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Review

Structural insight into the mitochondrial protein import system ☆

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ABSTRACT

Mitochondrial functions rely on precise and efficient transport of 1000–1500 different mitochondrial proteins from the cytosol to appropriate mitochondrial subcompartments. Those mitochondrial protein transport processes are mediated by the dedicated mitochondrial protein import system comprised of translocators in the outer and inner mitochondrial membranes and soluble factors in the cytosol, intermembrane space, and matrix. In the last decade, high-resolution structures of many of the components of the mitochondrial protein import machineries have become available, which has significantly advanced our understanding of the molecular mechanisms of mitochondrial protein transport. Here we review the currently available high-resolution structures of the components of the mitochondrial protein import machineries that afford structural and mechanistic insight into how the mitochondrial import system works. This article is part of a Special Issue entitled Protein translocation across or insertion into membranes.

Contents

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1. Introduction

Mitochondria are essential organelles in eukaryotic cells that consist of four subcompartments, the outer and inner membranes, the intermembrane space (IMS), and innermost matrix. Mitochondria contain about 1000–1500 different proteins, most of which are synthesized as precursor proteins in the cytosol and imported into mitochondria. Import and subsequent intramitochondrial sorting of mitochondrial proteins are mediated by membrane-protein complexes called translocators in the outer and inner membranes and soluble factors in the cytosol, IMS, and matrix [1–4]. Most mitochondrial proteins enter mitochondria via the outer-membrane translocator, the TOM40 complex. Then the protein-sorting pathway branches out for different mitochondrial subcompartments with the aid of distinct sorting-specific import machineries (Fig. 1). The TIM23 complex in the inner membrane mediates sorting of precursor proteins with an N-terminal cleavable presequence to the matrix and inner membrane. The TIM22 complex in the inner membrane facilitates insertion of polytopic membrane proteins without a presequence into the inner membrane. The TOB/SAM complex in the outer membrane mediates assembly of β-barrel membrane proteins into the outer membrane [5–7]. Tim40/Mia40 and Erv1 constitute a disulfide relay system in the IMS to facilitate import and oxidative folding of mainly small soluble proteins in the IMS [8–11].

Mitochondrial precursor proteins are classified into two groups on the basis of their mitochondrial-targeting signals, which are recognized by distinct receptors of the translocators. Most matrix proteins and some inner membrane proteins are synthesized as precursor proteins with an N-terminal presequence, which contains a mitochondrial-targeting signal and is cleaved off by the processing peptidase in the matrix upon import [12,13]. On the other hand, polytopic inner membrane proteins, soluble IMS proteins, and outer-membrane proteins are mainly synthesized without a cleavable presequence, but contain internal targeting signals within their mature parts.

In the last decade, information on the structural aspects of mitochondrial import systems has been accumulated. In particular, high-resolution structures have become available for many components of the mitochondrial protein import system, which contributed to enhancement of our understanding of the mechanisms of protein import and sorting on the basis of the structures. In this review, we will give a brief survey of the currently available high-resolution structures of the components of the protein import machineries and correlate the structural information with their functions in the mitochondrial protein trafficking.

