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# Complex II ambiguities — $FADH_2$ in the electron transfer system

Erich Gnaiger

Oroboros Instruments, Schöpfstrasse 18, A-6060 Innsbruck, Austria
Correspondence: erich.gnaiger@oroboros.at

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## Abstract

The prevailing notion that reduced cofactors NADH and $FADH_2$ transfer electrons from the tricarboxylic acid cycle to the mitochondrial electron transfer system creates ambiguities regarding respiratory Complex II (CII). CII is the only membrane-bound enzyme in the tricarboxylic acid cycle and is part of the electron transfer system of the mitochondrial inner membrane feeding electrons into the coenzyme Q-junction. The succinate dehydrogenase subunit SDHA of CII oxidizes succinate and reduces the covalently bound prosthetic group FAD to $FADH_2$ in the canonical forward tricarboxylic acid cycle. However, several graphical representations of the electron transfer system depict $FADH_2$ in the mitochondrial matrix as a substrate to be oxidized by CII. This leads to the false conclusion that $FADH_2$ from the β-oxidation cycle in fatty acid oxidation feeds electrons into CII. In reality, dehydrogenases of fatty acid oxidation channel electrons to the Q-junction but not through CII. The ambiguities surrounding Complex II in the literature and educational resources call for quality control, to secure scientific standards in current communications of bioenergetics, and ultimately support adequate clinical applications. This review aims to raise awareness of the inherent ambiguity crisis, complementing efforts to address the well-acknowledged issues of credibility and reproducibility.

## Introduction

Current studies on cellular and mitochondrial bioenergetics sparked a new interest in the tricarboxylic acid (TCA) cycle, also known as the citric acid cycle or Krebs cycle (1-4). TCA cycle metabolites are oxidized while reducing $NAD^+$ to $NADH+H^+$ in the forward cycle, or are transported into the cytosol mainly by passive diffusion dependent on concentration differences across the mitochondrial membranes (5, 6). Respiratory Complex II (CII, succinate dehydrogenase SDH; succinate-ubiquinone oxidoreductase SQR; EC 1.3.5.1) — discovered in 1909 (7, 8) — has a unique position in both the TCA cycle and the mitochondrial membrane-bound electron transfer system (membrane-ETS). All genes for CII are nuclear-encoded, with exceptions in some red algae and land plants (9, 10). SQRs favour oxidation of succinate and reduction of

quinone in the canonical forward direction of the TCA cycle (11). Operating in the reverse direction, quinol:fumarate reductases (QFRs, fumarate reductases) reduce fumarate and oxidize quinol (12, 13). The reverse TCA cycle has gained interest in studies ranging from metabolism in anaerobic animals (14, 15), thermodynamic efficiency of anaerobic and aerobic ATP production (16), reverse electron transfer and production of reactive oxygen species (17-19), hypoxia and ischemia-reperfusion injury (20), to evolution of metabolic pathways (21, 22). In cancer tissues CII plays a key role in metabolic remodeling (23, 24). Beyond its role in electron transfer in the TCA cycle and the membrane-ETS, CII and succinate serve multiple functions in metabolic signaling (25-27). CII is thus a target of current pharmacological developments (28, 29).

The pyridine derivative $NAD^+$ is reduced to $NADH+H^+$ during oxidation of pyruvate and through redox reactions catalyzed by TCA cycle dehydrogenases (DH) including isocitrate DH, oxoglutarate (α-ketoglutarate) DH, and malate DH. In turn, $NADH+H^+$ are the substrates in the oxidation reaction catalyzed by Complex I (CI; NADH:ubiquinone oxidoreductase; EC 1.6.5.3) which is linked to reduction of the prosthetic group flavin mononucleotide FMN to $FMNH_2$ and regeneration of $NAD^+$. Likewise, the prosthetic group flavin adenine dinucleotide FAD is reduced to $FADH_2$ during oxidation of succinate by CII (succinate DH). Confusion emerges, however, when NADH and $FADH_2$ are considered as the reduced substrates feeding electrons from the TCA cycle into the 'respiratory chain' — rather than NADH and succinate. This 'Complex II ambiguity' has deeply penetrated the scientific literature on bioenergetics without sufficient quality control. Therefore, a critical literature survey is needed to ensure scientific standards in communications on bioenergetics. By drawing attention to widespread CII ambiguities, subsequent erroneous portrayal and misinformation are revealed on the position of CII in pathways of energy metabolism, particularly in graphical representations of the mitochondrial electron transfer system.

While ambiguity is linked to relevant issues of reproducibility, it extends to the communications space of terminological and graphical representations of concepts (30). Type 1 ambiguities are the inevitable consequence of conceptual evolution, in the process of which ambiguities are replaced by experimentally and theoretically supported paradigm shifts to clear-cut theorems. In contrast, type 2 ambiguities are traced in publications that reflect merely a disregard and ignorance of established concepts without any attempt to justify the inherent deviations from high-quality science. There are many shades of grey between these types of ambiguity. The Cambridge Dictionary defines ambiguity as '*the fact of something having more than one possible meaning and therefore possibly causing confusion*' https://dictionary.cambridge.org/dictionary/english/ambiguity (retrieved 2023-09-23). This is opposite to 'productive ambiguity' (30) used in the sense of various isomorphic or complementary representations, describing a concept from different points of view. The word relates etymologically to 'double meaning' and 'equivocalness', from *ambi* (around, on both sides).

Ambiguities regarding Complex II (CII) emerge on several fronts. First, they arise when portraying $FADH_2$ within the mitochondrial matrix as both a product of succinate dehydrogenase (SDH) and a substrate of CII. Although misconstrued, this may be seen as electron transfer from $FADH_2$ in the SDHA subunit of CII to ubiquinone. Second, numerous publications introduce ambiguity through the presentation of incorrect figures, depicting $FADH_2$ instead of succinate as the substrate for CII. Third, this

confusion extends to the representation of the reduced flavin adenine dinucleotide ($FADH_2$) in various misconstrued forms, such as FADH or $FADH^+$, or the oxidized form FAD as $FAD^+$. Fourth, when illustrating the oxidation of $FADH_2$, several figures show reactions like $FADH_2 \rightarrow FAD + H^+$ or $FADH_2 \rightarrow FAD + 2H^+$. These hydrogen ions $H^+$ introduce a spectrum of uncertainties and blur the line between ambiguous interpretations and indisputable misinformation. Aiming at an open frame for discussion, the term ambiguity is used here in a collegial manner rather than a punctilious one. Nevertheless, these ambiguities have been a source of confusion even among established authors of specialized research reports, highly cited reviews, and editorials in leading journals. CII ambiguities have led to erroneous conclusions, as will be discussed below.

**Electron flow through CI and CII to the coenzyme Q junction**

The reduced flavin groups $FMNH_2$ of flavin mononucleotide and $FADH_2$ of flavin adenine dinucleotide are at functionally comparable levels in the electron transfer through CI and CII, respectively (Figure 1a,b). $FMNH_2$ and $FADH_2$ are reoxidized downstream in CI and CII, respectively, by electron transfer or more explicitly by transfer of $2\{H^+ + e^-\}$ to the ETS-reactive coenzyme Q (Q) (31), reducing ubiquinone (UQ) to ubiquinol ($UQH_2$). The convergent architecture of the electron transfer system (ETS; in contrast to a linear electron transfer chain ETC; a chain's length used to be a linear measure) with multiple branches feeding into the Q-junction is emphasized in Figures 1c,d (6, 32). Comparable to CII, several respiratory Complexes are localized in the mitochondrial inner membrane (mtIM) which catalyze electron transfer converging at the Q-junction, including electron transferring flavoprotein DH Complex in fatty acid oxidation, glycerophosphate DH Complex, sulfide-ubiquinone oxidoreductase, choline DH, dihydro-orotate DH, and proline DH (3, 6, 32-34). Electron transfer and corresponding capacities of oxidative phosphorylation (OXPHOS) are classically studied in mitochondrial preparations as oxygen consumption supported by various fuel substrates undergoing partial oxidation in the mt-matrix, such as pyruvate, malate, succinate, and others (6). Therefore, the matrix component of the ETS (matrix-ETS) is distinguished from the ETS bound to the mtIM (membrane-ETS; Figure 1c) (2).

