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Review

'Come into the fold': A comparative analysis of bacterial redox enzyme maturation protein members of the NarJ subfamily

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ABSTRACT

Redox enzyme maturation proteins (REMPs) are system-specific chaperones required for the maturation of complex iron sulfur molybdoenzymes that are important for anaerobic respiration in bacteria. Although they perform similar biological roles, REMPs are strikingly different in terms of sequence, structure, systems biology, and type of terminal electron acceptor that it supports for growth. Here we critically dissect current knowledge pertaining to REMPs of the nitrate reductase delta superfamily, specifically recognized in *Escherichia coli* to include NarJ, NarW, TorD, DmsD, and YcdY, also referred to as the NarJ REMP subfamily. We show that NarJ subfamily members share sequence homology and similar structural features as revealed by alignments performed on structurally characterized REMPs. We include an updated phylogenetic analysis of subfamily members, justifying their classification in this subfamily. The structural and functional roles of each member are presented herein and these discussions suggest that although NarJ subfamily members are related in sequence and structure, each member demonstrates remarkable uniqueness, validating the concept of system-specific chaperones.

Contents

Abbreviations: REMP, redox enzyme maturation protein; CISM, complex iron–sulfur molybdoenzyme; Tat, twin-arginine translocase; RR, twin-arginine

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1. Introduction

1.1. Anaerobic respiration in bacteria

Respiratory redox enzymes catalyze oxidation/reduction reactions by transferring electrons from a donor to an acceptor molecule. Many respiratory enzymes operate at the cytoplasmic membrane by forming a redox loop between periplasmic and cytoplasmic enzymes connected by the quinone pool [1,2]. In addition to oxygen, bacteria can utilize a variety of substrates as a terminal electron acceptor for respiration in anaerobic environments. A well characterized example of this is the facultative model organism, *Escherichia coli*, which has a variety of known anaerobic electron acceptors that include nitrate (NO_3^-), nitrite (NO_2^-), dimethyl sulfoxide ($(CH_3)_2SO$, DMSO), fumarate ($C_4H_4O_4$), and trimethylamine *N*-oxide ($(CH_3)_3NO$, TMAO) [2].

The respiratory enzymes that catalyze reduction of DMSO, TMAO, and nitrate are grouped under the molybdoenzyme superfamily [3–8]. They all contain a molybdenum-*bis*(pyranopterin guanine dinucleotide)

