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 TIM23 complexThe Translocase of the Inner Mitochondrial membranereceives proteins from the Translocase of the Outer Mitochondrial membraneand either directs them into the mitochondrial matrix or facilitates their integration into the mitochondrial inner membrane. The membrane-embedded core of the complex is composed of three essential proteins: Tim23p, Tim17p, and Tim50p. Tim23p and Tim17p, which share sequence similarity, comprise the twin-pore structure through which precursor proteins translocate. Tim23p alone has the ability to form a voltage-sensitive channel, but Tim17p is required in vivo for maintenance of the twin-pore architecture and for normal function of the pore. Tim17p also has a role in sorting incoming proteins to the mitochondrial matrix or the inner membrane. Tim50p interacts with precursor proteins and with Tim23p to guide precursors from the TOM complex to the TIM23 complex. Two additional non-essential components, Tim21p and Pam17p, interact with the core of the TIM23 complex and may modulate its activity.Proteins destined for the mitochondrial matrix require the action of a sub-complex of the TIM23 complex, known as the import motor or presequence translocase-associated motorcomplex. Its catalytic component is Ssc1p, a member of the heat shock 70 protein family commonly referred to as mtHsp70, which undergoes cycles of binding and release of the precursor, hydrolyzing ATP and changing conformation in the process. The nucleotide release factor Mge1p promotes this cycle by facilitating the dissociation of ADP from Ssc1p. Other components include Tim44p, an essential subunit that mediates the association of the core TIM23 complex with the PAM complex; Pam18p, a J-protein cochaperone that stimulates the ATPase activity of Ssc1p; and Pam16p, a J-like protein that binds to Pam18p and regulates its activity. Pam17p mediates the association between Pam16p and Pam18p. Once imported proteins reach the mitochondrial matrix, their correct folding is facilitated by a soluble complex consisting of Ssc1p and its cochaperones Mdj1p and Mge1p.A subset of proteins destined for insertion into the mitochondrial inner membrane is translocated via the TIM23 complex but then inserted laterally into the inner membrane rather than entering the mitochondrial matrix. This mechanism is currently not understood in detail. The TIM23 complex adopts different conformations during the two kinds of import, but it is unclear whether this inner membrane import is accomplished by the core complex alone, or by the entire TIM23 complex including the import motor subunits.About TIM21 TIM21 encodes a conserved but nonessential subunit of the TIM23 complex. The tim21 null mutant is viable and does not display any growth defects under normal conditions, but respiratory growth defects are apparent at high temperatures, and both respiratory and fermentative growth are slower under conditions of reduced mitochondrial membrane potential. Tim21p is an integral protein of the mitochondrial inner membrane, with a small N-terminal domain extending into the matrix and a C-terminal domain in the intermembrane space. It interacts with the TIM23 complex core subunits, with TOM complex subunits, and with respiratory chain enzymes. The role of Tim21p in import is not clear. One model proposes that the TIM23 complex exists either in an inner membrane import-competent form containing Tim21p but not the PAM complex, or in a matrix import-competent form lacking Tim21p and associated with the PAM complex, suggesting that Tim21p binding facilitates the inner membrane import pathway. An alternative model suggests that Tim21p and the PAM complex are both associated with the TIM23 core complex at all times, and that Tim21p and Pam17p may have opposing regulatory effects on import.