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The Biogenesis of Mitochondria

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During the past 5 years it has become well established that mitochondria contain their own DNA as well as a distinct transcription and translation machinery. There is mounting evidence that these components function as an integrated genetic system that synthesizes several essential mitochondrial constituents. On the other hand, it is clear that many, if not most mitochondrial proteins are coded for by nuclear cistrons and assembled on cytoplasmic ribosomes. The formation of a mitochondrion thus requires the intracellular co-operation of two separate genetic systems and presumably involves co-ordinating mechanisms that are still unknown.

One promising approach to this problem is the study of respiratory adaptation in yeast. Anaerobically grown cells of baker's yeast (*Saccharomyces cerevisiae*) lack a respiratory chain but rapidly form it on exposure to oxygen. Previous work from the author's laboratory suggested that this adaptive process leads to the differentiation of incomplete promitochondria that pre-exist in the anaerobic cells.

What is the role of the mitochondrial protein-synthesizing system in respiratory adaptation? In an attempt to answer this question, we have poisoned anaerobically grown yeast cells with cycloheximide and exposed them to [³H]leucine under sterile conditions and in the absence of oxygen. On fractionation of the labelled cells, 90–99% of the total protein-bound radioactivity proved to be associated with the promitochondria. This labelling of promitochondria *in vivo* was strongly inhibited by chloramphenicol and, most importantly, was not observed with anaerobically grown cells of a cytoplasmic petite mutant. It is thus clear that promitochondria already possess a functional protein-synthesizing system and that this system is inoperative in our petite mutant. Since these labelling experiments were carried out with intact yeast cells, they are not subject to the uncertainties inherent in most systems used *in vitro*. Moreover, the wild-type and the petite mutant were compared under conditions that eliminate virtually all phenotypic differences between these strains.

When the selectively labelled anaerobic cells of the wild-type were washed free of cycloheximide and aerated in the presence of unlabelled leucine, more than half of the promitochondrial radioactivity was recovered in the respiring mitochondria that had arisen during adaptation. Control experiments indicated that the other half of the label had been lost through normal turnover of the (pro)mitochondrial proteins. Promitochondria are thus genuine precursors of the functional mitochondria present in oxygen-adapted yeast.

Although either chloramphenicol or cycloheximide inhibits respiratory adaptation, significant adaptation occurs if the cells are first aerated in the presence of cycloheximide, then washed and further aerated in the presence of chloramphenicol (W. Rouslin & G. Schatz, *in press*). A detailed investigation of this 'delayed-adaptation' phenomenon suggested that oxygen can activate promitochondrial protein synthesis even when cytoplasmic protein synthesis is inhibited. This oxygen-dependent synthesis leads to the accumulation of an unidentified intermediate with a half-life of about 2 h that can be utilized for respiratory adaptation when cytoplasmic protein synthesis is restored.

These findings are consistent with the possibility that oxygen specifically de-represses some cistrons on mitochondrial DNA.