conditions, the main sites of ROS production are complex I (CI) and complex III (CIII) of the electron transport chain [28]. CI generates ROS both during forward electron transport and, more prominently, during reverse electron transfer (RET), a process favoured by mitochondrial hyperpolarization and low ADP levels and associated with conditions such as ischemia–reperfusion and inflammatory conditions [24,28–30]. Once RET is activated, it targets complex I for degradation. This mechanism constitutes a feedback loop in amplifying ROS production [29,31]. CIII produces ROS through semiquinone intermediates at the Qo site, a process that can be enhanced under conditions such as hypoxia or by inhibition of the Q cycle [24].

While excessive ROS can damage cellular components and lead to mitochondrial dysfunction and cell death [32–34], moderate ROS levels function as signalling molecules. In particular, H₂O₂ acts as a central redox messenger capable of reversibly modifying protein thiols and iron–sulfur clusters, thereby regulating enzyme activity and metabolic pathways. Through these mechanisms, ROS link mitochondrial function to adaptive cellular responses.

Interestingly, ROS are increasingly recognized as active regulators of protein kinase signalling. Many kinases are sensitive to the cellular redox state because critical cysteine residues within catalytic or regulatory domains can undergo reversible oxidation, leading to conformational changes that alter enzymatic activity. In receptor and non-receptor tyrosine kinases, ROS can enhance signalling either directly, by promoting kinase activation, or indirectly, by inhibiting protein tyrosine phosphatases, which shifts the balance toward phosphorylation-dependent signalling [35–38]. This redox–kinase coupling provides a rapid and reversible mechanism for translating metabolic stress into coordinated cellular responses. However, chronic or excessive ROS exposure can dysregulate kinase signalling networks, contributing to pathological states including inflammation, cancer, and metabolic disease [39–42].

3. Mitochondrial Kinases

Post-translational modifications (PTMs) are critical to allow cells to quickly adapt to changes occurring in their surroundings. PTMs come in a wide variety of forms and shapes (phosphorylated, sulfenylated, sulfinylated, sulfonylated, succinylated, ubiquitinated, sumoylated, acetylated, glycosylated, glutathionylated, nitrated, and/or malonylated), protein phosphorylation by kinases being the best characterized [43–45]. There are different types of protein kinases that pair with their corresponding phosphatases, depending on the amino acid residue to modify: Ser/Thr kinases or Tyr kinases. Kinases compartmentalize in different organelles as well as in the cytosol and plasma membrane, which enables a

coordinated and localized response when needed [46,47]. Up to now, at least 25 different protein kinases that are either associated with mitochondria or that can phosphorylate mitochondrial proteins have been described [48–51]. Several studies have shown the importance of these kinases in the context of mitochondrial dysfunction in cancer, obesity, cardiovascular diseases, neurodegenerative diseases, immune response and aging [51,52]. The main protein Ser/Thr kinases proposed to be associated with mitochondria are isoforms of PKA [53–56], PKC [57–60], AKT [61–64], ERK family [60,65,66], GSK-3 β [67,68], PINK1 [69–71], components of the MAPK signalling pathway (JNK, p38) [60,72,73], and LRRK2 [74]. On the other hand, protein Tyr kinases (PTKs) have also been found in mitochondria, and those include ABL [75–78]; the members of the Src family [79,80], such as FYN [81,82], SRC [81,83–85], LYN [81,86], FGR [87,88], CSK [81]; and the receptor tyrosine kinases, such as EGFR [89–92] or ERBB2 [93,94]. Many studies have been focused on understanding how mitochondria can respond and rapidly adapt to nutritional challenges or stress by studying the role of mitochondrial localized kinases and their targets.

To add another layer of regulatory control, kinases themselves are subjected to modulation [95]. Kinase regulation comes in different shapes that include protein–protein interactions; binding of ligands and allosteric modulation; reversible or irreversible covalent modifications, such as phosphorylation/dephosphorylation by other kinases/phosphatases upstream of their signalling pathway; and limited proteolysis. In addition, a new, interesting type of regulation is emerging as a field of research which is focused on redox-dependent modulation of PTKs in health and disease [96–99]. We have previously described how mitochondrial ROS can act as second messengers and trigger adaptive responses in cells and whole organisms [100,101]. In the context of mitochondrial kinase regulation, the redox-dependent regulatory mechanism becomes more important considering that the ETC is one of the main sources of ROS generation in the cell. Up to now, it has been well characterized how ROS can modulate Tyr kinase signalling by inhibiting the activity of Tyr phosphatases [102–104]. Recently, it has also been proposed that ROS can directly modulate the activity of PTKs [87,105,106]. Therefore, the study of mitochondrial kinases under the scope of mitochondrial (patho-)physiology emerges as a very promising field of research.

