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Review

Iron/sulfur proteins biogenesis in prokaryotes: Formation, regulation and diversity ☆

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ABSTRACT

Iron/sulfur centers are key cofactors of proteins intervening in multiple conserved cellular processes, such as gene expression, DNA repair, RNA modification, central metabolism and respiration. Mechanisms allowing Fe/S centers to be assembled, and inserted into polypeptides have attracted much attention in the last decade, both in eukaryotes and prokaryotes. Basic principles and recent advances in our understanding of the prokaryotic Fe/S biogenesis ISC and SUF systems are reviewed in the present communication. Most studies covered stem from investigations in *Escherichia coli* and *Azotobacter vinelandii*. Remarkable insights were brought about by complementary structural, spectroscopic, biochemical and genetic studies. Highlights of the recent years include scaffold mediated assembly of Fe/S cluster, A-type carriers mediated delivery of clusters and regulatory control of Fe/S homeostasis *via* a set of interconnected genetic regulatory circuits. Also, the importance of Fe/S biosynthesis systems in mediating soft metal toxicity was documented. A brief account of the Fe/S biosynthesis systems diversity as present in current databases is given here. Moreover, Fe/S biosynthesis factors have themselves been the object of molecular tailoring during evolution and some examples are discussed here. An effort was made to provide, based on the *E. coli* system, a general classification associating a given domain with a given function such as to help next search and annotation of genomes. This article is part of a Special Issue entitled: Metals in Bioenergetics and Biomimetics Systems.

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1. Introduction

Iron/sulfur (Fe/S) clusters are thought to rank among the most ancient and versatile inorganic cofactors found in all kingdoms of life [1,2]. Thanks to their chemical versatility, Fe/S centers can act as catalysts or redox sensors and are predicted to be used by a large number of protein species (over 150 in *Escherichia coli* and 50 in *Mycobacterium tuberculosis* [3,4]). Likewise, Fe/S proteins are found to participate in diverse biological processes such as respiration, central metabolism, DNA repair or gene regulation [5–8].

The most common types of Fe/S clusters are the rhombic [2Fe – 2S] and cubic [4Fe – 4S] types, which possess either ferrous (Fe^{2+}) or ferric (Fe^{3+}) iron and sulfide (S^{2-}). In a vast majority of proteins, cysteine residues coordinate the iron ions of the Fe/S cluster, but histidinyl residues can also function as ligands [1].

Although Fe/S clusters formation can be achieved spontaneously in vitro with inorganic iron and sulfur sources [9], the in vivo situation is more complex and requires so-called Fe/S biogenesis systems. These latter systems were identified in both prokaryotes and eukaryotes. Basic principles and key molecular actors required for the building of a Fe/S cluster are depicted in Fig. 1. Briefly, a cysteine desulfurase produces sulfur from L-cysteine, a scaffold provides a molecular platform allowing iron and sulfur to meet and form a cluster, and a carrier delivers a cluster to the terminal apotarget. The source of iron remains uncertain and multiple origins have been proposed such as frataxin, which will be discussed below in a dedicated section.

Additional factors can join this basic assembly line (Table 1). The number of Fe/S biogenesis systems varies depending upon the organism. Three systems have been identified in bacteria, namely NIF, ISC and SUF systems, the two latter systems being conserved in eukaryotes [10–13]. NIF, first discovered in the nitrogen-fixing bacterium *Azotobacter vinelandii*, is dedicated to maturation of nitrogenase [14,15]. In contrast, the ISC and SUF systems permit the maturation of all Fe/S proteins in the cell. Components homologous to ISC are found in mitochondria, and those homologous to SUF are present in the chloroplasts [16–18].

In the present review, we present the basic principles and most recent findings on how ISC and SUF systems carry out Fe/S cluster biogenesis in prokaryotes. A most significant part of this review deals with characteristics and roles of components assisting Fe/S biogenesis. Because *E. coli* has the two conserved systems, ISC and SUF, it offers a unique opportunity to investigate the interplays between the two systems and to look into an organism that takes advantage of redundancy to accommodate growth conditions and/or target specificity. An attempt was also made to describe the features of Fe/S biogenesis beyond

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model organisms and we aimed at giving a flavor of what biodiversity could make soon available to research in the field. Last, special attention was given to bacterial pathogens and the use they make of Fe/S biogenesis systems. For readers interested in the eukaryotic systems, an excellent and comprehensive review is presented in the same series [18].

2. Mechanism of Fe/S cluster assembly

2.1. The ISC system

The ISC-mediated assembly of Fe/S cluster is mediated by a five-protein complex (Fig. 2), wherein a rich choreography of controlled protein–protein interactions and associated conformational changes are taking place (Fig. 3). Biochemical in vitro studies have shown that IscU is able to act both as a sulfur and iron acceptor, to promote the assembly of the Fe/S cluster, and to transfer it to apotargets [19–27]. Moreover, in vivo, a dominant-negative allele that has a highly conserved aspartate residue changed to an alanine ($IscU^{D39A}$) was trapped with the sulfur donor IscS, in a non-covalent, non-dissociating complex that contains a Fe/S cluster [28]. These studies showed that cluster assembly and release could be uncoupled, and that Fe/S assembly on the scaffold occurred without dissociation of the IscU–IscS complex. These conclusions were later substantiated by in vitro Fe/S transfer assay and structural analysis (see below) [28–30]. Together, these studies provided convincing evidence that IscU acts as a scaffold.

IscS, a pyridoxal-5′-phosphate (PLP)-dependent enzyme, catalyzes the production of sulfur from L-cysteine [31]. The sulfur is transiently bound in the form of a persulfide to an active-site cysteine (Cys328) of IscS and is subsequently transferred to the scaffold IscU [20,21,24,32].