In most flavin-linked dehydrogenases the flavin adenine nucleotide is a tightly bound prosthetic group. In CII, it is even covalently and thus permanently bound to the enzyme during the catalytic cycle when the redox state is regenerated in each enzymatic turnover, as documented in early reports (35) and summarized in classical textbooks (36, 37). Structural studies of CII have expanded our knowledge on the mechanism of enzyme assembly (13), enzyme structure (38-40), kinetic regulation of CII activity (41, 42), and associated pathologies (3, 26-29).

$H^+$-linked two-electron transfer from succinate to flavin adenine dinucleotide reduces the oxidized prosthetic group FAD to $FADH_2$ with formation of fumarate. This $H^+$-linked electron transfer through CII is not coupled to $H^+$ translocation across the mtIM. Hence, CII is not a $H^+$ pump in contrast to the respiratory Complexes CI, CIII and CIV through which electron transfer – more appropriately $2\{H^+ + e^-\}$ transfer (Table 1) – drives and maintains the protonmotive force.

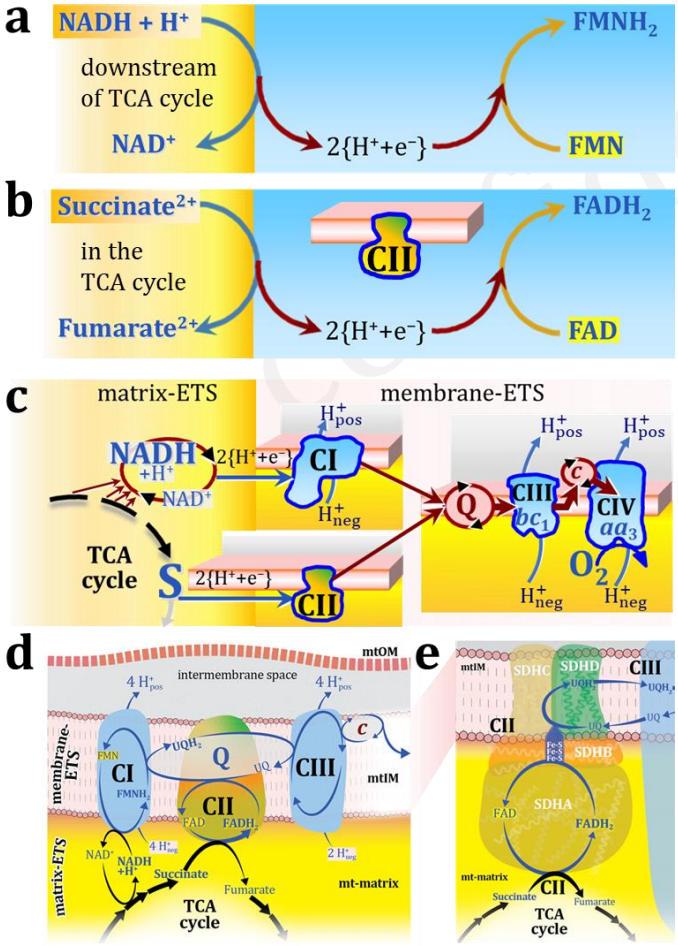


**Figure 1. Complex II (SDH) integrates $H^+$-linked electron transfer in the TCA cycle (matrix-ETS) and the electron transfer system (membrane-ETS) of the mt-inner membrane (mtIM).** **(a)** $NADH+H^+$ and **(b)** Succinate are substrates of $2\{H^+ + e^-\}$ transfer to the prosthetic groups FMN and FAD as the corresponding electron acceptors in CI and CII, respectively. **(c)** Symbolic representation of ETS pathway architecture. Electron flow converges at the N-junction, $NAD^+ + 2\{H^+ + e^-\} \rightarrow NADH + H^+$, and from $NADH + H^+$ and succinate S at the Q-junction, $UQ + 2\{H^+ + e^-\} \rightarrow UQH_2$. CIII passes electrons to cytochrome *c* and in CIV to molecular $O_2$, $2\{H^+ + e^-\} + 0.5\ O_2 \dashrightarrow H_2O$. **(d)** NADH and $NAD^+$ cycle between different matrix-dehydrogenases and CI, whereas FAD and $FADH_2$ remain permanently bound within the same CII-enzyme molecule during the catalytic cycle. Succinate and fumarate indicate the chemical entities irrespective of ionization, whereas charges are shown in NADH (uncharged), $NAD^+$, and $H^+$. Joint pairs of half-circular arrows distinguish the chemical reaction of electron transfer $2\{H^+ + e^-\}$ to CI and CII from vectorial $H^+$ translocation across the mtIM ($H^+_{neg} \rightarrow H^+_{pos}$). CI, CIII, and CIV pump hydrogen ions from the negatively (neg; yellow, mt-matrix) to the positively charged compartment (pos; grey, intermembrane space). **I** Iconic representation of SDH subunits. SDHA catalyzes the oxidation succinate → fumarate + $2\{H^+ + e^-\}$ and reduction $FAD + 2\{H^+ + e^-\} \rightarrow FADH_2$ in the soluble domain of CII. The iron–sulfur protein SDHB transfers electrons through Fe-S clusters to the mtIM domain where ubiquinone UQ is reduced to ubiquinol $UQH_2$ in SDHC and SDHD.

**Table 1. Three distinct types of transformation with hydrogen ions (hydrons) $H^+$.**

| Transformation | | Equation | | Type |
|---|---|---|---|---|
| 1. | acid-base equilibrium | $H_3O^+ \leftrightarrow H_2O + H^+$<br>$H_2CO_3 \leftrightarrow HCO_3^- + H^+$ | (*a*)<br>(*b*) | scalar, chemical, fast |
| 2a. | $H^+$-linked electron transfer, oxidation | $Malate^{2-} \longrightarrow Oxaloacetate^{2-} + 2\{H^+ + e^-\}$<br>$Succinate^{2-} \longrightarrow Fumarate^{2-} + 2\{H^+ + e^-\}$ | (*c*)<br>(*d*) | scalar, chemical, slow |
| 2b. | $H^+$-linked electron transfer, reduction | $2\{H^+ + e^-\} + NAD^+ \longrightarrow NADH + H^+$<br>$2\{H^+ + e^-\} + E\text{-}FAD \longrightarrow E\text{-}FADH_2$ | (*e*)<br>(*f*) | scalar, chemical, slow |
| 3. | transport, translocation | pumping: $H^+_{neg} \longrightarrow H^+_{pos}$<br>diffusion: $H^+_{pos} \longrightarrow H^+_{neg}$ | (*g*)<br>(*h*) | vectorial, compartmental, transmembrane |

The reversible oxidoreduction of dicarboxylate (succinate/fumarate) is catalyzed in the soluble domain of CII extending from the mtIM into the mt-matrix. Succinate donates 2{$H^+$+$e^-$} to FAD bound to the subunit SDHA which contains the catalytically active dicarboxylate binding site. The oxidized yellow (450 nm) form FAD functions as the hydrogen acceptor from succinate to the reduced internal product $FADH_2$ while fumarate is formed as the oxidized external product in the TCA cycle. $FADH_2$ relays electrons further through a series of iron-sulfur redox centers in SDHB to reduce UQ to $UQH_2$ in the membrane domain harboring SDHC and SDHD (9-13, 39) (Figure 1e).

