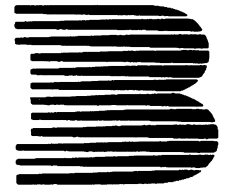


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## A mitochondrial machinery for membrane translocation of precursor proteins

NIKOLAUS PFANNER and WALTER NEUPERT

*Institut für Physiologische Chemie, Universität München,  
Goethestr. 33, D-8000 München 2, F.R.G.*

### *Introduction*

Mitochondria contain several hundred specific different proteins. Over 95% of these proteins are encoded by nuclear genes and are synthesized as precursor proteins on cytosolic polysomes [1-3]. The studies on the transfer of precursor proteins into and across the mitochondrial membranes comprise several basic problems of intracellular protein sorting: the specific recognition of precursor proteins by cell organelles, the mechanisms of protein translocation across

biological membranes and the intraorganellar modification and sorting of imported proteins. Many mitochondrial precursor proteins carry *N*-terminal signal sequences (presequences). The precursor proteins appear to be recognized by specific receptor proteins on the mitochondrial surface. Insertion of precursor proteins into the mitochondrial membranes requires a loosely folded conformation of the precursors. Most proteins are imported at sites of close contact between mitochondrial outer and inner membranes (contact sites). Entrance of precursor proteins into the inner membrane requires the presence of the membrane potential across the inner membrane. Upon arrival in the matrix, the inner mitochondrial subcompartment, the presequences are proteolytically removed by the enzyme, the matrix-processing peptidase. The proteins are sorted to their sub-mitochondrial destination and are functionally assembled.

Abbreviations used: MOM, mitochondrial outer membrane protein; GIP, general insertion protein; ISP, import site protein.

Here we focus on the properties of the mitochondrial machinery that is responsible for recognition and membrane translocation of precursor proteins. In the past years, these steps were analysed by use of translocation intermediates, i.e. precursor proteins that were reversibly arrested at distinct stages of their import pathway, and some of the participating components were identified.

#### *Mitochondrial import receptors*

Precursor proteins can be bound to the surface of isolated mitochondria. The binding sites are saturable and can be degraded by added proteinases, suggesting that they are proteinaceous in nature [4]. The binding is productive, as precursor proteins accumulated at these putative receptor sites can be efficiently imported. Competition studies with different precursor proteins suggested that at least two distinct receptors exist on the mitochondrial surface [4].

Two proteins of the mitochondrial outer membrane have been subsequently identified as receptors for precursor proteins. MOM19 (a mitochondrial outer membrane protein of 19 kDa) functions as the receptor for precursor proteins destined for all four mitochondrial subcompartments. In particular, all precursor proteins studied that carried *N*-terminal signal sequences used MOM19 for entry into mitochondria [5]. A proteolytic fragment of MOM19 with a molecular mass of 17 kDa is able to mediate import of some precursor proteins, suggesting that the MOM19 molecule possesses distinct portions for interaction with various precursor proteins. The precursor for the most abundant mitochondrial protein, the inner membrane protein ADP/ATP carrier, however, does not appear to employ MOM19 for import into mitochondria [5]. We found that an outer membrane protein of 72 kDa, termed MOM72, represented the import receptor for this precursor that contains non-*N*-terminal signal sequences [6]. The precursor of ADP/ATP carrier remains tightly bound to MOM72 after lysis of mitochondria with non-ionic detergent, allowing the co-purification of ADP/ATP carrier and MOM72.