The crystal structure of the *E. coli* apoIscU–IscS complex was obtained by X-ray crystallography showing each IscU molecule interacts with one subunit of the IscS dimer leading to a 2:2 stoichiometry [33]. The catalytic Cys328 residue of IscS was located in a disordered region, but was estimated to be too far from any of the three Fe/S Cys ligands (Cys37, Cys63 and Cys106) of IscU for sulfur transfer, unless movement of the loop occurred [33]. Such movement was likely trapped in the structure of the holoIscU–IscS complex from *Archeoglobus fulgidus* recently characterized. This complex includes the $IscU^{D39A}$ allele that contains a stable [2Fe–2S] cluster (see above), and the IscS active site containing loop that is well ordered and points at the cluster-binding site of IscU [30]. Remarkably, the catalytic Cys residue of IscS is used as a ligand of the [2Fe–2S] cluster together with the three Cys residues of IscU. This structural analysis shows that the D39 residue plays a critical role in the dissociation of the IscU–IscS complex. Its modification to alanine prevents release of the cluster just formed, hence yields a dominant negative allele [30].

NMR methods provided information on the apoIscU–IscS complex, which were quite divergent from those obtained with X-ray crystallography. In fact, NMR investigations of IscU protein have repeatedly pointed to a highly dynamic structure. Early observations with the *Thermotoga maritima* enzyme suggested a “molten globule” type of the structure, whereas the Zn-bound IscU from *Haemophilus influenzae* was largely structured [34,35]. In line with these studies, recent investigations by NMR analysis have proposed that *E. coli* apoIscU could exist in two slowly inter-converting conformational states: one disordered (D) and one structured (S). Importantly, the dynamics of the S/D inter-conversion could be modified by adding Zn^{2+} in the medium, which favored the S state, or by the D39A mutation in IscU [36]. These results suggest that the D state of apoIscU could be the primary substrate for IscS, which would then be converted to an S state that stabilizes the [2Fe–2S] cluster form [37]. Another actor in Fe/S assembly, ferredoxin, has been proposed to participate in the reductive coupling of two $[2Fe–2S]^{2+}$ clusters to form a single $[4Fe–4S]^{2+}$ cluster on IscU [26].

For the Fe/S cluster release process, IscU interacts with two other partners, HscA and HscB, members of the DnaK/DnaJ chaperones/co-chaperones families, respectively [38]. The presence of the specialized HscA and HscB greatly increases the cluster transfer rate in an ATP-dependent manner [39–42]. HscA recognizes a specific LPPVK sequence motif of IscU and its interaction with the scaffold protein is regulated by the co-chaperone HscB, whose interaction with IscU involves hydrophobic residues [43–47]. A model for the mechanism by which the chaperone facilitates cluster release was recently proposed, based on the spectroscopic and kinetic properties of Fe/S transfer of IscU mutants [48]. In this model, among the conformational isomers of IscU2 [2Fe–2S] having different [2Fe–2S] cluster affinity, the chaperone binds and stabilizes an isomer with low [2Fe–2S] cluster affinity, thereby favoring the release of the Fe/S cluster from IscU [48].

As mentioned above, these series of studies have led to picture that the assembly and release steps act as a highly concerted interplay between different conformational states of the scaffold, chaperone and target as depicted in Fig. 3 [37,49]. As we described below, Fe/S carrier proteins are likely to act at a step between cluster assembly on the scaffold and transfer to the target, but these carrier proteins were not included in the Fig. 3 as in vitro Fe/S transfer can occur in their absence.

2.2. The SUF system

The SUF-mediated assembly of Fe/S clusters requires two sub-complexes constituted by the SufBCD and the SufSE proteins, respectively (Fig. 2). The SufBCD complex can bind and transfer a

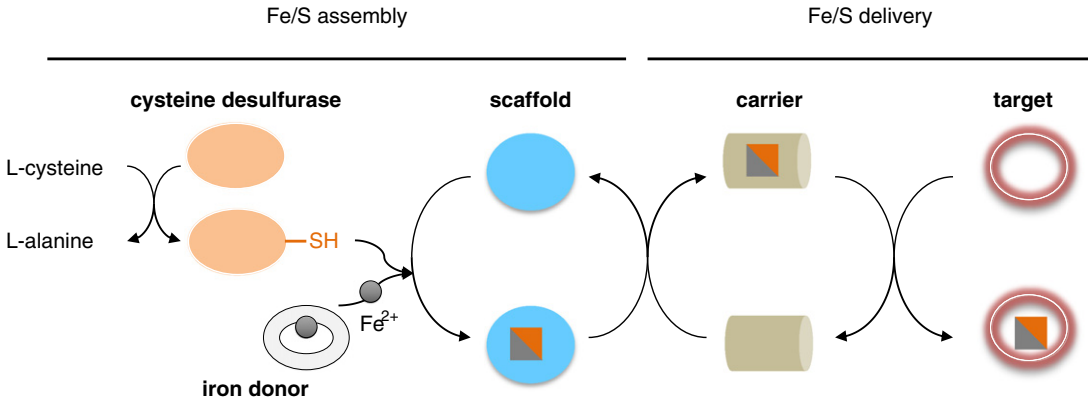

Fig. 1. General principles of Fe/S cluster biogenesis. The Fe/S cluster assembles on a scaffold protein, which receives sulfur from a cysteine desulfurase and iron from an as yet non identified source. Then, the pre-formed Fe/S cluster is transferred to a carrier protein, which delivers it to the final apotarget.

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