Simple arrows (Figure 1a-c) or pairs of rounded arrows – an external arrow touching the enzyme and an internal arrow within the enzyme – indicate chemical reactions of $H^+$-linked electron transfer (Figure 1d,e). The term $H^+$-coupled electron transfer (43) is replaced by $H^+$-*linked* electron transfer, to avoid confusion with *coupled* $H^+$ translocation. Caution is warranted to distinguish three types of transformation with hydrogen ions, for which IUPAC suggests the term 'hydrons' (44): (i) Acid-base reactions equilibrate fast without catalyst. (ii) '*The terms reducing equivalents or electron equivalents are used to refer to electrons and/or hydrogen atoms participating in oxidoreductions*' (36). Redox transfer of hydrogen atoms is slow and depends on a catalyst. The symbol 2{$H^+$+$e^-$} is introduced to indicate $H^+$-linked electron transfer of two hydrons and two electrons in a redox reaction. (iii) Vectorial $H^+$ transport is either active with translocation through $H^+$ pumps or passive as diffusion driven by the electrochemical pressure difference across cellular compartments (6) (Table 1).

**Sources and consequences of Complex II ambiguities**

'*No representation is ever perfectly expressive, for if it were it would not be a representation but the thing itself*' (30).

Ambiguities emerge if the representation of a concept is vague to an extent that allows for equivocal interpretations. As a consequence, even a basically clear concept (Figure 1) may be communicated as a divergence from an established 'truth'. The comparison between NADH linked to CI and $FADH_2$ (instead of succinate) linked to CII leads us astray, as illustrated by the following textbook quotes (45) which require correction (Figure 2).

(*1*) '*Electrons from NADH enter the electron transport chain in complex I, .. A distinct protein complex (complex II), which consists of four polypeptides, receives electrons from the citric acid cycle intermediate, succinate'* (Figure 2b; ref. 45)*. 'These electrons are transferred to* $FADH_2$*, rather than to NADH, and then to coenzyme Q.*' Note the suggestive comparison of $FADH_2$ and NADH.

(*2*) '*In contrast to the transfer of electrons from NADH to coenzyme Q at complex I, the transfer of electrons from* $FADH_2$ *to coenzyme Q is not associated with a significant decrease in free energy and, therefore, is not coupled to ATP synthesis.*' Note that CI catalyzes electron transfer from NADH to coenzyme Q. In contrast, electron transfer from $FADH_2$ to coenzyme Q is downstream of succinate oxidation by CII. Thus instead of the Gibbs force ('*decrease in free energy*') in $FADH_2 \rightarrow Q$, the total Gibbs force (6) in $S \rightarrow Q$ must be accounted for. In contrast to the extensive quantity Gibbs energy [J], Gibbs force [$J \cdot mol^{-1}$] is an intensive quantity expressed as the partial derivative of Gibbs energy [J] per advancement of a reaction [mol] (6, 46). (In parentheses: Redox-driven proton translocation must be distinguished from phosphorylation of ADP driven by the protonmotive force).

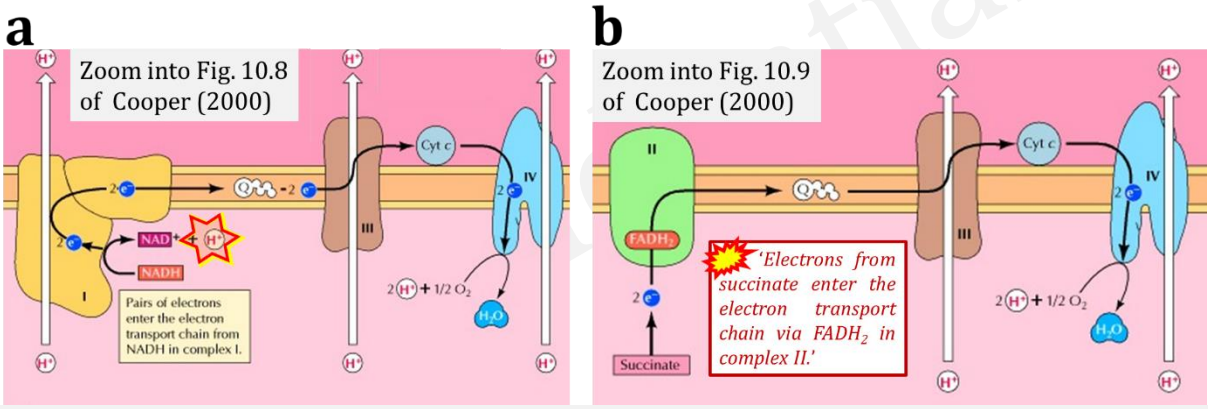


**Figure 2. Electron transfer to CI and CII**. Zoom into figures of ref. 45. **(a)** $H^+$ (marked) is shown to be consumed in $H^+$-linked electron transfer instead of being produced (cf. Figure 1a). **(b)** Marked quote inserted from the legend to Fig. 10.9 of ref. 45.

(*3*) '.. *electrons from succinate enter the electron transport chain via* $FADH_2$ *in complex II.*' Note that CII receives electrons from succinate via FAD. The ambiguity is caused by a lack of unequivocal definition of the electron transfer system ('*electron transport chain*'). Two contrasting definitions are implied of the '*electron transport chain*' or ETS. (*a*) CII is part of the ETS. Hence electrons enter the ETS in the succinate branch from succinate but not from $FADH_2$ **–** from the matrix-ETS to the membrane-ETS (Figure 1c,d). (*b*) If electrons enter the '*electron transport chain* via $FADH_2$ *in complex II*', then subunit SDHA would be upstream and hence not part of the ETS (to which conclusion obviously nobody would agree). Electrons enter CII and thus the membrane-ETS from succinate (Figure 1) but not from $FADH_2$ as the 'product' of succinate dehydrogenase in the TCA cycle, as erroneously shown in Figures 3a,b.

### The $FADH_2$ - FAD confusion in the succinate-pathway

'*Like drops of water on stone, one drop will do no harm, but over time, grooves are cut deep*' (47).

The narrative that the reduced cofactors NADH and $FADH_2$ feed electrons from the TCA cycle into the mitochondrial electron transfer system causes confusion. As a consequence, the prosthetic group $FADH_2$ appears erroneously as the substrate of CII in the ETS linked to succinate oxidation. This error is widely propagated in publications found from 2001 to 2023 (4, 23, 48-356) and numerous educational websites (357). The following examples illustrate the transition from ambiguity to erroneous representation.

*(1)* Ambiguities appear in graphical representations, where $FADH_2$ is the product of SDH and the substrate of CII **–** synonymous with SDH (explicit in Figures 3a,b; implicit in Figure 3c).

*(2)* Ambiguity evolved to misconception in graphical representations (Figures 3d-f).

(*3*) Instead of $NADH+H^+ \rightarrow NAD^+$ (Figure 1a) there appears $NADH \rightarrow NAD^+ + H^+$ or $+2H^+$ and by analogy $FADH_2 \rightarrow FAD+2H^+$ (Figures 3g,h). The analogy $NADH \rightarrow NAD^+$ is taken further to include a charge for FAD or even writing $FADH^+$ (Figures 3i,j). Disturbing patterns are shown in various figures with analogous representations of oxidation of NADH and $FADH_2$ (Table 2).