Upon recognition by MOM19 and MOM72, the precursor proteins are inserted into the outer mitochondrial membrane. We postulated that the various precursor proteins use a common membrane insertion site, termed the 'general insertion protein' (GIP) [4, 7]. The characterization of GIP was promoted by the discovery of a high molecular mass complex in the outer membrane. A fraction of MOM19 and MOM72 are present in this 'mitochondrial receptor complex' that, in addition, contains a protein of 38 kDa (MOM38) (R. Pfaller, T. Söllner, G. Griffiths, N. Pfanner & W. Neupert, unpublished work). A precursor protein accumulated at the GIP-site co-purifies with the mitochondrial receptor complex, indicating that GIP is among the proteins of the complex. The properties of the functionally characterized GIP-site correlate well with those of MOM38. MOM38 probably represents the general insertion protein (R. Pfaller, T. Söllner, G. Griffiths, N. Pfanner & W. Neupert, unpublished work). A 42 kDa outer membrane protein is involved in import of precursor proteins into yeast mitochondria. This 'import site protein 42' (ISP 42) [8] may represent the equivalent of MOM38 that was identified in mitochondria from *Neurospora crassa*.

#### *Mitochondrial contact sites*

Translocation of precursor proteins across the mitochondrial membranes takes place predominantly at sites of contact between mitochondrial outer and inner membranes. This was demonstrated by reversible accumulation of precursor proteins in contact sites in a two-membrane spanning

fashion: the *N*-terminal presequence was cleaved by processing peptidase in the mitochondrial matrix, while a *C*-terminal portion of the precursor was located in the cytosol [9, 10]. Precursor proteins without cleavable presequence, such as the ADP/ATP carrier, are also imported through contact sites [11], emphasizing the general role of contact sites in mitochondrial protein uptake.

Precursor proteins arrested in contact sites were labelled with specific antibodies and protein A-gold particles, which enabled visualization in electron micrographs. Thereby, the identity of the biochemically characterized translocation contact sites with the morphologically described zones of adhesion between both mitochondrial membranes could be confirmed [10]. Contact sites are saturable with precursor proteins [12, 13], and precursor proteins accumulated in the two-membrane spanning fashion are extractable from the membranes with 'protein denaturants' such as urea [14]. These results suggested that proteins represent essential parts of contact sites. However, a true contact site component, i.e. a component that is exclusively located in contact sites, has not been identified so far.

#### *A dynamic model*

Investigations into the location of proteins of the mitochondrial import machinery, with respect to contact sites, yielded surprising results. The receptor MOM19 was distributed over the entire mitochondrial surface with only a slight enrichment in contact site regions [5]. About half of the MOM72 molecules were concentrated in contact site regions (corresponding to 10–15% of the mitochondrial surface); the rest of MOM72, however, was distributed over the remaining outer membrane [6]. We suggest that import receptors collect precursor proteins from all over the mitochondrial surface and eventually transfer them to contact sites. This would imply a lateral mobility of the receptors in the outer membrane; upon binding of a precursor protein, the receptors may diffuse towards contact sites ('dynamic model'). A fraction of MOM38 and ISP 42 may also be located in contact sites (R. Pfaller, T. Söllner, G. Griffiths, N. Pfanner & W. Neupert, unpublished work) [8].

Transport components in the inner mitochondrial membrane may exhibit a similar dynamic behaviour. Experiments involving yeast mitochondria with disrupted outer membrane demonstrated that precursor proteins could be directly translocated across the inner membrane, thereby bypassing the import machinery of the outer membrane and that located in contact sites [15]. The physiological significance of this translocation across the inner membrane is unclear. It suggests, however, that translocation components are not only present in contact sites, but are also distributed over the inner membrane. In the assumption that at least some components are shared by both, the contact site machinery and the 'inner membrane transport apparatus', this may imply a lateral mobility of transport components in the inner membrane.

In summary, we propose that mitochondrial contact sites possess structural components that keep the two membranes in stable contact. Import receptors and other outer membrane proteins (MOM38, ISP 42) involved in further stages of import may diffuse laterally in the outer membrane. This would increase the probability for binding of precursor proteins and ensure their efficient transfer to contact sites. Assembly of the proteins in the receptor complex may preferentially occur near contact sites. Putative import components of the inner membrane may possess a similar lateral mobility with possible cycles of assembly and disassembly, although further experimental evidence has to be accumulated to speculate on the role of such possible processes.

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