CDC53 encodes a scaffolding subunit or cullin for multiple related RING-type E3 ubiquitin-ligase complexes, generically referred to as Skp1-Cullin-F-boxubiquitin protein ligases. SCF-mediated ubiquitination involves three sequential enzymatic steps: ATP-dependent activation of ubiquitin through the formation of a high-energy thioester linkage with a ubiquitin-activating enzyme; transfer of the activated ubiquitin to a ubiquitin-conjugating enzyme; and the E2-catalyzed transfer of activated ubiquitin to a specific lysine residueof the target protein, aided by substrate-specific components of SCF-ubiquitin ligase complexes. This sequence is repeated until multiple chains of ubiquitin are attached, thereby marking the protein for rapid degradation by the 26S proteasome.SCF ubiquitin protein ligase complexes function as target recognition modules that regulate cell cycle progression and signal transduction by bringing E2s and substrates into close proximity, thereby facilitating substrate polyubiquitination. SCF ubiquitin-ligase complexes are composed of several shared subunits including Skp1p, an adaptor protein that binds and recruits a variety of F-box containing proteins; Cdc53p, a cullin family member that recruits the ubiquitin conjugating enzyme Cdc34p to Skp1p/F-box proteins; Hrt1p, a RING-H2 domain protein that stimulates ubiquitin ligase activity; and Cdc34p, a ubiquitin-conjugating enzyme that catalyzes the transfer of activated ubiquitin to the target protein. In addition, to these shared subunits, SCF complexes also contain one of several unique F-box motif containing proteins, including Cdc4p, Grr1p, Met30p, Dia2p, or Saf1p, that function as substrate specific adaptors or specificity determinants recruiting multiply phosphorylated substrates to the SCF core complex. Multiple substrates have been identified for specific SCF-F-box protein complexes. SCF-Cdc4p facilitates the polyubiquitination of Sic1p, Far1p, Cdc6p, Clb6pand Hac1p; substrates of SCF-Grr1p include Cln1p, Cln2p, Gic1p, and Gic2p; substrates of SCF-Met30p include Met4pand Swe1p; SCF-Dia2p polyubiquitinates Tec1p; and SCF-Saf1p polyubiquitinates Aah1p. The F-box proteins CDC4, GRR1 and MET30 are also intrinsically unstable and are able to catalyze their own SCF-mediated ubiquitination and destruction via an autocatalytic mechanism proposed to facilitate rapid switching among multiple SCF complexes. Finally, a subcomplex containing Cdc53p and Hrt1p functions as a ubiquitin-ligase module capable of activating the autoubiquitination of Cdc34p.cdc53 was originally identified as a cell division cyclemutant that arrests at the G1/S phase transition with multiple elongated buds and unreplicated DNA, similar to cdc4, cdc34 and hrt1 mutants. Cln2p and Sic1p are stabilized in both cdc53-1 and cdc34-2 mutants arrested at the restrictive temperature; overexpression of either CLN2 or CLN3 in cdc53-1 or cdc34-2 mutants exacerbates this phenotype, impairing colony formation at the permissive temperature. Deletion of the CDK inhibitor SIC1 alters the terminal phenotype of cdc53, cdc34 and cdc4 mutants, resulting in cells that now arrest at the G2/M phase transition of the cell cycle with replicated DNA and a single round bud.Cdc53p is regulated by neddylation, a ubiquitin-like modification in which the protein Rub1pis conjugated to its substrate. Neddylation of cullins has been proposed to positively regulate E3 ligase activity and assembly of SCF complexes.Cdc53p is evolutionarily conserved and multiple homologs exist in many species. Cullins were first identified in C. elegans, and CUL-1 mutants exhibit tissue hyperplasia resulting from a decreased ability to exit the cell cycle during development, and accelerated G1-to-S phase progression. Human CUL1, the closest human CDC53 cullin homolog, is a subunit of a functionally conserved SCF ubiquitin ligase complex that is involved in the degradation of key regulators of the mammalian cell cycle. Human CUL1 complements the growth defect of conditional CDC53 mutants and assembles into functional chimeric ubiquitin ligase complexes with yeast components.