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Review

The significance of peroxisomes in methanol metabolism in methylotrophic yeast

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Abstract

The capacity to use methanol as sole source of carbon and energy is restricted to relatively few yeast species. This may be related to the low efficiency of methanol metabolism in yeast, relative to that of prokaryotes. This contribution describes the details of methanol metabolism in yeast and focuses on the significance of compartmentalization of this metabolic pathway in peroxisomes.

Keywords: Peroxisome; Yeast; Methanol metabolism

1. Methylotrophy in prokaryote and eukaryote micro-organisms

A limited number of yeast species is capable to grow on methanol as sole source of carbon and energy. To enable this, these organisms use highly specialized metabolic pathways that are partly compartmentalized in peroxisomes. Consequently, peroxisomes are abundantly present in methanol-grown cells but strongly reduced in number in cells in which methanol utilization is repressed (see Fig. 1). Organisms that are capable to grow on C1 compounds, like methanol, are designated methylotrophs. These organisms share the remarkable capacity to derive all energy and cell carbon from reduced molecules that have no C–C bond. Methylotrophy is confined to a few prokaryote and eukaryote micro-organisms. Prokaryote methylotrophs are capable to grow on a variety of C1 compounds (e.g. methanol, methylamine, methane) whereas in eukaryotes methylotrophy is limited to methanol utilization.

The general mode of methylotrophs to assimilate carbon is to convert three C1 molecules into a C3 compound via a cyclic pathway (like in photosynthesis). In prokaryotes, three different pathways are known (i.e. the ribulose bisphosphate cycle, the ribulose monophosphate cycle and the serine pathway), but in methylotrophic yeast the xylulose monophosphate cycle uniquely operates in C1 assimilation. For the initial oxidation of methanol, prokaryotes and eukaryotes use different enzymes, namely a dehydrogenase or oxidase, respectively. For further details on methylotrophy the reader is referred to a comprehensive overview in *Biochemistry of Methylotrophs* (Anthony, 1982 [1]).

Oxidation of the relatively toxic compound methanol in yeast results in the formation of two other very reactive compounds, formaldehyde and hydrogen peroxide. The enzyme that catalyses this reaction, alcohol oxidase (AO) is compartmentalized in peroxisomes, together with catalase (CAT) which decomposes hydrogen peroxide into water and oxygen (Fig. 2A). The presence of hydrogen peroxide producing oxidases and catalase is a characteristic feature of peroxisomes in all eukaryotes and has the advantage that the enzymes that produce and decompose hydrogen peroxide are closely associated, preventing diffusion of this hazardous compound into the cytoplasm [2,3].

In methylotrophic yeast a third enzyme of methanol metabolism is localized to peroxisomes, namely dihydroxyacetone synthase (DHAS). DHAS is a component of the xylulose-5-phosphate cycle and catalyses the first step of formaldehyde