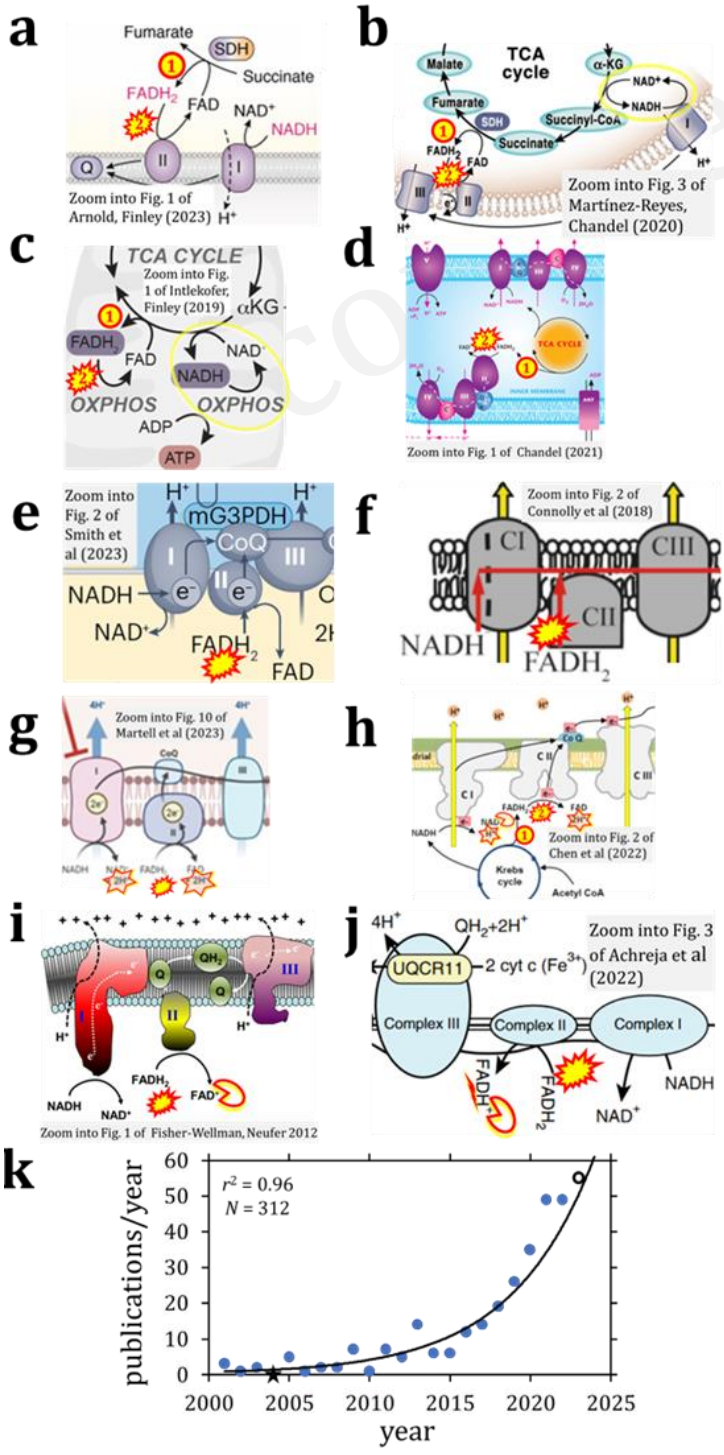


**Figure 3. Complex II ambiguities.** $FADH_2$ depicted as **(1)** product and **(2)** substrate of Complex II by **(a)** (4), **(b)** (80), as in ref. 48-99, 104, 192, 193, 195, 200, 202-207, 210-212, 214, 216-221, 223, 226-228, 232, 234, 237, 240,-242, 246, 272, 281, 286, 292-296, 305-307, 309, 312, 313, 315, 321, and 331. NADH and $NAD^+$ cycle between different types of enzymes (yellow circle), in contrast to the FAD/$FADH_2$ cycle located within the same enzyme molecule (SDH and CII are synonyms). **(c)** From ambiguous NADH-$FADH_2$ analogy (73) to **(d)** graphical misconception (58), as in ref. 100-241. NADH and $FADH_2$ at the doors of CI and CII, respectively, shown by **(e)** an international team (169) and **(f)** an international consortium suggesting guidelines (199); $FADH_2$ cannot enter – it functions always inside CII like FAD which receives electrons from the substrate succinate. **(g)** The redox reaction of the flavin adenine dinucleotide is copied from the nicotinamide adenine dinucleotide with unjustified indication of $2H^+$ formation in the mt-matrix, confusing in the context of the protonmotive force. The figure from ref. 265 is similar or identical to zooms into 33 figures from ref. 49, 57, 70, 72, 133, 154, 186, 245, 247, 250, 252-256, 258, 263-265, 268, 270, 271, 273, 274, 276-281, 318, and 320. **(h)** The CII ambiguity in $FADH_2 \rightarrow FAD+2H^+$ (243-281) fires back at the CI-catalyzed reaction when $NAD^+$ is shown like FAD as NAD without charge (246, 272). **(i)** The $NADH \rightarrow NAD^+$ analogy is taken to the level of copying a charge to $FAD^+$ (289, as in 282-320) or **(j)** $FADH^+$ (332, as in 333). **(k)** Exponential increase of publications with graphical Complex II ambiguities, 2001 to October 2023. Open symbol: the count of 46 publications in 2023 was adjusted for the full year by a multiplication factor of 12/10. Asterisc: zero count in 2004 set at 0.1 for exponential fit. *N*=312 is the number of publications found with graphical CII ambiguities (Table 2).

**Table 2. Misconceptions in graphical representations of electron entry into CI and CII**. $2\{H^+ + e^-\}$ is donated to CI in the oxidation NADH + $H^+$ ⟶ $NAD^+$ + $2\{H^+ + e^-\}$, and to CII in the oxidation $Succinate^{2-}$ ⟶ $Fumarate^{2-}$ + $2\{H^+ + e^-\}$.

| CI e-input errors | | Ref. | CII e-input errors | | Ref. |
|---|---|---|---|---|---|
| NADH | ⟶ $NAD^+ + H^+$ | 45,97,99 | $FADH_2$ | ⟶ FAD | 4,23,48-99[a] |
| NADH | ⟶ NAD | 52,56[b] | $FADH_2$ | ⟶ FAD | 52,56[b] |
| NAD | ⟶ NADH | 56[c] | FAD | ⟶ $FADH_2$ | 56[c] |
| NADH | ⟶ $NAD^+ + H^+$ | 106,122,156,157, 163,172,181 | $FADH_2$ | ⟶ FAD | 100-187[d] |
| NADH | ⟶ NAD | 123,125,130,168, 177,184 | | | |
| NADH +$H^+$ | ⟶ $NAD^+ + 2H^+$ | 149 | | | |
| NADH | ⟶ $NAD^+ + H^+$ | 228,239 | $FADH_2$ | ⟶ | 188-241[e] |
| NADH | ⟶ NAD | 221,228 | | | |
| NADP | | 241 | | | |
| NADH | ⟶ $NAD^+ + H^+$ | 242 | $FADH_2$ | ⟶ FAD + $H^+$ | 242 |
| NADH | ⟶ $NAD^+ + H^+$ | 243,249,260-262, 266,269,275 | $FADH_2$ | ⟶ FAD + $2H^+$ | 243-281[f] |
| NADH | ⟶ NAD + $H^+$ | 244,246,272,279 | | | |
| NADH | ⟶ $NAD^+ + 2H^+$ | 245,247,248,250-259,263-265,267, 268,270,271,274, 276-281 | | | |
| NADH | ⟶ NAD + $2H^+$ | 273 | | | |
| NADH | ⟶ NAD | 287 | $FADH_2$ | ⟶ $FAD^+$ | 282-311[g] |
| NADH +H | ⟶ $NAD^+$ | 308 | $FADH_2$ | ⟶ $FAD^+$ | 308 |
| NADH | ⟶ NAD + $H^+$ | 312 | $FADH_2$ | ⟶ $FAD^+ + H^+$ | 312 |
| NADH | ⟶ $NAD^+ + H^+$ | 313 | $FADH_2$ | ⟶ $FAD^+ + H^+$ | 313 |
| NADH | ⟶ $NAD^+ + H^+$ | 314,316,317,319 | $FADH_2$ | ⟶ $FAD^+ + 2H^+$ | 314-320 |
| NADH | ⟶ $NAD^+ + 2H^+$ | 315,318,320 | $FADH_2$ | ⟶ $FAD^+ + 2H^+$ | |
| | | | $FADH_2$ | ⟶ $FAD^{2+}$ | 321 |
| NADH + $H^+$ | ⟶ NADH | 322 | $FADH_2$ | ⟶ FADH | 322-330 |
| NADH | ⟶ NAD | 327 | | | |
| NADH | ⟶ $NAD^+ + H^+$ | 331 | $FADH_2$ | ⟶ FADH + $H^+$ | 331 |
| | | | $FADH_2$ | ⟶ $FADH^+$ | 332,333[h] |
| | | | FADH | ⟶ | 334,335 |
| NADH | ⟶ NAD + $H^+$ | 336,337 | FADH | ⟶ FAD | 336,337 |
| | | | FADH | ⟶ $FAD^+$ | 338-340 |
| NADH | ⟶ $NAD^+ + H^+$ | 341 | FADH | ⟶ $FAD^+ + H^+$ | 341 |
| NADH | ⟶ $NAD^+ + H^+$ | 342 | FADH | ⟶ $FAD^+ + 2H^+$ | 342 |
| | | | $FADH^+$ | ⟶ FAD | 343 |
| | | | FAD | ⟶ $FADH_2$ | 344-346[i] |
| | | | $FAD^+$ | ⟶ $FADH_2$ | 347 |
| | | | $FADH_2$ | ⟶ FAD + $2H^+$ | 348[j] |
| | | | $FADH_2$ | ⟶ CI ⟶ CII | 349 |
| | | | ETF | ⟶ CII ⟶ CIII | 350-356[k] |
| NADH | ⟶ $NAD^+ + H^+$ | 242 | CI | ⟶ CII ⟶ CIII | 129,166,171,176, 183,224,242,340, 349 |
| $NAD^+ + H^+$ | ⟶ NADH | 386[l] | | | |