4. Src-Family Kinase Regulation

Src-family kinases (SFKs) are a family of non-receptor tyrosine kinases involved in the regulation of proliferation, survival, migration, differentiation and immune signalling [107–110]. In vertebrates, the family comprises nine members: SRC, LCK, LYN, BLK, HCK, FYN, FGR, YES and YRK, although YRK is restricted to chickens and is usually omitted from discussion of mammalian SFKs [111]. Despite their different tissue distributions and biological outputs, SFKs share a conserved multidomain organization and a common core regulatory logic [112]. Among Src-family kinases, only a subset has been convincingly linked to mitochondrial function [50,80,86,88,113,114]. SRC and FGR represent the best-characterized examples, with direct phosphorylation of ETC components and clear effects on respiratory activity. Other family members, such as LYN and FYN, have also been detected in mitochondria and implicated in mitochondrial regulation, although their specific substrates and mechanisms remain less well defined. In contrast, for several SFKs, mitochondrial localization is largely based on descriptive studies with limited functional evidence [50].

All mammalian SFKs contain an N-terminal region involved in membrane association, followed by SH3 and SH2 domains and a C-terminal kinase domain [112]. In the canonical inactive state, the SH3 domain binds in cis to the SH2–kinase linker, while the phosphorylated C-terminal tail tyrosine (classically referred to as Tyr527 in SRC numbering) binds intramolecularly to the SH2 domain [115]. These contacts stabilize a compact, closed

conformation that restrains kinase activity. Phosphorylation of the tail tyrosine is mediated by the major negative regulators CSK and CHK, whereas disruption of SH3:linker and SH2:tail interactions, either by dephosphorylation or by engagement of binding partners, shifts the kinase toward an open, active conformation [116,117]. Structural and biophysical work on SRC and HCK strongly support the idea that this autoinhibited architecture is broadly conserved across the family.

Transition to the active state is initiated by disruption of the intramolecular interactions that maintain SFKs in a closed conformation. This can occur through dephosphorylation of the C-terminal inhibitory tyrosine or through competition for SH2 and SH3 domain binding by external ligands or protein partners, which displace these regulatory contacts. As a result, the kinase undergoes a conformational opening that releases the catalytic domain from autoinhibition [118,119]. Disruption of the SH2 and SH3 interaction allows the kinase domain to adopt an “open” configuration, in which key structural elements rearrange to expose the substrate-binding site. Central to this process is the autophosphorylation of the activation-loop tyrosine (Tyr416 in c-Src numbering), which stabilizes the active conformation of the kinase domain [118]. Phosphorylation of Tyr416 promotes, therefore, the proper alignment of catalytic residues within the active site, enhancing ATP binding and substrate access. Thus, the classical view of SFK regulation is that kinase activation/inactivation is determined by a balance between tail phosphorylation, intramolecular assembly, activation-loop phosphorylation, and interactions with activating partners.

However, some particularities for each member of the family are particularly relevant. Recent work by Cui et al. [120] indicates that SRC does not behave as a simple ON/OFF switch between inactive and active states. Instead, SRC has dynamic conformational populations with transient intermediate states also, allowing it to remain catalytically engaged and phosphorylate substrates in a processive manner. This means that once active, the kinase can modify multiple targets without fully dissociating, highlighting the importance of conformational flexibility in shaping kinase activity beyond classical regulatory mechanisms.

