Iron-sulfur protein biogenesis in eukaryotes

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Iron-sulfur (Fe/S) protein biogenesis in eukaryotic cells requires three complex proteinaceous machineries: The mitochondrial iron-sulfur cluster (ISC) assembly machinery is needed for the generation of all cellular Fe/S proteins. It was inherited from bacteria and is conserved in (most) eukaryotes from yeast to man. Cytosolic/nuclear Fe/S protein assembly additionally depends on the mitochondrial ISC export and the cytosolic iron-sulfur protein assembly (CIA) apparatus. Components of the latter two machineries are highly conserved in eukaryotes.

The mitochondrial ISC assembly machinery can currently be divided into three major groups: i) Components playing a role in cluster assembly on the scaffold proteins Isu1/2 such as the cysteine desulfurase Nfs1 acting as a sulfur donor, frataxin Yfh1 serving as an iron donor, and the ferredoxin/ferredoxin reductase Yah1/Arh1 presumably needed for reduction. ii) Components acting after cluster assembly on Isu1/2 such as the Hsp70/40/Mge1 chaperone system and the glutaredoxin Grx5. iii) Components with no apparent function in the major Isu1/2-dependent pathway such as Isa1/2 and Nfu1. We will present a combination of *in vivo* and *in vitro* studies trying to unravel the functions of the ISC components.

The maturation of cytosolic/nuclear Fe/S proteins crucially requires the mitochondrial ISC machineries, but the molecular reason for this dependence is still unclear. According to a current working model the mitochondrial ISC export machinery translocates a component required for Fe/S protein assembly in the cytosol. Constituents of this machinery are the ABC transporter Atm1 of the mitochondrial inner membrane, the sulfhydryl oxidase Erv1 of the intermembrane space, and glutathione. Maturation of cytosolic/nuclear Fe/S proteins further requires the function of the CIA machinery consisting of the two P-loop NTPases Cfd1 (identified by W. Walden) and Nbp35, the iron-only hydrogenase-like Nar1, and the WD40 protein Cia1. The molecular mechanisms by which these factors assist the assembly process is still unknown. Interestingly, the mitochondrial ISC machineries, but not the CIA components perform a dual function in that they also have a strong impact on cellular iron homeostasis through a signalling pathway to the Aft1/Aft2 transcription factors.

The majority of the mitochondrial ISC and cytosolic/nuclear CIA proteins are essential for life underlining the importance of Fe/S protein biogenesis in eukaryotes. To date, only one essential Fe/S protein termed Rli1 is known that explains the indispensable character of this biosynthetic pathway. Rli1 is conserved in Archaea and Eukarya and performs a crucial role in the biogenesis of cytosolic ribosomes thus linking two evolutionary ancient processes. The essential character of Rli1 for the first time explains why mitochondria are indispensable organelles in virtually all eukaryotes.

References:

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