Mitochondrion 34 (2017) 56–66

Contents lists available at ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Fumarate reductase superfamily: A diverse group of enzymes whose evolution is correlated to the establishment of different metabolic pathways

Douglas Jardim-Messeder [a], Caroline Cabreira-Cagliari [a], Rafael Rauber [b], Andreia Carina Turchetto-Zolet [a], Rogério Margis [b], Márcia Margis-Pinheiro [a,*]

[a] Departamento de Genética, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
[b] Centro de Biotecnologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

ARTICLE INFO

Article history:
Received 26 September 2016
Received in revised form 21 December 2016
Accepted 10 January 2017
Available online 11 January 2017

Keywords:
Fumarate reductase
Succinate dehydrogenase
Mitochondria
Chloroplast
Endosymbiosis

ABSTRACT

Fumarate and succinate are known to be present in prebiotic systems essential for the origin of life. The fumarate and succinate interconversion reactions have been conserved throughout evolution and are found in all living organisms. The fumarate and succinate interconversion is catalyzed by the enzymes succinate dehydrogenase (SDH) and fumarate reductase (FRD).

In this work we show that SDH and FRD are part of a group of enzymes that we propose to designate "fumarate reductase superfamily". Our results demonstrate that these enzymes emerged from a common ancestor and were essential in the development of metabolic pathways involved in energy transduction.

1. Introduction

The "Origin of Life" is the process which gave rise to living organisms from non-living matter, such as simple organic compounds, and occurred on Earth about 3.5 billion years ago (Awramik, 1992). In this context, a non-enzymatic reverse tricarboxylic acid (TCA) cycle that provided a core mechanism to produce carbon compounds from CO_2 and water under prebiotic conditions has been hypothesized (Wachtershauser, 1993). Thus, the intermediate molecules in the TCA cycle, such as succinate and fumarate, are present in prebiotic systems of organic molecules essential for the origin of life. Corroborating this hypothesis, the reaction pathways involving fumarate and succinate have been conserved throughout evolution, and enzymes catalyzing their interconversion are found in virtually all living organisms, including eubacteria, eukaryotes and Archaea (Hederstedt and Ohnishi, 1992).

The succinate:quinone oxidoreductases (SQOR) (EC 1.3.5.1) – succinate dehydrogenase (SDH) and fumarate reductase (FRD) – are oligomeric isoenzymes that catalyze the interconversion of fumarate and succinate under physiological conditions (Hirsch et al., 1963). SDH activity was first detected in frog muscle in 1909 (Thunberg, 1909). SDH catalyzes the oxidation of succinate to fumarate (reaction 1), a vital process in organisms that use the TCA cycle for central carbon metabolism. In addition, this reaction is coupled to the reduction of ubiquinone (UQ) to ubiquinol (QH_2) (reaction 2), thereby donating electrons to the aerobic electron transport chain (ETC). On the other hand, FRD is a key component of anaerobic respiration which catalyzes the reverse reactions. Thus, in the absence of oxygen, fumarate acts as a final electron acceptor for anaerobic respiration (Blaut et al., 1989). The interconversion of succinate and fumarate by SQOR enzymes is reversible, besides *in vivo* the oxidation and reduction reactions preferentially occur according to each enzyme (SDH or FRD). In *Escherichia coli*, for example, the FRD

Abbreviations: CoB-S-H, coenzyme B; CoM-S-H, coenzyme M; ETC, electron transporter chain; FRD, fumarate reductase; FRDS, soluble NADH: fumarate reductase; LASPO, L-aspartate reductase; MQ, menaquinone; MQH_2, menaquinol; RQ, rhodoquinone; RQH_2, rhodoquinol; SDH, succinate dehydrogenase; SQOR, succinate: quinone oxireductase; TCA, tricarboxylic acid; TFRD, thiol: fumarate reductase; UQ, ubiquinone; UQH_2, ubiquinol.

* Corresponding author at: Av. Bento Gonçalves 9500, Prédio 43312/Sala 206, CEP 91501-970 Porto Alegre, RS, Brazil.
E-mail addresses: douglas.messeder@gmail.com (D. Jardim-Messeder), carol.cabreira@yahoo.com.br (C. Cabreira-Cagliari), rauber_rafa@yahoo.com.br (R. Rauber), aturchetto@gmail.com (A.C. Turchetto-Zolet), rogerio.margis@ufrgs.br (R. Margis), marcia.margis@ufrgs.br (M. Margis-Pinheiro).

http://dx.doi.org/10.1016/j.mito.2017.01.002
1567-7249/

is also able to catalyze succinate oxidation; however, with a lower activity (Cecchini et al., 1986; Sucheta et al., 1993)

$$\text{succinate} \rightarrow \text{fumarate} + 2H^+ + 2e^- \quad \text{(reaction1)}$$

$$\text{quinone} + 2H^+ + 2e^- \rightarrow \text{quinol} \quad \text{(reaction2)}$$

SDH preferentially catalyzes the oxidation of succinate to fumarate ($E^\circ = +30$ mV) using an electron acceptor with a high reduction potential, such as ubiquinone (UQ) ($E^\circ = +100$ mV). Finally, in the aerobic ETC, oxygen has the high reduction potential ($E^\circ = 820$ mV), thus operating as a final electron acceptor. On the other hand, FRD catalyzes the reverse reaction, oxidizing an electron donor and reducing fumarate to succinate. For this, the electron donor used by FRD must possess a lower redox potential than the fumarate/succinate. Thus, FRD cannot use UQH_2 as an electron donor, and the fumarate reduction is coupled to the oxidation of a lower reduction potential quinol, such as menaquinol (MQH_2) ($E^\circ = -73$ mV) (Fig. 1A).