Moreover, in contrast to the canonical model of Src-family kinase regulation, Shen et al. [121] demonstrated that FGR does not strictly couple its conformational state to catalytic activity. Although structural analyses showed that FGR adopts a closed conformation similar to that of other family members, its kinase activity remained largely unaffected. Disruption of SH2- and SH3-mediated intramolecular interactions, which strongly activate kinases such as HCK, had minimal impact on FGR activity. Moreover, wild-type FGR exhibited transforming capacity comparable to that of a tail mutant lacking the inhibitory tyrosine, further indicating that its activity is not tightly controlled by canonical regulatory mechanisms. These findings were attributed to differences in the activation-loop sequence of FGR (small difference in the peptide sequence, with proline rather than alanine at the +2 position relative to the activation loop tyrosine), which may favour spontaneous adoption of active conformations. Together, this study supports the idea that FGR displays a higher basal activity and a reduced dependence on classical autoinhibitory constraints compared with other Src-family kinases.

5. FGR and Fuel Use

Cells are normally exposed to a mix of different signals, which need to be integrated and coordinated to achieve a balanced adaptive response. These responses are complex and involve different partners and metabolic processes. Membrane receptors and transporters, the intracellular compartmentalization of molecules, the enzymatic balance of each metabolic step, and the elimination of by-products have to be perfectly orchestrated. These coordinated arrangements allow for an appropriate cellular response to proliferation and

differentiation and to environmental changes, including survival in response to diverse insults [122].

One of the most common sources for these adaptive mechanisms is the response to fuel utilization. The different fuels (glucose, fatty acids, ketone bodies, and amino acids) that the cell metabolizes fulfil a program to synthesize new metabolites as well as the use of those metabolites to produce energy. Cells must respond rapidly to changes upon stress conditions, fuel deprivation or fuel availability in order to survive [123,124]. Failure to adapt results in disease pathogenesis. The concept of metabolic plasticity that was initially described in muscle adapting to exercise [125] has been extended to other tissues and stress conditions [126–129]. At the centre of these metabolic adaptations is the ability of mitochondria to select and switch fuel use in response to nutritional stress [130]. When responding to changes in fuel source, mitochondria must modify their location, structure, and ionic and metabolite fluxes in order to facilitate anabolism (lipogenesis and antioxidant defences from citrate, gluconeogenesis, serine and glycine biosynthesis from pyruvate, nucleotide biosynthesis) or catabolism (TCA cycle, β -oxidation, oxidative phosphorylation). As we described before, mitochondria are central to ATP synthesis, redox balance, and ROS production, parameters directly dependent on fuel use. One of the key players in stress adaptation is the production of ROS and the ROS-triggered signalling in a time- and cell-location-dependent manner. In this context, PTKs and, more importantly, mitochondria-localized PTKs play a crucial role. As mentioned, several Tyr protein kinases (SRC, LYN, and FGR) and the regulator of Src-type tyrosine kinases CSK (itself a Tyr kinase) have been reported to localize in mitochondria [50,79,80,88]. These kinases have been reported to be activated under stress conditions such as oxygen deprivation or immune cell activation, but the specific response of the mitochondrial subpopulation of PTKs under these conditions has not been explored until recently. In our previous work [88], we described that H_2O_2 directly activates FGR and that there is a pool of FGR that localizes to the mitochondrial matrix, despite not having an evident signalling peptide for mitochondrial import. This is not, however, exceptional. Most mitochondrial proteins are indeed targeted by an N-terminal mitochondrial sequence that directs them through the TOM/TIM import machinery. However, a substantial subset of mitochondrial proteins lack a cleavable targeting sequence and still get imported using alternative pathways. These cases are especially interesting because they illustrate the diversity of mitochondrial import mechanisms [131–133].

Under these stress conditions, ROS are generated (specifically, hydrogen peroxide) and directly activate FGR. Once FGR is activated, it phosphorylates one of the catalytic subunits of succinate dehydrogenase (SDHA), increasing its activity (Figure 1). CII upregulation comes with a decrease in CI activity, switching the preferential fuel use and increasing the proportion of electron entrance to the ETC towards $FADH_2$ -containing enzymes. We have previously shown that when switching fuels from glucose to fatty acids ($NADH/FADH_2$ electron proportions decrease) there is a reorganization of supercomplexes by which CI amount is reduced, leaving freer CIII to receive electron fuelling from CII [12,31]. The mechanism that triggers complex I reduction is reverse electron transfer, or RET [10]. This phenomenon of fuel switch also happens upon immune cell activation of T cells [134,135] and macrophages [136–138], in which cells switch from oxidative to glycolytic metabolism and enter into a proliferative cycle and where we have shown that FGR plays an important role in allowing the metabolic switch needed [88,139]. Recently, more studies are focusing on deciphering the role of Pyruvate Kinase (PYK) activation in cancer, where metabolic reprogramming and proliferation are the main hallmarks of tumour progression and aggressiveness [140,141]. A promising field of research involves the inhibition of PYK in cancer immunotherapy, which is still not fully understood since, although it seems very effective,