[a] FAD a substrate of SDH and $FADH_2$ a substrate of CI (Figure 3a-c).
[b] Oxidation by CI and CII of NADH and $FADH_2$, respectively, from the TCA cycle.
[c] Reduction by CI and CII of NAD ($NAD^+$) and FAD from β-oxidation.
[d] Figure 3d and e.
[e] Figure 3f.
[f] Figure 3g and h.
[g] Figure 3i.

[h] Figure 3j.
[i] Electron transfer into the Q-junction does not occur from a common $FADH_2$ pool from CII and CGpDH, as Fig. 6 of ref. 346 suggests, but through functionally separate branches converging at the Q-junction.
[j] Paradoxically, *oxidation* of $FADH_2$ is linked to *oxidation* of succinate (S) with formation of FAD and fumarate (F) and $2H^+$; S + $FADH_2$ ⟶ FAD + F + $2H^+$.
[k] The pathway is either shown from β-oxidation to CII or explicitly from ETF to CII (Figure 5).
[l] Fig. 7 of ref. 386 shows reduction of $NAD^+$ by CI, where it should be oxidation of NADH.

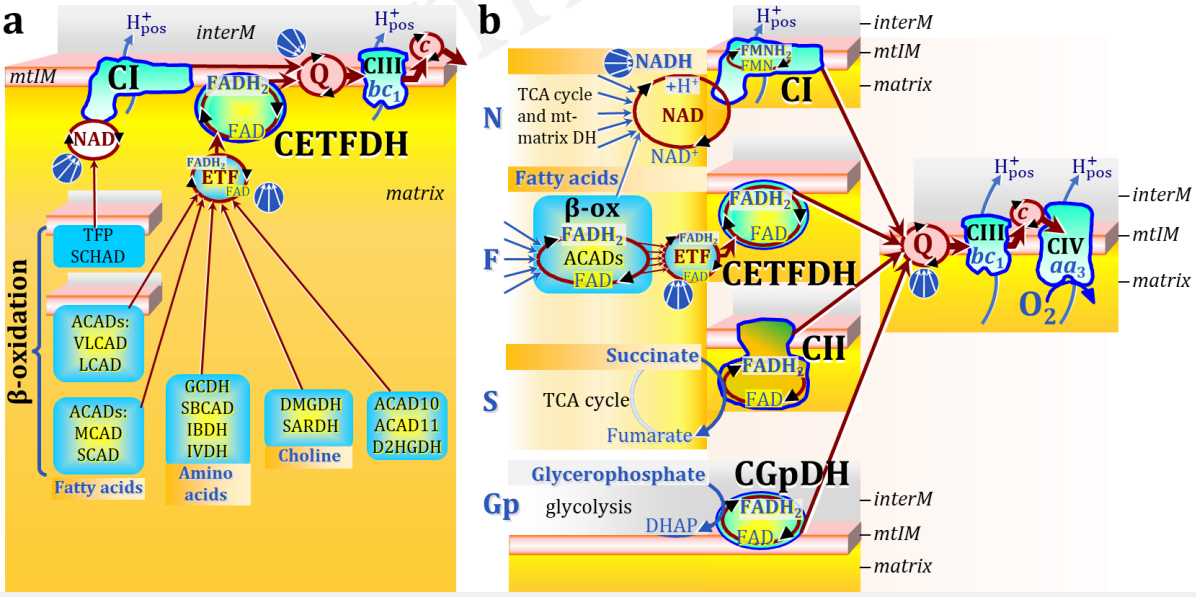


**Figure 4. Convergent electron transfer into the NAD junction, ETF junction, and Q-junction indicated by convergent arrows**, without showing the alignment of supercomplexes. Inter-membrane space (interM) indicated in grey and mt-matrix in yellow-orange. **(a)** Convergent FAD-linked electron transfer into the ETF junction as the first step in β-oxidation from very long- and long-chain acyl-CoA dehydrogenases (ACADS, membrane-bound), medium-, and short-chain ACADs including short/branched-ACAD (SBCAD) and Complex I assembly factor ACAD9; in branched-chain amino acid oxidation from glutaryl-CoA DH (GCDH), SBCAD, isobutyryl-CoA DH (IBDH) and isovaleryl-CoA DH (IVDH); in choline metabolism from dimethylglycine DH (DMGDH) and sarcosine DH (SARDH); and from acyl-CoA DH family members 10 and 11 (ACAD10, ACAD11) and D-2-hydroxyglutarate DH (D2HGDH). References 358, 361, and 362. ETF is the redox shuttle feeding electrons into the membrane-bound electron transferring flavoprotein Complex (CETFDH on the matrix side of the mtIM) and further into Q. Steps two to four in β-oxidation of long- and medium-chain fatty acids are catalyzed by trifunctional protein (TFP, membrane-bound). Step three reduces $NAD^+$+$H^+$ to NADH, feeding electrons into the NAD-cycle, catalyzed by TFP and short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD). **(b)** N: N-pathway through Complex I (CI; see Fig. 1). F: F-pathway of fatty acid oxidation through the β-oxidation cycle (β-ox) with ACADs binding noncovalently FAD; converging electron transfer through ETF to CETFDH, and dependence on the N-pathway. S: S-pathway through CII. Gp: Gp-pathway through mt-glycerophosphate DH Complex (CGpDH on the inter-membrane side of the mtIM) oxidizing glycerophosphate to dihydroxyacetone phosphate (DHAP) in the inter-membrane space.

(*4*) Finally, error propagation from graphical representation (Figure 3) leads to misinformation in the text: '*SDH reduces FAD to $FADH_2$, which donates its electrons*

*to complex II*'; '*each complete turn of the TCA cycle generates three NADH and one $FADH_2$ molecules, which donate their electrons to complex I and complex II, respectively*'; '*complex I and complex II oxidize NADH and $FADH_2$, respectively*' (4).