In Gammaproteobacteria, the succinate oxidation and fumarate reduction are carried out by independent enzymes which act as SDH or FRD. On the other hand, in other bacterial clades and in Archaea, only one enzyme with both activities can be found. Eukaryotes possess only one enzyme that acts as a SDH *in vivo*. Despite the large scale genome sequencing projects which have provided SDH and FRD sequences from various organisms, the classification of these enzymes is not obvious because it is based only on biochemical data, which has not yet been determined for many species. Thus, without prior knowledge of the physiological role of a particular enzyme in the metabolism of a given bacterium, it is not possible to predict whether the enzyme functions as a FRD or a SDH *in vivo*.

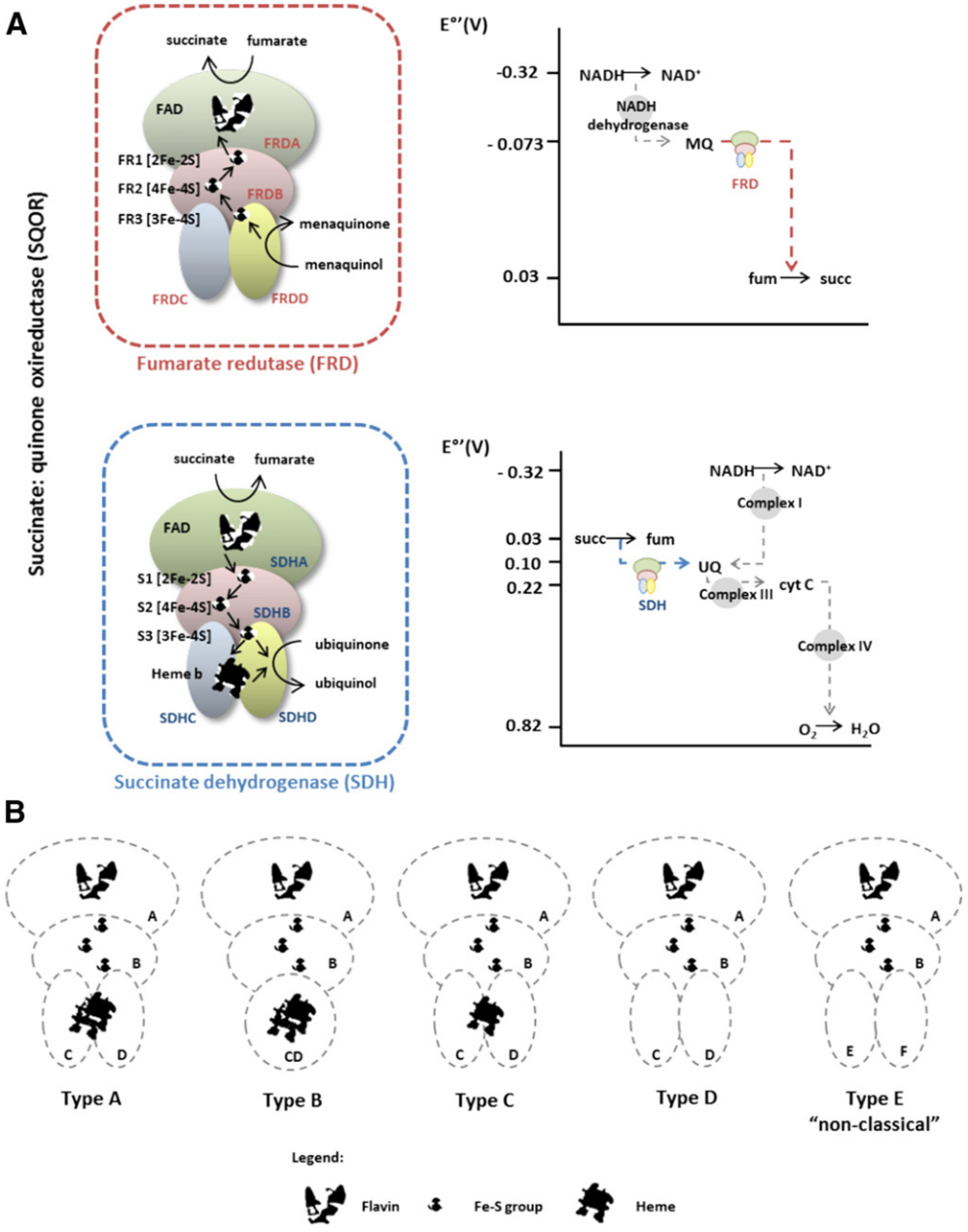

Fig. 1. Schematic representation of the succinate:quinone oxidoreductase family. (A) Schematic representation of fumarate reductase (FRD) and succinate dehydrogenase (SDH) activities. The graphics to the right represent the reduction potential of different components of aerobic and anaerobic electron transport chains. (B) Classification (types A–E) of succinate: quinone oxidoreductases (SQOR) based on their hydrophobic domains and heme content. UQ – ubiquinone; cyt C – cytochrome C; MQ – menoquinone.