cancer resistance and a number of adverse effects still preclude the implementation in humans [99,142–144]. One of the potential drawbacks of inhibiting PYKs might be due to their similarity in function and structure, as they can compensate for each other. Another element to consider is the different intracellular localization of kinases, as it might be necessary to establish targeted inhibition to the different pool localization of these kinases. A better understanding of the role of the different kinase pools and how they regulate the different steps in the metabolic adaptation would reduce the adverse effects reported and would increase the efficiency of the treatments.

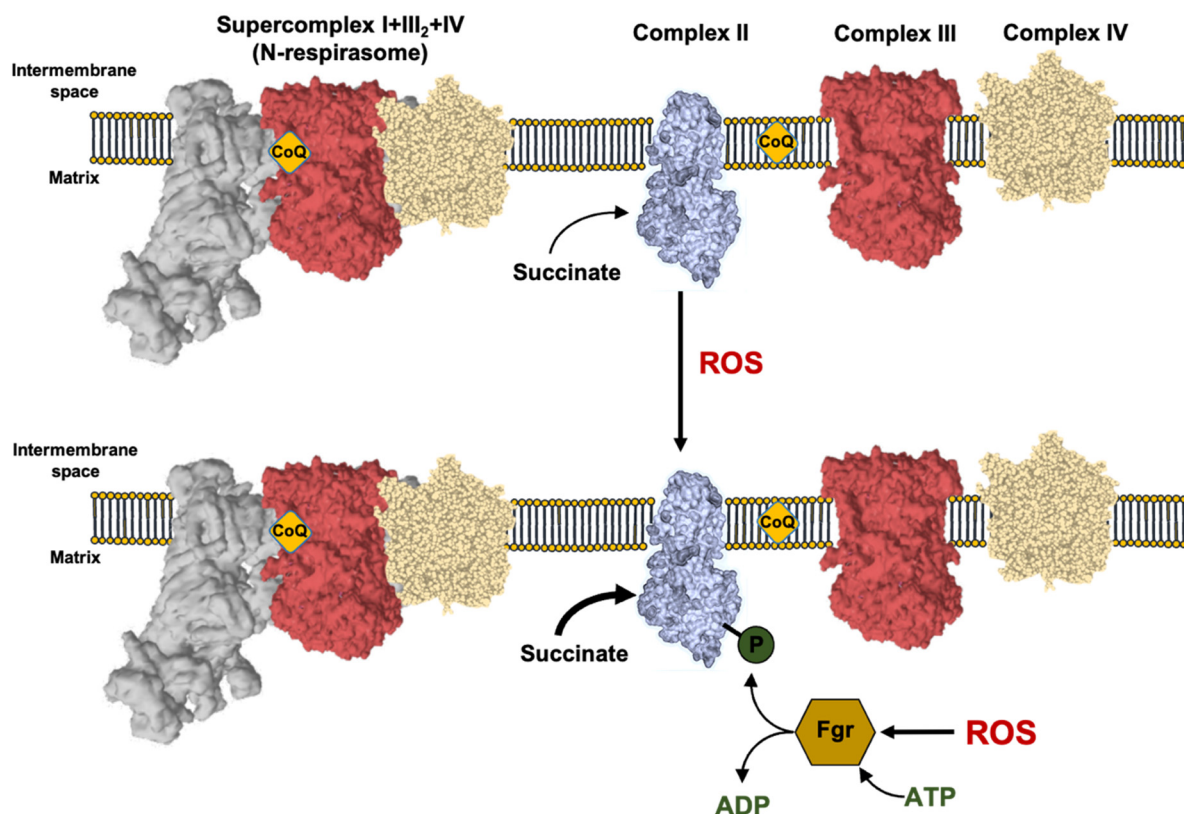


Figure 1. ROS production activates Fgr Tyr kinase to increase CII activity. Production of ROS by a variety of cellular sources activates Fgr Tyr kinase, which phosphorylates the subunit SDHA from CII. This leads to an over-activation of CII, which increments its succinate consumption to boost respiration.