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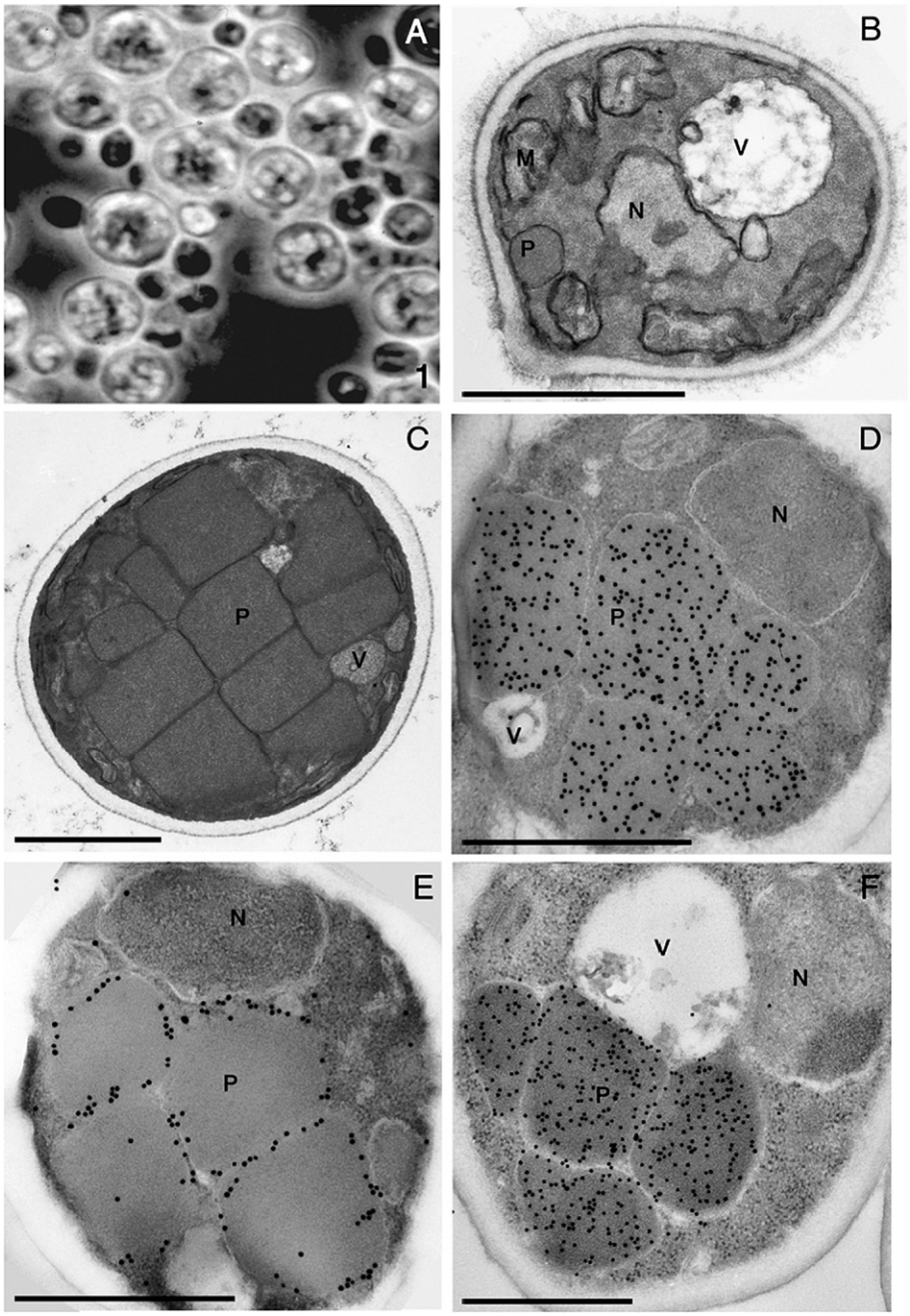

Fig. 1. (A) shows a light micrograph of *H. polymorpha* cells that are grown in a methanol-limited chemostat culture. In the cells the cuboid inclusions that represent peroxisomes are evident. (B) shows an electron micrograph of the same organism, grown in batch culture on glucose. These cells contain only a single small peroxisome. (C) shows the morphology of peroxisomes in methanol-limited grown *H. polymorpha*. (D–F) Immunocytochemical localization of AO (D), CAT (E) and DHAS protein (F) in peroxisomes of cells grown in batch cultures on methanol. Note that DHAS is randomly present over the organelle whereas catalase is predominantly located at the edges of the organelle. For immunocytochemistry specific polyclonal antibodies against the three indicated proteins are used. M—mitochondrion; N—nucleus; P—peroxisome; V—vacuole. The bar represents 1 μm.

assimilation to form two C3 molecules (dihydroxyacetone and glyceraldehyde-3-phosphate) from one C1 (formaldehyde) and one C5 (xylulose-5-P) molecule (Fig. 2A). The peroxisomal localization of AO, CAT and DHAS is essential to allow methylotrophic yeast cells to grow on methanol [4,5]. This characteristic has been an important tool in the isolation of peroxisome-deficient mutants (*pex*) of methylotrophic yeast species, as such mutants have lost the capacity to utilize methanol despite the fact that they do contain all enzymes involved in methanol metabolism [6,7]. Detailed physiological studies of yeast *pex* mutants have revealed why compartmentalization is essential for methylotrophic growth of yeast [8] (see Section 4). All other enzymes required for methanol utilization are cytosolic in yeast. These include the enzymes for the oxidation of formaldehyde to CO_2 (formaldehyde dehydrogenase, *S*-formylglutathione hydrolase, and formate