STE14 encodes the founding member of a protein family of eukaryotic methyltransferases called the isoprenylcysteine carboxyl methyltransferasefamily. The Ste14p carboxymethyltransferase mediates methylation of the cysteine residue in the C-terminal CAAX motif that is present in some signal transduction proteins, such as Ras2p and a-factor pheromone. The CAAX motif is the site of protein isoprenylationof the protein, and methylation by Ste14p occurs after attachment of the isoprenyl group to the cysteine and cleavage of the terminal AAX species. The net effect of these post-translational modifications is to increase the hydrophobicity of the prenylated proteins to direct them to membranes.Ste14p localizes to the endoplasmic reticulum membrane. Topology studies have led to the proposal that Ste14p has six transmembrane spans, with two loops exposed to the ER lumen and the others present in the cytosol. A consensus sequence characteristic of ICMT proteins lies in the C terminus; it is comprised of a stretch of hydrophobic amino acids that form a helical hairpin and are flanked by two regions of amino acid conservation. Null mutations in STE14 prevent mating because they block the carboxymethlyation step of a-factor pheromone maturation. The resulting unmethylated form remains a substrate for further N-terminal processing of a-factor, but the final form cannot be exported from the cell by the ABC transporter Ste6p to initiate the mating response.STE14 homologs have been identified in a number of organisms, and the Schizosaccharomyces pombe, Arabidopsis thaliana, and humanhomologs have each been shown to complement the defects caused by a ste14 mutation in yeast. Studies with small molecule inhibitors of ICMT proteins suggest that they are a good anticancer target for treatment of Ras-based cancers.