6. FGR and the Immune Response

The immune system is a complex network that protects the organism from pathogens and from any toxins or other allergenic elements [145,146]. It involves a variety of different cell types that need to be activated in order to orchestrate an adequate and synchronized response to prevent any damage in the organism. From a molecular point of view, activation of the different subsets of immune cells requires metabolic rewiring [147–149]. To achieve this metabolic switch, immune cells need to coordinate and translate the external changes into signalling pathways. This communication web gets even more complicated when the response involves cross-talk between different tissues where cytokines are produced by the immune cells upon certain stimuli, which can modulate and reprogram the response in other tissues in the organism [150–152].

Immune cell activation engages ROS production, an intrinsic activator of PYKs [96,153–155] and, more specifically, of the family of Src tyrosine kinases, SFKs [105,156,157]. There are extensive studies characterizing the metabolic adaptation involved in immune cell activation and how these changes lead to cytokine production and

downstream cross-talk response events between cells or even tissues [158–160]. However, the role of SFKs' activation and their phosphorylation network in immune cells beyond their redox regulation [97,105,156,161] have been poorly characterized until recently.

Among SFKs, HCK, LCK, BLK, FGR, and LYN kinase are highly present in monocytes, macrophages, granulocytes, and dendritic cells. Redox modulation of SFKs kinases has been reported to participate in leukocyte, lymphocyte and dendritic cell activation [153,162–166]. Less clear is the specific involvement of SFKs in the signalling network of macrophages, which, though they are involved in triggering macrophage responses, seem to have overlapped and/or complementary functions [167–169]. For that reason, it was very challenging to attribute specific roles to any member of this family when it came to macrophage activation [167,170–172] until recently [46,88,139].

Macrophage polarization is a process where macrophages respond to their microenvironment to adapt to the responses in the context of innate immune response (classically, activated macrophages or M1) or tissue repair and debris elimination (alternatively, activated macrophages or M2) [173–175]. This simplistic classification has been challenged lately, as a variety of different macrophage phenotypes have been found, and their role still needs to be fully characterized in vivo [176–179]. Macrophage polarization into proinflammatory macrophages mediated by the Toll-like receptor 4 (TLR4) undergoes a metabolic switch by which macrophages enhance glycolysis while glutamine fuelling compensates the TCA cycle through glutaminolysis [180,181]. This metabolic rewiring promotes the accumulation of succinate and the increase in the glycolytic enzyme hexokinase-1, which ultimately leads to the production of the pro-inflammatory cytokine interleukin-1 β (IL-1 β) by regulating the transcription of pro-IL-1 β [181] and the activation of the NLRP3 inflammasome [182], respectively. Accumulation of the TCA cycle intermediate citrate [180] can be metabolized to itaconate, which has antibacterial properties, and thus, contributes to the antimicrobial functions of macrophages [183,184]. Recently, we have demonstrated that FGR activation plays an important role in macrophage polarization [46,139]. FGR kinase was initially described as a proto-oncogene [185] found to be overexpressed and constitutively active in many human cancers [186]. Indeed, inhibition of FGR and other Src-family kinases has been explored as a potential therapeutic strategy in cancer [187–191]. In resting conditions, FGR is restricted to a subset of monocyte/macrophage lineage [192]; however, upon stimulation its expression augments [193]. Interestingly, the role of FGR in macrophage activation and phagocytic capacity seems controversial [194]. Studies in peritoneal macrophages and bone marrow-derived macrophages (BMDMs) lacking FGR showed increased opsonized phagocytic function [194], whereas FGR is also required for TLR-mediated priming of macrophages to do phagocytosis [139]. This apparent contradiction can be solved when studying the partners involved in the different phagocytic processes [195–197]. Opsonization is a phagocytic process mediated by dectin-1 and Fc receptors through indirect or direct recognition of the target [198–200], whereas TLR triggers production of cytokines and chemokines that will end up in phagocytosis [201,202]. The latter involves a more complex network of responses in the cell, where the signal starts at the macrophage cell membrane and travels inside the cell using ROS as a second messenger. ROS activates the mitochondrial pool of FGR kinase that phosphorylates and increases CII activity and CI degradation [88,139]. This metabolic rewiring is essential for macrophage reprogramming into the pro-inflammatory stage with an increase in cytokine production and antibacterial response [139]. In line with this, recent work from Hidalgo's group [203] using in vivo behavioural mapping of inflammation identified FGR as a key driver of a pathogenic neutrophil state, with its inhibition protecting against inflammatory injury. Also, we have shown that obesity induced by feeding mice with a high-fat diet also triggers FGR activation, macrophage infiltration in white adipose tissue, liver steatosis,

