Proline is a member of the glutamine family of amino acids, whose biosynthesis depends on the carbon skeleton of glutamic acid. Proline biosynthesis, shown here, occurs in the cytosol and begins with activation of glutamate, by the Pro1p gamma-glutamyl kinase, to form glutamate-5-phosphate. This unstable intermediate is subsequently converted to glutamate semialdehyde by the gamma-glutamyl phosphate reductasePro2p. Glutamate semialdehyde spontaneously cyclizes to form delta 1-pyrroline-5-carboxylate, which is then converted to proline by Pro3p, a P5C reductase. In S. cerevisiae, the P5C reductase enzyme also catalyzes the fourth step in arginine degradation. Since these two pathways converge at this step, the requirement for proline in pro1 and pro2 mutant cells can be satisfied by arginine. In contrast, pro3 mutants require the addition of proline for growth. A unique property of all the pro mutant strains is that they cannot grow on standard YPD rich media..Many of the genes involved in S. cerevisiae amino acid biosynthesis are coregulated by a process known as the general amino acid control system. In response to starvation for any single amino acid, the expression of many biosynthetic enzymes is upregulated. Mutational studies suggest that PRO1 and PRO2 expression is regulated by general amino acid control mediated by the transcriptional activator Gcn4p. However, microarray expression profiling indicates that only PRO2 is a target of Gcn4p. This study also shows that PRO1 expression is repressed in response to histidine starvation imposed by 3-aminotriazole.In humans, the activities of Pro1p and Pro2p reside in a single enzyme, the delta 1-pyrroline-5-carboxylate synthetase ALDH18A1. Mutations in this gene lead to hyperammonemia, hypoornithinemia, hypocitrullinemia, hypoargininemia, and hypoprolinemia and may be associated with neurodegeneration, cataracts, and connective tissue diseases.