Clarification is required (see page 48 in ref. 6) to counteract the accelerating propagation of a fundamental bioenergetic misunderstanding (Figure 3k). Electron transfer from succinate in the TCA cycle to the prosthetic group FAD is a redox reaction, where oxidation (ox) of succinate yields $2\{H^+ + e^-\}$ – two hydrons and two electrons – which are donated in the reduction (red) of FAD to $FADH_2$ (Table 1),

ox: $Succinate^{2-} \longrightarrow Fumarate^{2-} + 2\{H^+ + e^-\}$ (Eq. 1a)
red: $2\{H^+ + e^-\} + SDHA\text{-}FAD \longrightarrow SDHA\text{-}FADH_2$ (Eq. 1b)

The net redox reaction equation is

redox: $Succinate^{2-} + SDHA\text{-}FAD \longrightarrow SDHA\text{-}FADH_2 + Fumarate^{2-}$ (Eq. 1)

Commonly the charges of succinate, fumarate (Eq. 1), and other metabolites are not shown explicitly to simplify graphical representations of metabolic pathways. But $NAD^+$ (oxidized) must be distinguished from NAD (total $NAD^+$ + NADH). In $2\{H^+ + e^-\} + NAD^+ \longrightarrow NADH + H^+$ the final $H^+$ is frequently omitted (Figure 3). One hydrogen atom is transferred directly from the hydrogen donor (e.g. malate) to $NAD^+$ without dilution by the aqueous $H^+$ whereas the other forms an aqueous hydrogen ion (32). The equilibrium (Eq. *e* in Table 1) depends on pH. In contrast, Eq. 1b (Eq. *f* in Table 1) is independent of pH. The fundamental difference between $2H^+$ and $2\{H^+ + e^-\}$ in Eq. *e* (Table 1) is lost in representations such as Figures 3g,h.

In summary, two-electron oxidation of succinate is redox-linked to reduction of SDHA-FAD to SDHA-$FADH_2$, and the final electron transfer step in CII reduces UQ to $UQH_2$. In terms of electron entry into CII many publications show it in the wrong direction, i.e. oxidation of $FADH_2$ as electron donor from the TCA cycle to CII (Figure 3). This erroneous presentation has the logical consequence of putting CII into the wrong position of mitochondrial core energy metabolism. Several electron transfer pathways reduce the prosthetic group FAD of different enzymes to $FADH_2$ and then converge separately at the Q-junction (Figure 4). In ambiguous graphs, CII can be seen as an enzyme receiving reducing equivalents from $FADH_2$ and thus mitigating electron transfer into the Q-junction not only from succinate in the TCA cycle but from other flavoprotein-catalyzed pathways feeding into the membrane-ETS. This is incorrect as clarified in the next sections.

**Complex II and fatty acid oxidation**

In the β-oxidation cycle of fatty acid oxidation (FAO), acetyl-CoA and the reducing equivalents $FADH_2$ and NADH are formed in reactions catalyzed by mt-membrane or matrix acyl-CoA dehydrogenases (ACADs) and hydroxyacyl-CoA dehydrogenases (HADs), respectively (358). The ACADs are flavoproteins containing FAD/$FADH_2$ as prosthetic group (358). The $FADH_2$ of the ACADs is reoxidized by reducing FAD noncovalently bound to electron transferring flavoprotein ETF (358-362). Comparable to electron transfer from CIII to CIV by the heme group of cytochrome *c* (363), the small redox protein ETF mediates the transfer of reducing equivalents from $FADH_2$ of ACADs to the respiratory Complex of the membrane-ETS called electron flavoprotein dehydrogenase ETFDH (361) or electron transfer flavoprotein:ubiqinone oxidoreductase ETF-QO (364). This ETFDH Complex (CETFDH) receives $2\{H^+ + e^+\}$ from $FADH_2$ in ETF, linking electron transfer in β-oxidation to electron entry into the Q-

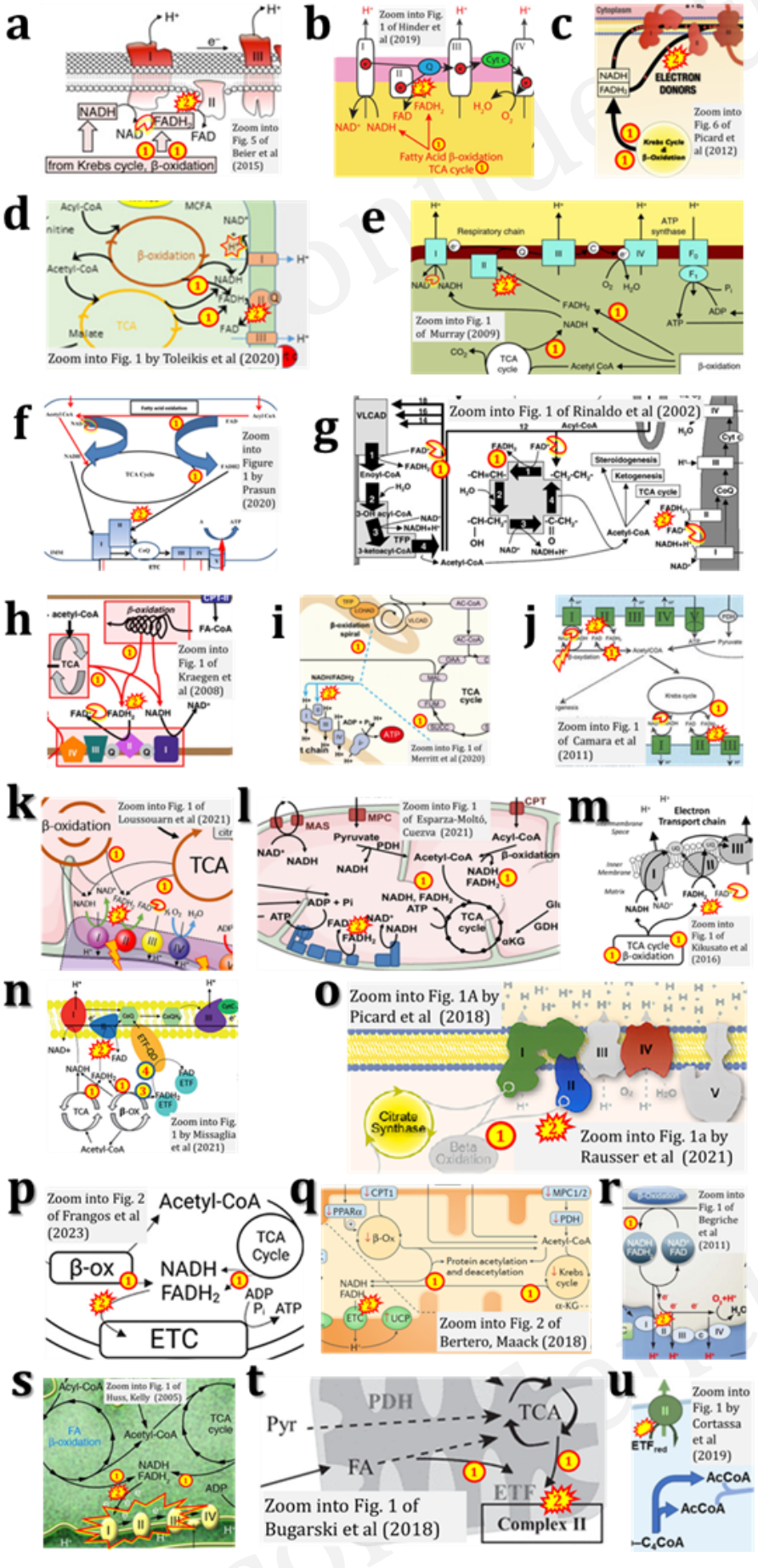


**Figure 5. When $FADH_2$ is erroneously shown (1) as a substrate of CII, then (2) a dubious role of CII in oxidation of $FADH_2$ from β-oxidation is suggested as a consequence.** Zoom into figures **(a)** (52); **(b)** (71); **(c)** (226); **(d)** (97); **(e)** (221); **(f)** (228); **(g)** (284, 300); **(h)** (294); **(i)** (219); **(j)** paradoxical oxidation of $FADH_2$ and NADH in β-oxidation and reduction by CI of NAD ($NAD^+$) from β-oxidation (56); **(k)** (296); **(l)** (62); **(m)** (292); **(n)** (83); **(o)** (350, 353-356); **(p)** (205); **(q)** (192); **(r)** (51) as in (66); **(s)** (349); **(t)** (351); **(u)** (352).

junction independent of CII. CETFDH and CI are the respiratory Complexes involved in convergent electron entry into the Q-junction during FAO (Figure 4). In contrast to the membrane-ETS redox shuttle cytochrome *c*, ETF is a matrix-ETS redox shuttle (or a redox shuttle closely associated with the

mtIM on its matrix side) where multiple electron transfer pathways converge (Figure 4a). Thus the prosthetic group $FADH_2$ in ETF – or simply ETF – is the substrate of CETFDH, comparable to the substrates succinate for CII, glycerophosphate for the respiratory Complex glycerophosphate dehydrogenase (CGpDH), and NADH for CI at the Q-junction, or cytochrome *c* for CIV (Figure 4b). The supercomplex formed between CETFDH and CIII illustrates the CII-independent path of electron transfer from $FADH_2$ bound to ETF into the Q-junction (361).

