S7 Biogenesis

7L1

The mitochondrial peptidasome PreP and Alzheimer’s disease
Elżbieta Glaser
Department of Biochemistry and Biophysics, Stockholm University, SE-106 91 Stockholm, Sweden
E-mail: e.glaser@dubb.su.se

A novel mitochondrial peptidasome, the Presequence Protease (PreP) was shown to be responsible for degradation of organelar targeting peptides as well as other unstructured peptides in the mitochondrial matrix. PreP belongs to the pitrilysin oligopeptidase family (M16C) containing an inverted zinc-binding motif. The crystal structure of Arabidopsis thaliana PreP, AtPreP, refined at 2.1 Å, revealed a novel mechanism of proteolysis, in which two halves of the enzyme connected by a hinge region enclose large catalytic chamber opening and closing in response to peptide binding. Double knock-out mutant of AtPreP results in a severe phenotype, including decreased size and growth rate, chlorosis and organelar abnormalities, such as altered morphology, partial loss of the integrity of the inner mitochondrial membrane and reduced mitochondrial respiration. PreP homologues are present in yeast and humans. Interestingly, human PreP has been associated with Alzheimer’s disease (AD) as it is responsible for degradation of amyloid-beta (Aβ) peptide in brain mitochondria. Accumulation of Aββ has been shown in brain mitochondria from AD patients and mutant transgenic mice over-expressing Aββ precursor protein. Recent studies showed that PreP activity is reduced in AD patients and AD mice models comparing to age-matched controls, which correlated with an enhanced ROS production in mitochondria. The molecular mechanism of hPreP oxidation and its protection against ROS have been studied. As increasing data are pointing towards the important role of mitochondrial dysfunctions in progression of AD, clearance of mitochondrial Aββ by PreP may play an essential role in the pathology of AD.

doi:10.1016/j.bbabio.2012.06.185

7L2

Energetic basis of the biogenesis of iron–sulfur proteins
Roland Lill
Institut für Zytobiologie, Philipps-Universität Marburg, Robert-Koch-Str. 6, 35032 Marburg, Germany
E-mail: Lill@staff.uni-marburg.de

Iron–sulfur (Fe/S) clusters are simple and evolutionary ancient inorganic cofactors of proteins with a function in catalysis, electron transfer and regulation. The molecular basis of Fe/S cluster synthesis and its assembly into apoproteins in a living cell have been subject to intense research activities over the past years (Lill, R. (2009) Nature 460, 831–838). Biogenesis is accomplished by three complex proteinaceous machineries. Mitochondrial Fe/S proteins require the iron–sulfur cluster (ISC) assembly machinery which was inherited from bacteria during evolution. Cytosolic and nuclear Fe/S protein assembly also depends on the function of this machinery, yet additionally requires the mitochondrial ISC export apparatus and the cytosolic iron–sulfur protein assembly (CIA) machinery. The assembly processes in both the mitochondria and the cytosol/nucleus follow general biosynthetic principles, even though the ISC and CIA components do not show any sequence similarity. The components of all three systems (more than 25 proteins) are highly conserved from yeast to man suggesting similar mechanisms of Fe/S protein assembly in all eukaryotes. Malfunction of Fe/S protein biogenesis, e.g., by genetic mutations, results in several hematological, neurological and metabolic diseases.

This presentation will concentrate on the energetics of cellular Fe/S protein biogenesis. In mitochondria, the assembly process requires the input of both electrons and ATP. The electron transfer chain comprised of NAD(P)H, ferredoxin reductase (yeast Arh1/human AdR), and ferredoxin (Yah1/Fdx2) has been shown to contribute its electrons for de novo Fe/S cluster synthesis on the scaffold protein Isu1. Biochemical reconstitution of this process has recently allowed its thorough functional analysis. ATP is used by the dedicated mitochondrial Hsp70 chaperone Ssq1 which interacts with both Isu1 and the monothiol glutaredoxin Grx5. The latter transfers the newly synthesized Fe/S cluster on to how ATP/GTP and Grx5 functionally cooperate in this process has recently been unraveled. A need for ATP/GTP and electrons has also been documented for cytosolic Fe/S cluster assembly on the Cfd1–Nbp35 scaffold proteins which belong to the family of P-loop NTPases. Recent studies revealed first insights into how the flavoprotein Tah18 and the Fe/S protein Dre2 transfer the electrons and into how ATP/GTP might be used for cytosolic Fe/S cluster synthesis.

doi:10.1016/j.bbabio.2012.06.186

7L3

Biogenesis of cytochrome cbb2 Oxidase: Analysis of the copper delivery pathway
Grzegorz Pawlik, Seda Ekici, Petru-Julian Trasnea, Eva Lohmeyer, Sebastian Schröder, Xinpei Jiang, Fevzi Daldal, Hans-Georg Koch
Institute for Biochemistry and Molecular Biology, Albert-Ludwigs University Freiburg, Germany; Department of Biology, University of Pennsylvania, Philadelphia, USA
E-mail: Hans-Georg.Koch@biochemie.uni-freiburg.de

Iron–sulfur (Fe/S) clusters are simple and evolutionary ancient inorganic cofactors of proteins with a function in catalysis, electron transfer and regulation. The molecular basis of Fe/S cluster synthesis and its assembly into apoproteins in a living cell have been subject to intense research activities over the past years (Lill, R. (2009) Nature 460, 831–838). Biogenesis is accomplished by three complex proteinaceous machineries. Mitochondrial Fe/S proteins require the iron–sulfur cluster (ISC) assembly machinery which was inherited from bacteria during evolution. Cytosolic and nuclear Fe/S protein assembly also depends on the function of this machinery, yet additionally requires the mitochondrial ISC export apparatus and the cytosolic iron–sulfur protein assembly (CIA) machinery. The assembly processes in both the mitochondria and the cytosol/nucleus follow general biosynthetic principles, even though the ISC and CIA components do not show any sequence similarity. The components of all three systems (more than 25 proteins) are highly conserved from yeast to man suggesting similar mechanisms of Fe/S protein assembly in all eukaryotes. Malfunction of Fe/S protein biogenesis, e.g., by genetic mutations, results in several hematological, neurological and metabolic diseases.

This presentation will concentrate on the energetics of cellular Fe/S protein biogenesis. In mitochondria, the assembly process requires the input of both electrons and ATP. The electron transfer chain comprised of NAD(P)H, ferredoxin reductase (yeast Arh1/human AdR), and ferredoxin (Yah1/Fdx2) has been shown to contribute its electrons for de novo Fe/S cluster synthesis on the scaffold protein Isu1. Biochemical reconstitution of this process has recently allowed its thorough functional analysis. ATP is used by the dedicated mitochondrial Hsp70 chaperone Ssq1 which interacts with both Isu1 and the monothiol glutaredoxin Grx5. The latter transfers the newly synthesized Fe/S cluster on to how ATP/GTP and Grx5 functionally cooperate in this process has recently been unraveled. A need for ATP/GTP and electrons has also been documented for cytosolic Fe/S cluster assembly on the Cfd1–Nbp35 scaffold proteins which belong to the family of P-loop NTPases. Recent studies revealed first insights into how the flavoprotein Tah18 and the Fe/S protein Dre2 transfer the electrons and into how ATP/GTP might be used for cytosolic Fe/S cluster synthesis.

doi:10.1016/j.bbabio.2012.06.186