and insulin resistance [46]. Furthermore, elimination of FGR or blunting its activation by neutralizing mitochondrial ROS production in the immune cells is able to correct the diet-induced obesity [46]. These findings describe, for the first time, the role of FGR kinase in macrophage polarization in vivo and in vitro, independently of other kinases from the SFK family. Moreover, it identifies a signalling pathway that can be inhibited to correct the harmful effects induced by diet-induced obesity, since we have found a strong correlation with FGR expression and obesity traits in human cohorts [46].

7. Implications of FGR Activation in (Patho-)Physiology

Stimulation of CII through FGR can have further implications in physiology. As described by Bianchi and co-workers, CII is fully rate-limiting on succinate oxidation [21]. Thus, stimulation of CII activity through Fgr is able to increase respiration [46,139], which would translate into increased H^+ pumping by CIII and CIV and, ultimately, into mitochondrial hyperpolarization (Figure 2).

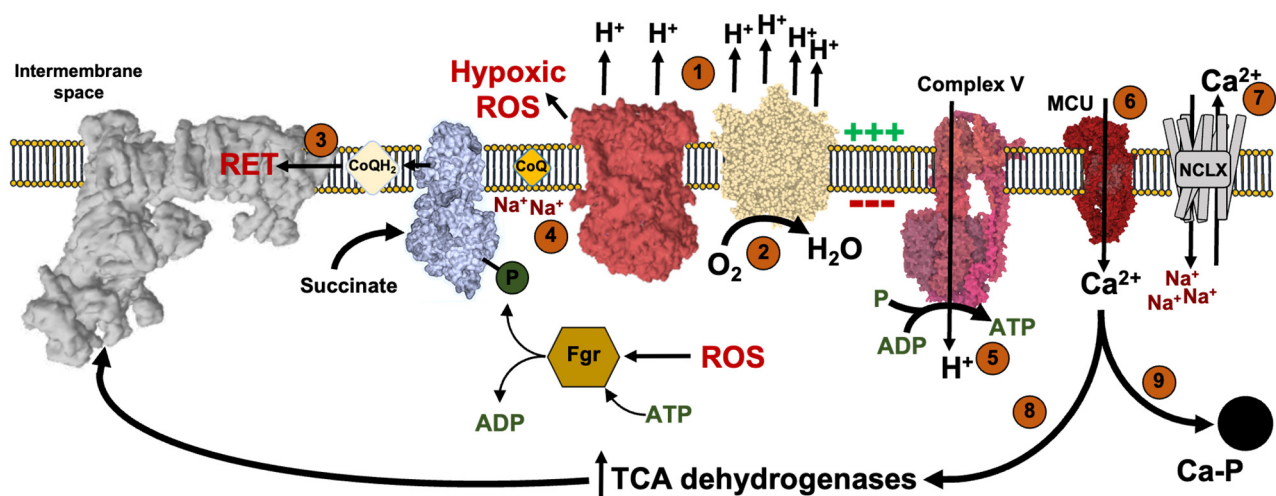


Figure 2. Potential pathways activated after FGR dependent CII phosphorylation. Increases in CII activity may lead to mitochondrial hyperpolarization (1) which, in turn, would lead to higher oxygen consumption rates by the mETC (2). Mitochondrial hyperpolarization may potentiate RET-dependent (3) or Na^+ -dependent (4) ROS production. Hyperpolarization can potentially increase the production of ATP by CV (5) and promote Ca^{2+} entry (6) and exit (7) through the MCU and NCLX, respectively. Mitochondrial Ca^{2+} is, in turn, able to boost mitochondrial dehydrogenase turnover, providing more NADH for CI activity (8) or precipitating into Ca-P (9), the latter being facilitated by a more alkaline pH after hyperpolarization.