When $FADH_2$ is erroneously shown free floating in the mt-matrix as a substrate of CII, a dubious role of CII in FAO is suggested as a consequence. In Figures 5a-m, $FADH_2$ (i) is generated by the TCA cycle and β-oxidation and (ii) donates electrons from a misconstrued '$FADH_2$ junction' to CII (52, 56, 62, 71, 97, 219, 221, 226, 228, 284, 292, 294, 296, 300); see also (50, 237). In Figure 5n, two alternative pathways of $FADH_2$ are shown from β-oxidation to CII and CETFDH (83), similar to ref. 84 (Figure 6j) and ref. 202. Picard and colleagues link β-oxidation directly to CII in Figure 5o used in five publications (350, 353-356). In Figure 5p, $FADH_2$ from the TCA cycle and β-oxidation donates reducing equivalents to the 'electron transport chain' (205), where 'ETC-specific respiration' is considered to proceed through CI and CII. Compare with refs. 51, 104, 192, 207, 209, 216, 217, and 240 (Figures 5q,r). Combined with respiratory Complexes defined as CI, CII, CIII, and CIV in numerical sequence, the concept of a linear 'electron transport chain' ETC (in contrast to the convergent ETS) led to the presentation of linear electron flow as (NADH, $FADH_2$) → CI → CII → CIII (349; Figure 5s), with a similar misconception or ambiguity in figures of refs. 129, 166, 171, 176, 183, 224, 242, 340 (Table 2). Electron transfer is even shown to poceed from fatty acids through ETF to CII (351, 352) (Figure 5t,u).

Lemmi et al (365) noted: '*mitochondrial Complex II also participates in the oxidation of fatty acids*'. This holds for the oxidation of acetyl-CoA generated in the β-oxidation cycle and oxidized in the TCA cycle, forming NADH and succinate with downstream electron flow through CI and CII, respectively, into the Q-junction (Figure 1). In contrast, electron transfer from primary flavin dehydrogenases in β-oxidation proceeds through ETF, which functions as the electron ($2\{H^+ + e^-\}$) carrier to CETFDH.

**$FADH_2$ reducing equivalents independent of CII: glycerophosphate oxidation and ETF-linked pathways in addition to fatty acid oxidation**

Comparable to the display of a putative role of CII in FAO (Figure 5), the misconstrued pathway from $FADH_2$ to CII has led to the incorrect notion that CII receives electrons from $FADH_2$ formed in several branches of the ETS upstream of the Q-junction, particularly in the mitochondrial glycerophosphate DH Complex, CGpDH (59, 84, 90, 346, 366-371). '*$FADH_2$ is produced by acyl CoA dehydrogenase (in the β-oxidation cycle), succinate dehydrogenase (in the TCA cycle), and glycerol-3-phosphate dehydrogenase (reoxidation of NADH+ $H^+$ produced in glycolysis by the glycerol-3-phosphate shuttle). These enzymes form part of the inner mitochondrial membrane in close association with Complex II*' (209). The CII ambiguity (Figure 6a) misleads to such direct or indirect suggestions that CII in the ETS is positioned downstream of CGpDH (Figures 6b-d). For carification, the glyceraldehyde-3-phosphate shuttle (366-371) does not transfer $FADH_2$ into the mt-matrix (Figures 6e,f). There is no '$FADH_2$ junction' receiving reducing equivalents and feeding electrons downstream into CII (59, 84, 346) (Figures 6g-j). The term '$FADH_2$ linked substrates' (91) is ambiguous and misleading. In convergent electron transfer into the Q-junction,

the independent part of CII played in the ETS is clarified by recognition of succinate (but not $FADH_2$) as the substrate generated in the TCA cycle and feeding $2\{H^+ + e^-\}$ into the CII-branch of the Q-junction (Figure 4b).

