Skp2 directs Myc-mediated suppression of p27Kip1 yet has modest effects on Myc-driven lymphomagenesis.

The universal cyclin-dependent kinase inhibitor p27(Kip1) functions as a tumor suppressor, and reduced levels of p27(Kip1) connote poor prognosis in several human malignancies. p27(Kip1) levels are predominately regulated by ubiquitin-mediated turnover of the protein, which is marked for destruction by the E3 ubiquitin ligase SCF(Skp2) complex following its phosphorylation by the cyclin E-cyclin-dependent kinase 2 complex. Binding of phospho-p27(Kip1) is directed by the Skp2 F-box protein, and this is greatly augmented by its allosteric regulator Cks1. We have established that programmed expression of c-Myc in the B cells of Emu-Myc transgenic mice triggers p27(Kip1) destruction by inducing Cks1, that this response controls Myc-driven proliferation, and that loss of Cks1 markedly delays Myc-induced lymphomagenesis and cancels the dissemination of these tumors. Here, we report that elevated levels of Skp2 are a characteristic of Emu-Myc lymphomas and of human Burkitt lymphoma that bear MYC/Immunoglobulin chromosomal translocations. As expected, Myc-mediated suppression of p27(Kip1) was abolished in Skp2-null Emu-Myc B cells. However, the effect of Skp2 loss on Myc-driven proliferation and lymphomagenesis was surprisingly modest compared with the effects of Cks1 loss.
Collectively, these findings suggest that Cks1 targets, in addition to p27(Kip1), are critical for Myc-driven proliferation and tumorigenesis.