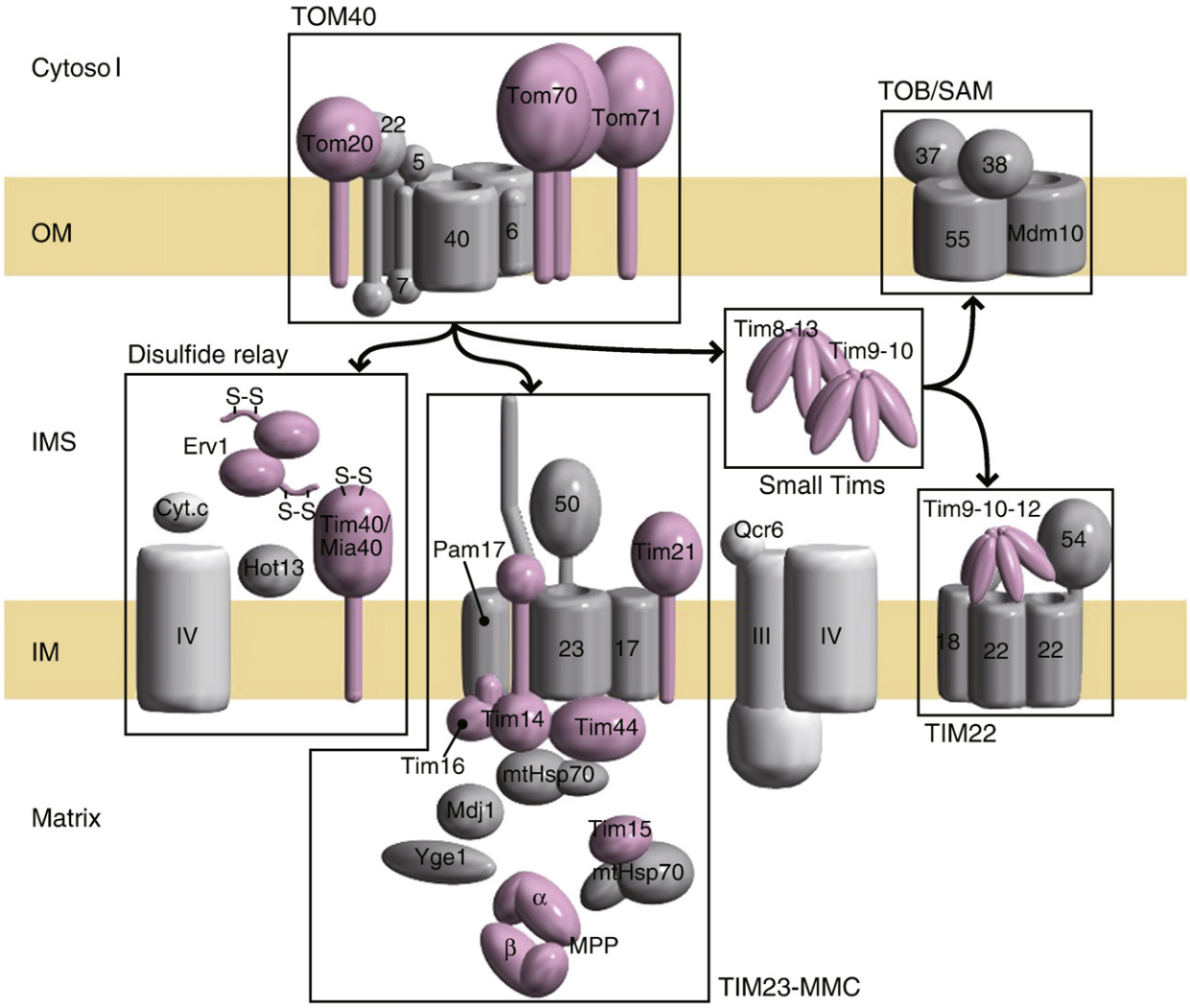

Fig. 1. Mitochondrial protein import pathways and translocators. The components whose high-resolution structures are available are shown in pink. TOM40, the TOM40 complex (40, Tom40; 22, Tom22; 7, Tom7; 6, Tom6; 5, Tom5); TOB/SAM, the TOB/SAM complex (55, Tob55/Sam50; 38, Tom38/Tob38/Sam35; 37, Mas37/Sam37/Tom37); Disulfide relay, the disulfide relay system (Cyt. c, cytochrome *c*; IV, the respiratory chain complex IV); TIM23–MMC, the TIM23 complex and MMC proteins (50, Tim50; 23, Tim23; 17, Tim17); TIM22, the TIM22 complex (54, Tim54; 22, Tim22; 18, Tim18); III, the respiratory chain complex III.