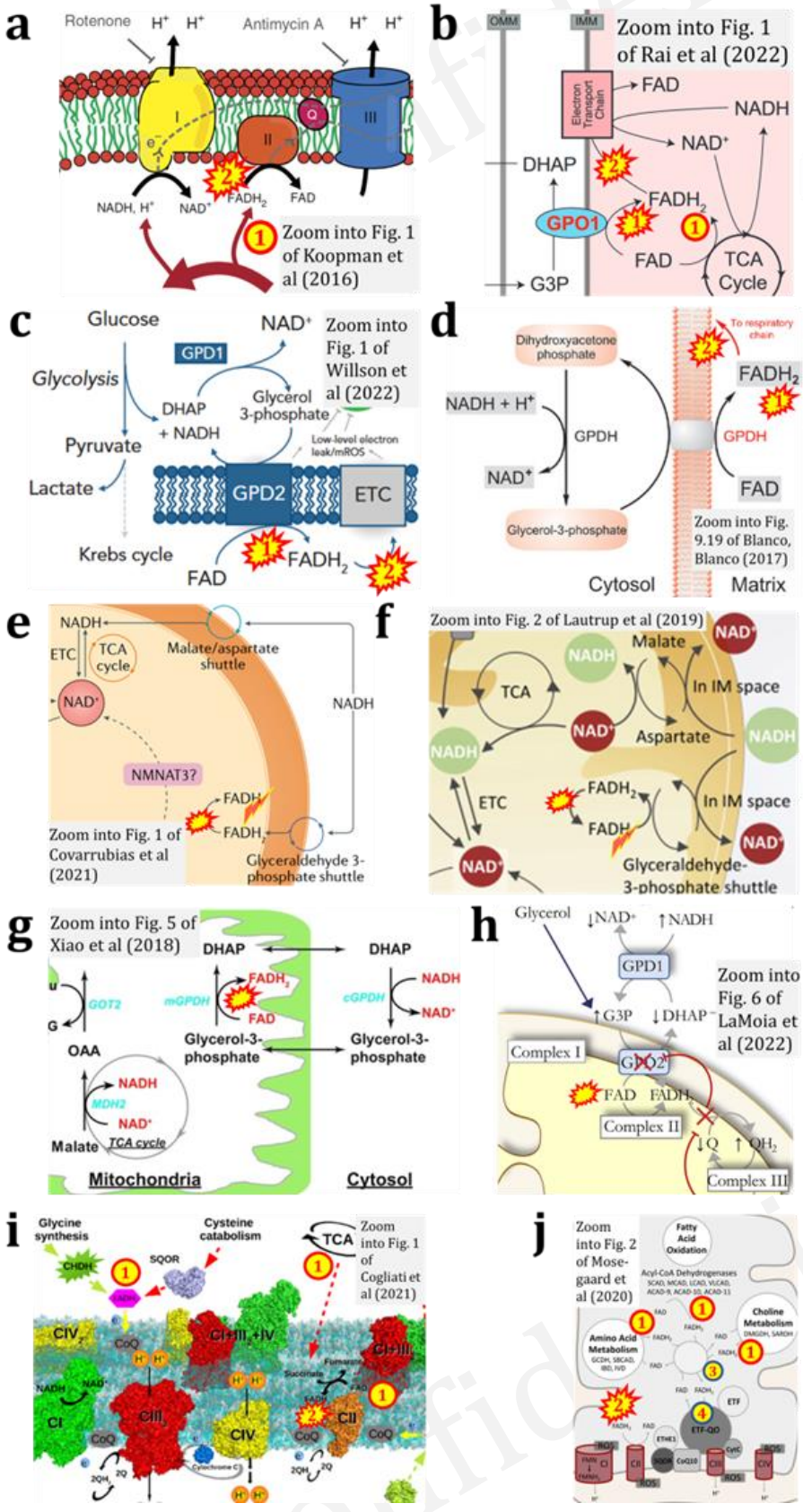


**Figure 6. Ambiguous conclusions on a direct role of CII in the oxidation of glycerophosphate and other '$FADH_2$-linked' pathways**, analogous to false representations of CII involved in fatty acid oxidation (Figure 5). $FADH_2$ **(1)** formed in the mt-matrix as a product of the TCA cycle and **(2)** feeding into CII: **(a)** (75); among 312 examples of CII-ambiguities; and $FADH_2$ **(1)** formed in the mt-matrix from **(b)** GPO1 (90), **(c)** GPD2 (371), or **(d)** GPDH (366), and **(2)** feeding into the ETS. GPO1, GPD2, and GPDH indicate the respiratory Complex CGpDH on the inter-membrane side of the mtIM (Figure 4b). **(e), (f)** and **(g)** The glyceraldehyde-3-phosphate shuttle is erroneously shown to transfer the redox pair FAD/$FADH_2$ (not FADH/$FADH_2$) into the mt-matrix (367, 359, 371). **(h)**The figure (346) suggests that electron transfer

into the Q-junction occurs from a common $FADH_2$ pool generated by CII and CGpDH (GPD2). **(i,j)** The FAD/$FADH_2$ redox system is implicated in various electron transfer pathways independent of CII, but the CII ambiguity does not make this sufficiently clear (59, 84).

## Conclusions

There is currently ambiguity surrounding the precise role of Complex II in core metabolic pathways of mitochondrial electron transfer, particularly fatty acid oxidation. While Complex II is not essential for fatty acid oxidation, it plays a regulatory role by sensing changes in metabolic demand and activating the TCA cycle for oxidation of acetyl-CoA depending on the metabolic conditions. This regulatory function may be particularly important during periods of low oxygen availability or high energy demand. The integration of FAO with the membrane-bound ETS (361) has significant implications for understanding and treating disorders related to β-oxidation and oxidative phosphorylation.

Do misinformed diagrams – from ambiguous electron transfer to presentation of CII as a $H^+$ pump (304, 342, 372-374) – cast doubts on the quality of the publication? Authors and publishers may enjoy artistic graphs as motivational ornaments rather than informational design. Whether using iconic or symbolic elements in graphical representations, incorporating complementary text not only enhances the communication of intended meaning but diagrams will be improved in the process. Using precisely defined terminology prevents misunderstandings (2).

When peer review provides insufficient help for corrections, post-peer review by editors and critical readers is required for revisions of articles which may be updated and re-published as living communications (375). The present review aims to raise awareness in the scientific community about the inherent ambiguity crisis, complementary to addressing the widely recognized issues of the reproducibility and credibility crisis (376). The term ‘crisis’ is rooted etymologically in the Greek word *krinein*: meaning to ‘separate, decide, judge’. In this sense, science and communication in general are a continuous crisis at the edge of separating clarity or certainty from confusing double meaning down to fake-news. Reproducibility relates to the condition of repeating and confirming calculations or experiments presented in a published resource. Apart from critizising established textbooks (377), their acknowledgement with reference to expert bioenergetics reviews (11, 26) and terminological consistency (2) will pave the way out of the CII ambiguity crisis.

As defined in the introduction, the present critical review addresses type 2 ambiguities in redox reactions and bioenergetic pathways involving respiratory Complex II and electron transfer into the Q-junction. In the 312 listed references on CII ambiguities, several figures show $H^+$ or $2H^+$ being formed in the oxidation of $FADH_2$. Formation of $H^+$ or $2H^+$ in the oxidation of succinate is displayed in many more references which are not included here. The ambiguous use of the symbol $H^+$ makes no distinction between (i) $2H^+$ indicating reducing equivalents $2\{H^+ + e^-\}$ participating in oxidoreductions, (ii) $H^+$ in chemiosmotic translocation across a membrane, and (iii) $H^+$ in acid/base reactions (Table 2). Several type 2 CII-ambiguities, however, may be more appropriately classified as errors and incorrect representations of scientific facts, resulting from ignorance of the relevant literature. On the other side of the spectrum we find productive type 1 ambiguities (30), when different points of view lead to innovation. A prominent case of ambiguity in the grey zone between types 1 and 2 has

been uniquely demonstrated by analysis of the popular notion of 'oxidative stress' – a term more frequently found than 'mitochondria' in PubMed, widely used with vague definitions and without expression by numerical values and corresponding units (378). Another example closer to type 2 ambiguity is the use of the terms and experimental application of 'hypoxia' and 'normoxia' in bioenergetics, when air-level normoxic conditions for isolated mitochondria and cultured cells are effectively hyperoxic and may cause oxidative damage (379, 380). Another ambiguity in bioenergetics links to the confusing use of the terms uncoupling, decoupling, dyscoupling, where rigorous definition is warranted (2). Linking bioenergetics to physical chemistry and the thermodynamics of irreversible processes, the ambiguous use (type 1) of the terms force and pressure (381-385) has deep consequences on the enigmatic concept of non-ohmic flux-force relationships in the context of mitochondrial membrane potential and the protonmotive force (6).

The present review adds Complex II ambiguities to the growing list. The trust in the science of bioenergetics is at stake — the trust of students, the general public, granting agencies, and stakeholders in the research-based health system. Clarification instead of perpetuation of Complex II ambiguities leads to a better representation of fundamental concepts of bioenergetics and helps to maintain the high scientific standards required for translating knowledge on metabolism into clinical solutions for mitochondrial diseases.

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**Conflict of interest**

E. Gnaiger is editor-in-chief of *Bioenergetics Communications*.

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## Abbreviations and definitions

| | |
|---|---|
| $2\{H^+ + e^-\}$ | redox equivalents in $H^+$-linked electron transfer |
| CI | Complex I |
| CII | Complex II, SDH |
| CETFDH | electron transferring flavoprotein dehydrogenase Complex |
| CGpDH | mt-glycerophosphate dehydrogenase Complex |
| DH | dehydrogenase |
| FAD | oxidized flavin adenine dinucleotide |
| $FADH_2$ | reduced flavin adenine dinucleotide |
| FAO | fatty acid oxidation |
| FMN | oxidized flavin mononucleotide |
| $FMNH_2$ | reduced flavin mononucleotide |
| mt-matrix | mitochondrial matrix |
| mtIM | mitochondrial inner membrane |
| NAD | nicotinamide adenine dinucleotide, oxidation state is not implied |
| $NAD^+$ | oxidized nicotinamide adenine dinucleotide |
| $NADH_2$ | reduced nicotinamide adenine dinucleotide |
| Q | ETS-reactive coenzyme Q, oxidation state is not implied |
| QFR | mena-quinol-fumarate oxidoreductase |
| SQR | succinate-ubiquinone oxidoreductase |
| SDH | succinate dehydrogenase, CII |
| TCA cycle | tricarboxylic acid cycle |

Cofactor: ‘*an organic molecule or ion (usually a metal ion) that is required by an enzyme for its activity. It may be attached either loosely (coenzyme) or tightly (prosthetic group)*’ (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=23357; retrieved 2023-09-23).

Coenzyme or cosubstrate: a cofactor that is attached loosely and transiently to an enzyme, the ‘*dissociable, low-relative-molecular-mass active group of an enzyme which transfers chemical groups, hydrogen, or electrons. A coenzyme binds with its associated protein (apoenzyme) to form the active enzyme (holoenzyme)*‘ (387).

Prosthetic group: ‘*a tightly bound, specific nonpolypeptide unit in a protein determining and involved in its biological activity*’ (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:26348; retrieved 2023-09-23).