INTRODUCTION. Ubiquitin-mediated proteolysis controls the timed destruction of numerous cellular regulatory proteins. The specificity of the ubiquitin system is achieved by the use of a large number of ubiquitin ligases, which are either single subunits or multiprotein complexes that act as recognition factors for substrates to be ubiquitinated. SCF complexes represent a large family of ubiquitin ligases, and are so called, because they are composed of Skp1, Cul1, an F-box protein and Roc1. It is the F-box protein (FBP) component of the SCF complex that is directly responsible for substrate recognition. FBPs are defined by a 40 amino acid motif called the F-box and characterized by additional protein-protein interaction domains such as WD-40 repeats or leucine-rich repeats (LRRs). FBPs bind Skp1 through their F-box to link to Cul1, Roc1 and the E2 enzyme that ultimately ubiquitinylates the substrate (see Fig. 1). In turn, the FBPs recruit phosphorylated substrates through their diverse protein-protein interaction domains. This system allows for specific recognition of a variety of substrates by SCF complexes through different FBPs. It is well documented that SCF complexes are key in controlling the abundance of cell cycle regulatory proteins including cyclins and cyclin-dependent kinase (CDK) inhibitors.
RESULTS. The SCF complex containing the FBP Skp2 coordinates the ubiquitinylation of p21 and p27, two CDK inhibitors, which function during G1 phase to block the activity of complexes containing Cdk2 (1-3). Degradation of p21 and p27 allows for Cdk2 activation and entry into S phase. Ubiquitinylation of p21 and p27 by SCFSkp2 also requires an accessory factor called Cks1, which promotes the binding of phosphorylated p27 to Skp2 (3,4). Recognition of p27 by the LRRs of Skp2 requires that p27 be phosphorylated on Thr187 and part of a trimeric complex with Cdk2 and either Cyclin E or Cyclin A 5. The free amino group of the N-terminal methionine of p21 is a site for ubiquitinylation in vivo demonstrating that the presence of lysines is dispensable for p21 ubiquitinylation 6. Skp2 and its cofactor Cks1 are also unstable proteins in G1, and their degradation prevents unscheduled degradation of p21 and p27, and premature entry into S-phase. Significantly, degradation of Skp2 and Cks1 during G1 is controlled by another cell cycle-regulated ubiquitin ligase, the anaphase-promoting complex/cyclosome (APC/C) (Bashir and Pagano, unpublished).

Not only does the APC/C control SCF but the opposite is also true. The SCF complex containing the FBP β-Trcp1 is responsible for the ubiquitin-dependent degradation of Emi1, an inhibitor of the APC/C, during prometaphase 7. Inactivation in mice of the BTRC gene, encoding β-Trcp1, results in reduced fertility correlating with an accumulation of metaphase I spermatocytes. In addition, β-Trcp1-/- mouse embryo fibroblasts (MEFs) display a lengthened mitosis, centrosome overduplication, multipolar metaphase spindles, and misaligned chromosomes. Furthermore, Emi1 is stabilized in mitotic β-Trcp1-/- MEFs and extracts from these cells are unable to sustain Emi1 ubiquitinylation unless supplemented with recombinant β-Trcp1. These results show that β-Trcp1 regulates the timely order of meiotic and mitotic events, and demonstrate that in addition to their role at the G1/S transition, SCF complexes function during meiosis and mitosis.

Studies on p27 degradation have been expanded to the clinic. It was originally found that aggressive human carcinomas contain high p27-specific degradation activity 8. Additionally, the absence of p27 is a
powerful prognostic marker for poor survival in patients with breast, esophageal, lung and colorectal carcinomas. Although transformation has often been shown to involve the inactivation of some CDK inhibitors, no homologous deletions or mutations of the CDKN1b gene, encoding p27, have been found so far in human tumors. In contrast, low p27 expression observed in human carcinomas can result from its enhanced ubiquitin-mediated degradation of p27 rather than altered p27 gene expression. Significantly, Skp2 levels inversely correlate with p27 expression in human cancers, such as breast cancers and lymphomas, and Skp2 cooperates with activated N-Ras in an in vivo model of lymphomagenesis.

**DISCUSSION.** Temporally coordinated destruction of cell cycle proteins by the ubiquitin-proteasome pathway represents an important regulatory mechanism that drives progression through the cell division cycle in a unidirectional and irreversible manner. There is increasing evidence that in addition to genetic alterations, aberrant proteolysis of cell cycle regulators contributes significantly to tumorigenesis, and is indeed found in many types of human cancer. For instance, Skp2 is an oncoprotein, due to its involvement in p27 degradation (see Fig. 2). Future studies will focus on whether additional FBPs have tumor suppressive or oncogenic properties due to the nature of their substrates.

**Figure 2.** The p27 pathway
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