Regarding the production of ROS, mitochondrial hyperpolarization is a prerequisite of RET [32,204,205]. Thus, it is possible that activation of ROS-dependent FGR is the anteroom for RET-dependent ROS production (Figure 2). As previously mentioned, ROS-dependent FGR is required for the early immunological-metabolic checkpoint to adjust macrophage activation to bacterial infection [139]. As FGR becomes activated, CII stimulates its activity and increases respiration [21]. This may lead to mitochondrial hyperpolarization. Interestingly, it was shown later on that macrophage reprogramming after LPS stimulation required mitochondrial hyperpolarization in order to further produce ROS through RET [30]. It is also possible that stimulated CII activity promotes further ROS production by CIII as long as there is higher intramitochondrial Na^+ , resembling the hypoxic ROS mechanism recently described (Figure 2) [24]. Indeed, fibroblasts with decreased ability of extruding mitochondrial Na^+ , such as those from Leber's hereditary optic neuropathy patients [27], have stimulated CII activity through FGR, as they have lower CI-dependent respiration. In

this way, this pathway would increase the production of ROS through the hypoxic pathway, namely, slowed electron transfer (SET) [206,207]. In these settings, FGR may possibly act as a necessary intermediate for ROS-dependent ROS production mechanisms such as those seen in Parkinson's [208] or hypoxic pulmonary vasoconstriction [209].

Mitochondrial hyperpolarization can also have profound implications in other aspects of mitochondrial and cell physiology. For instance, it would facilitate ATP production by CV [46] or augment mitochondrial Ca^{2+} entry through the MCU [210] and Na^{+} entry through the mitochondrial $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger [211]. This may boost the activity of mitochondrial dehydrogenases [212] and, ultimately, CI activity (Figure 2), promoting in this way an overall increase in mitochondrial oxygen consumption. On the other hand, increased mitochondrial Ca^{2+} , together with a more alkaline mitochondrial matrix due to hyperpolarization, would promote the formation of Ca^{2+} -phosphate (Ca-P) precipitates [24,213,214] (Figure 2), increasing the storage of Ca^{2+} and phosphate by mitochondria but also rendering the organelles more susceptible to Ca^{2+} overload after acidification [24,213].

Stimulation of CII through FGR can also impact the metabolic status of the cell, as the overconsumption of succinate may impact the levels of upstream metabolites such as those in the Krebs cycle, signalling an adaptation to several physiological or pathological situations. Accumulation of succinate is necessary for ROS production in brown adipocytes together with a higher CII activity [215]. In our previous work [88], we identified the residue Y604 of SDHA as that phosphorylated by FGR. Genetic analysis, including site direct mutagenesis or the use of FGR null mice, allowed us to demonstrate that Y604 phosphorylation by FGR is necessary and sufficient to explain the metabolic adaptation. Y604 is conserved among mammals and was previously proposed as an FGR target in *in vitro* phosphorylation assays [87]; phosphoproteomic approaches have also confirmed the residue identity. Therefore, over-activation of CII triggered by basal FGR-mediated phosphorylation of SDHA poses this mechanism as central for adipocyte thermogenesis. Importantly, accumulation of succinate also occurs during ischemia, leading to an exacerbated RET-dependent ROS production during reperfusion [29]. As hypoxia produces ROS, which can potentially activate FGR, it is possible that CII stimulates its activity during reperfusion due to FGR. Thus, FGR would arise as a potential therapeutic target for ischemia–reperfusion injury [203,216].

In conclusion, regulation of CII activity through FGR controls several physiological and pathological scenarios. From mitochondrial ROS to succinate-mediated signalling and disease, CII may be modulated in such a way that its activity becomes restrained and injury is lowered. Also, in situations in which CII stimulation is advantageous, FGR activation may be beneficial for the disease outcome. Thus, modulation of CII activity through FGR ensures further research and arises as a potential therapeutic target.

