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Increased phosphate levels alter responses to nongenotoxic xenobiotics in *Candida albicans* ATCC 36232

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Regulation of cellular processes in response to extracellular signals is fundamental to all living cells, independent of whether the cell is multicellular or unicellular. Regulation of internal processes is especially critical in unicellular organisms as they are entirely immersed in their environment. Regulation of these critical processes, therefore, relies heavily on transmembrane protein complexes. In unicellular organisms, a large number of specialized structures exist that perform dual roles as transporters and sensors of specific water-soluble molecules. Of particular interest are complexes that are used to regulate the passage of ions across the membrane. Inorganic phosphate (P_i) is one essential ion required for many metabolic processes, including synthesis of nucleic acids, phospholipids and energy stores. In the yeast *Saccharomyces cerevesiae*, the vacuole is the major storage compartment for phosphate [1]. The abundance of the vacuoles in yeast is attributable to availability of the phosphates. In yeast, acquisition, storage, release and integration of P_i is dependent on several enzymes. The activities of these enzymes in *Saccharomyces* are regulated by the P_i signal transduction (*PHO*) pathway, which also serves to sense and respond to varying P_i levels [2-4]. In *Candida albicans*, phosphate is actively transported with a K_m of about 100 – 200 □M, with transport being vanadate-sensitive [5]. For *C. albicans,* transport function may be related to a PHO-like kinase, termed CaPho85 as it shares sequence homology with Pho85 from *S. cerevesiae* [6]. No functional significance of this protein has been reported, although it may be assumed that phosphate sensors/transporters may be present. To date, the only physiological data related to high phosphate levels in *C. albicans* is that concentrations up to 600 mM reportedly induce pseudohyphae formation [7]. Our laboratory is currently undertaking investigations on the role(s) of extracellular inorganic phosphates on plasma membrane and mitochondrial membrane potentials. Our preliminary data suggested that the plasma and mitochondrial membranes alter their potentials when *C. albicans* is grown in the presence of 100 mM phosphate. In this study, we tested the effects of increased inorganic phosphate in conjunction with environmental stressors. Cultures of *C. albicans* strain ATCC 36232 grown in media supplemented with 100 mM inorganic phosphate were exposed to either 0.5% dibutylphthalate (DBP), 0.05% Tween 80, or both (DBPT). Cultures were examined for routine morphology by TEM and for catalase localization.

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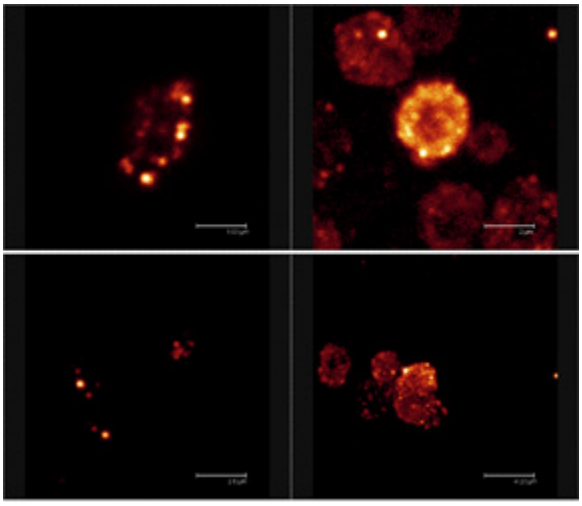

Figure 1. *C. albicans* grown in high phosphate. The cells were spheroplasted by lyticase digestion of the cell wall. A. Control cells exhibit relatively low levels of catalase activity. B. In DBP-treated cells, the catalase activity is more intense than control cells. C. Tween 80-treated cells, the catalase levels are less than controls and DBP-treated cells. D. In the DBPT-treated cells, the catalase levels are greater than in controls, but less than in DBP- or Tween 80-treated cells.

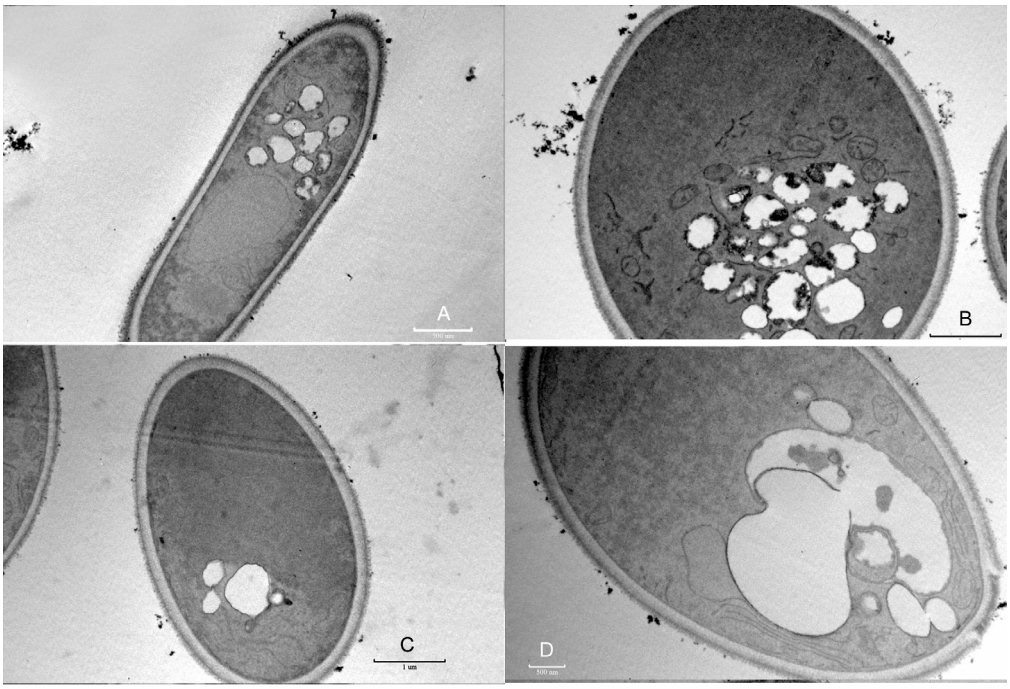

Figure 2. Transmission electron micrographs of *C. albicans* grown in high phosphate. A. Control cells contain more vacuoles as a result of high phosphate. B. In the DBP-treated cells, the vacuole content is increased over controls and contain abundant electron-dense inclusions. C. In the Tween 80-treated cells, the total area of vacuoles is decreased over control and DBP-treated, but the cell wall is significantly thicker than control or DBP-treated cells. D. In the DBPT-treated cells, the vacuoles attain the highest area of all treatments, and the cell wall is thicker than control and DBP-treated, but not Tween 80-treated cells.

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