VMA3 encodes the c subunit of the yeast V-ATPase V0 domain. Vacuolar-ATPasesare ATP-dependent proton pumps that acidify intracellular vacuolar compartments. Vacuolar acidification is important for many cellular processes, including endocytosis, targeting of newly synthesized lysosomal enzymes, and other molecular targeting processes. The V-ATPase consists of two separable domains. The V1 domain has eight known subunits, is peripherally associated with the vacuolar membrane, and catalyzes ATP hydrolysis. The V0 domain is an integral membrane structure of five subunits, and transports protons across the membrane. The structure, function, and assembly of V-ATPases are reviewed in references 6, 7, 8 and 9. The V0 c, c', and c''subunits are highly hydrophobic integral membrane proteolipids, and have similar amino acid sequences; all three are required for V-ATPase activity. Vma3p is also involved in copper and iron homeostasis. The vma3 null mutant is viable but lacks vacuolar-ATPase activity, and is defective in vacuolar acidification, vacuole biogenesis, vacuolar protein targeting, and endocytosis. The a and b V0 subunits do not assemble in the absence of Vma3p. V-ATPases have been identified in numerous eukaryotes; c subunit homologs have been identified in Drosophila, Manduca sexta, and Nephrops norvegicus, and the Drosophila and Nephrops genes can rescue the vma3 null phenotype.