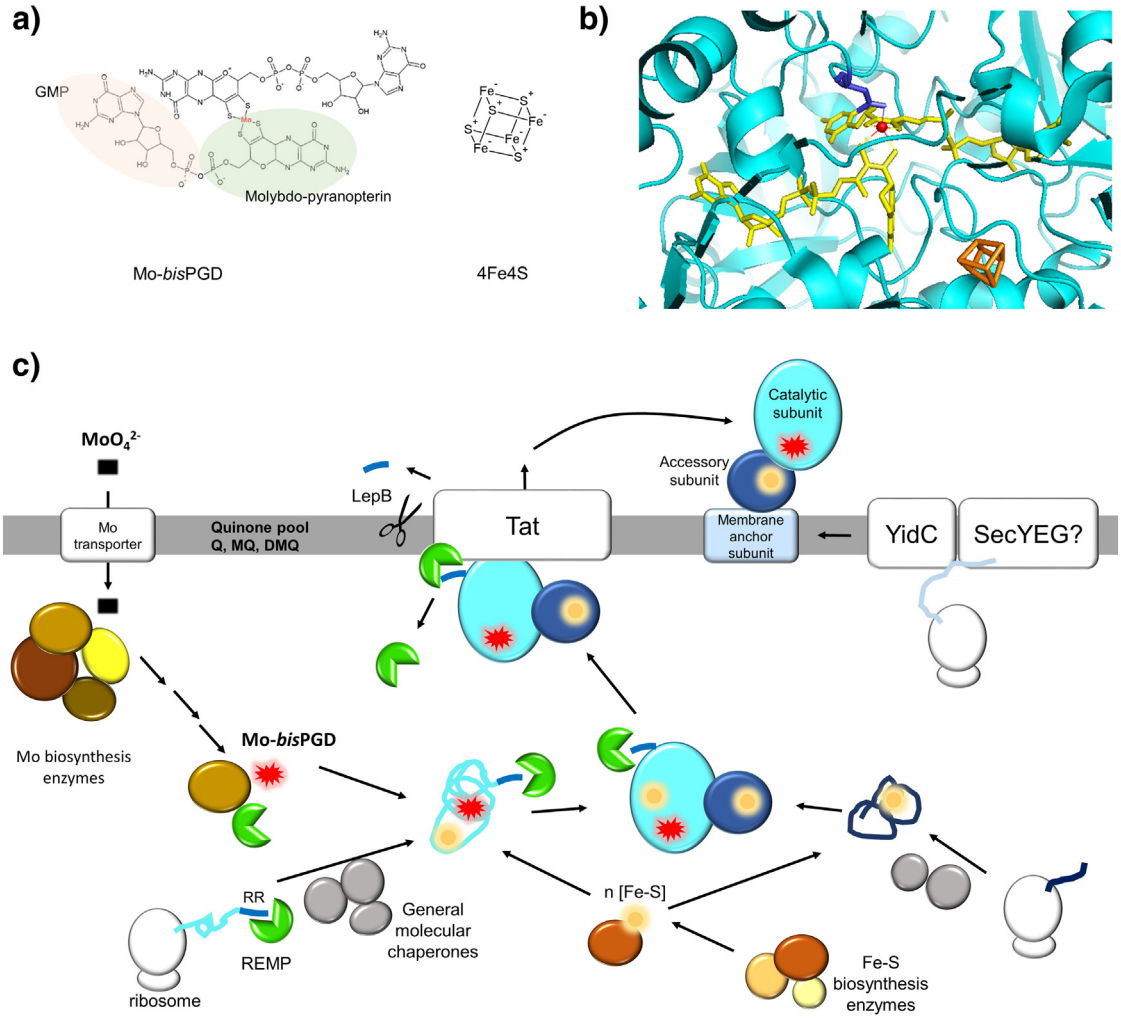

Fig. 1. Complex iron sulfur molybdoenzymes in bacteria. a) Structures of the catalytic cofactor Mo-*bis*PGD and the iron–sulfur cluster (typically [4Fe–4S]) found in a bacterial CISM. b) Example of how Mo-*bis*PGD and [4Fe–4S] is coordinated in the NarG catalytic subunit of *E. coli* nitrate reductase A (PDB ID: 1Q16). The Mo atom (red) is coordinated by the two pyranopterins (yellow) and the carboxylate group of Asp222 (blue). Proximity of the [4Fe–4S] to Mo-*bis*PGD is also shown (orange). c) Maturation pathway of a typical three-subunit CISM begins with protein translation from the ribosome. The large catalytic subunit is synthesized with a twin-arginine (RR) leader peptide and folding is aided by general molecular chaperones and likely its cognate REMP. It is bound by the REMP chaperone at the RR-leader and folding is assisted along with insertion of the Mo-*bis*PGD cofactor, which was synthesized by the molybdenum cofactor biosynthesis pathway proteins. At the same time, the small accessory subunit is translated, folded, and its [Fe–S] iron–sulfur cluster(s) are coordinated. The two subunits come together to and are targeted towards the Tat machinery by the REMP by a 'piggyback' or 'hitchhiker' mechanism. The complex is translocated across the cytoplasmic membrane and RR-leader is cleaved by leader peptidase I (LepB). The subunits attach to its membrane anchor subunit, which was inserted into the cytoplasmic membrane via the YidC pathway that may or may not involve the SecYEG translocon. The redox loop is completed through transfer of electrons via the quinone pool, consisting of ubiquinone (Q), menaquinone (MQ), and demethyl-menaquinone (DMQ) in the cytoplasmic membrane.