Previous reviews, including the comprehensive analysis by Kotrasová et al. [188], have systematically catalogued mitochondrial kinases and their phosphorylation targets across processes such as metabolism, oxidative phosphorylation, and apoptosis. These works largely adopt a descriptive framework in which individual kinases are presented as parallel regulators of mitochondrial function. Here, we introduce a different perspective; we provide a unifying conceptual perspective by positioning the Src-family kinase FGR as a central redox-sensitive hub that integrates reactive oxygen species (ROS) signalling, electron transport chain remodelling, and metabolic rewiring. Specifically, we propose a mechanistic feedback circuit linking ROS production, FGR activation, and complex II-driven respiration, thereby providing a systems-level model for mitochondrial adaptive responses. By further extending this model to immunometabolism (demonstrating how FGR-dependent control of mitochondrial fuel utilization shapes macrophage activation

and inflammatory signalling), the field shift from a catalogue of phosphorylation events to a coherent regulatory paradigm. This integrative perspective not only reconciles disparate observations across metabolic and disease contexts, but also establishes FGR as a potential therapeutic node in conditions characterized by mitochondrial dysfunction, including inflammation, cancer, and metabolic disease.

The clinical implications of this framework are substantial. Dysregulated mitochondrial metabolism and ROS signalling are central features of a broad range of human diseases, including chronic inflammatory disorders, metabolic syndrome, neurodegeneration, ischemia–reperfusion injury, and cancer. By identifying FGR as a key regulator that couples redox state to electron transport chain activity and metabolic reprogramming, our model highlights a previously underappreciated therapeutic entry point. Targeting FGR or its downstream signalling axis could enable selective modulation of mitochondrial ROS production and substrate utilization, offering opportunities to attenuate pathological inflammation, restore metabolic flexibility in obesity and diabetes, or limit tumour cell adaptation to hypoxic environments. Moreover, the link between FGR activity and macrophage polarization underscores its potential relevance in diseases where immune infiltration and inflammation are critical and where fine-tuning mitochondrial metabolism is increasingly recognized as a strategy to control immune cell function. Thus, the conceptual advance presented here is not only mechanistically significant, but also provides a translational framework for developing mitochondria-targeted interventions across multiple disease areas.

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Abbreviations

ADP	Adenosine diphosphate
AKT	Protein kinase B
AOX	Alternative oxidase
ATP	Adenosine triphosphate
BMDM	Bone marrow-derived macrophage
Ca ²⁺	Calcium ion
CI	Complex I
CII	Complex II
CIII	Complex III

CIV	Complex IV
CV	Complex V
CoQ	Coenzyme Q (ubiquinone)
CSK	C-terminal Src kinase
cyt c	Cytochrome c
ΔpH	Mitochondrial pH gradient
$\Delta\psi_{\text{mt}}$	Mitochondrial membrane potential
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal-regulated kinase
ETC/mETC	Electron transport chain/mitochondrial ETC
FADH_2	Flavin adenine dinucleotide (reduced form)
FGR	Gardner–Rasheed feline sarcoma viral oncogene homolog (Fgr kinase)
H_2O_2	Hydrogen peroxide
H^+	Proton
IMS	Intermembrane space
IMM	Inner mitochondrial membrane
JNK	c-Jun N-terminal kinase
LCK	Lymphocyte-specific protein tyrosine kinase
LRRK2	Leucine-rich repeat kinase 2
MAPK	Mitogen-activated protein kinase
MCU	Mitochondrial calcium uniporter
Na^+	Sodium ion
NADH	Nicotinamide adenine dinucleotide (reduced)
NCLX	$\text{Na}^+/\text{Ca}^{2+}$ exchanger
NLRP3	NOD-, LRR-, and pyrin domain-containing protein 3
OMM	Outer mitochondrial membrane
OXPHOS	Oxidative phosphorylation
PKC	Protein kinase C
PTK(s)	Protein tyrosine kinase(s)
PTM	Post-translational modification
RET	Reverse electron transfer
ROS	Reactive oxygen species
SCAF1	Supercomplex assembly factor 1
SDHA	Succinate dehydrogenase subunit A
Ser/Thr	Serine/Threonine
SFK(s)	Src-family kinase(s)
SH2/SH3	Src homology domains 2 and 3
SRC	Proto-oncogene tyrosine-protein kinase Src
TCA	Tricarboxylic acid cycle
TLR4	Toll-like receptor 4
Tyr	Tyrosine

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