Fus3p is a member of the mitogen-activated protein kinasefamily of serine/threonine-specific kinases, which mediate phosphorylation reactions in signaling pathways that link receptor activation to control of cell proliferation. The S. cerevisiae genome encodes six MAP kinase-like proteins: Fus3p, Kss1p, Smk1p, Slt2p, Hog1p, and Ykl161p. Five of these are known to function in pathways that mediate mating, responses to nutrient deprivation, cell wall remodelling, and responses to osmolarity changes. MAPK pathways comprise a three-component module of kinases that is conserved from yeast to humans. These kinases activate in a sequential order, often referred to as a cascade: a MAPK kinase kinaseactivates a MAPK kinase, which activates a MAPK. In the mating pathway, Ste11p is the MEKK, Ste7p is the MEK, and both Fus3p and Kss1p are the MAPKs.Haploid yeast cells, which exist as either MATa or MATalpha mating types, initiate mating to form diploids through production of peptide pheromones. Pheromones bind to seven-transmembrane receptor proteins on cells of the opposite type: Ste2por Ste3p, leading to activation of the heterotrimeric G-protein composed of alpha subunit Gpa1p, beta subunit Ste4p, and gamma subunit Ste18p. Activation is mediated by exchange of GDP for GTP on the alpha subunit, causing it to dissociate from the heterotrimer. The resulting Ste4p-Ste18p dimer recruits the scaffolding protein Ste5p and its associated MAP kinase cascade components, Ste11p, Ste7p, and Fus3p, to the membrane, where Ste11p is phosphorylated by the PAK kinase Ste20p; Ste11p then phosphorylates Ste7p, which phosphorylates Fus3p and Kss1p. Both MAPKs phosphorylate the transcription activator Ste12p, which induces a number of mating-specific genes; in addition, Fus3p phosphorylates the cell cycle regulator Far1p, which mediates cell cycle arrest and is also involved, with Cdc24p, in polarized growth toward the mating partner. This difference in substrate specificity between Fus3p and Kss1p is one factor that contributes to the greater importance of Fus3p in pheromone response, while Kss1p is more prominent in activating the filamentous growth pathway. Two additional substrates of Fus3p include Bni1p, a formin homologue required for polarized growth, and Sst2p, which is involved in attenuating the signal.The kinase cascade of Ste20p, Ste11p, and Ste7p, and the transcriptional activator Ste12p, function in mating and are also required for activating genes involved in filamentous growth; thus, the cell must have mechanisms for preventing inappropriate activation of either pathway. It has been shown that Fus3p inhibits filamentous growth during mating through degradation of Tec1p, which is a cofactor for Ste12p in the expresson of filamentation genes. During pheromone response, Fus3p phosphorylates a site in Tec1p, which leads to ubiquitination and degradation through an 31146>SCF ubiquitin protein ligase. Tec1p is not a substrate for Kss1p, so Tec1p remains stable during filamentous growth. The scaffold protein Ste5p plays a role in insulating the mating pathway from the filamentation pathway, as shown by analysis of a point mutation in Ste5p that confers increased activation of Kss1p and reduced Fus3p-dependent degradation of Tec1p.Phosphorylation of Fus3p in response to pheromone treatment is rapid and occurs at residues threonine-180 and tyrosine-182. Pheromone also stimulates an increase in nuclear accumulation of Fus3p, which shuttles between the cytoplasm and nucleus in vegetative cells. Nuclear accumulation is reversed by interaction with Gpa1p and the phosphatase Msg5p; their action along with dephosphorylation of Fus3p by the phosphatase Ptp3p downregulates Fus3p and promotes recovery of cells from pheromone.Mitogen-activated protein kinases are widely conserved in eukaryotic cells. The closest human homolog to Fus3p is MAPK1with 51% identity.