About mitochondrial importWhile the mitochondrial genome encodes a handful of proteins, most of the hundreds of proteins that reside in the mitochondrion are encoded by nuclear genes, translated in the cytoplasm, and imported into mitochondria via a series of complex molecular machines. Many of the proteins imported into mitochondria are involved in respiration, which is not an essential process: S. cerevisiae is able to carry out either fermentative growth on carbon sources such as glucose, or respiratory growth on nonfermentable carbon sources such as glycerol and ethanol. However, since maintenance of the mitochondrial compartment is essential to life, mutations that completely disrupt mitochondrial import are lethal.About the TIM22 complex The TIM22 complex of the mitochondrial inner membrane mediates the insertion of large hydrophobic proteins, typically transporterswith multiple transmembrane segments, into the inner membrane. These proteins travel through the outer membrane via the translocase of the outer mitochondrial membranecomplex. Their transit across the intermembrane space to the TIM22 complex in the inner membrane is mediated by complexes of small soluble protein chaperones: Tim8p with Tim13p, and Tim9p with Tim10p. The membrane-embedded core of the TIM22 complex consists of Tim54p, Tim22p, Tim18p, and Sdh3p; additionally, the small Tim proteins Tim9p, Tim10p, and Tim12p are associated with the complex on the intermembrane space side.About the small Tim proteins Five small, related proteins involved in mitochondrial importreside in the mitochondrial intermembrane space. Tim9p and Tim10p, both essential proteins, form a soluble hexameric complex consisting of three molecules each of Tim9p and Tim10p that displays protein refolding activity. The Tim9p-Tim10p complex assembles into a soluble complex with Tim12p, which then docks onto the TIM22 complex. Incoming carrier proteins bind to the Tim9p-Tim10p-Tim12p complex that is peripherally associated with the TIM22 complex, and are subsequently inserted into the inner membrane. There is also evidence that the Tim9p-Tim10p complex is involved in import of integral outer membrane proteins, mediating their transfer between the translocase of the outer mitochondrial membranecomplex and the sorting and assembly machinerycomplex. Conditional mutants of each of the three essential small TIM genesdisplay a petite-negative phenotype: loss of the mitochondrial genome is lethal to the mutant strains. The two nonessential small Tim proteins, Tim8p and Tim13p, form a soluble complex with each other. The tim8 null mutation is synthetically lethal with a conditional tim10 mutation, suggesting that the two Tim complexes functionally interact. Genetic and physical evidence suggests that the Tim8p-Tim13p complex mediates the transit across the intermembrane space of a subset of proteins destined for the inner membrane. The small TIM proteins are evolutionarily conserved. Orthologs of each of the five S. cerevisiae genes are found in human; some organisms have fewer than five related genes. One of the human orthologs, TIMM8A or DDP1, is implicated in the neurodegenerative disorder Mohr-Tranebjaerg syndrome, also known as dystonia-deafness syndrome.