Specific lentiviral shRNA-mediated knockdown of cyclin D1 in mantle cell lymphoma has minimal effects on cell survival and reveals a regulatory circuit with cyclin D2.

Cyclin D1 overexpression is the hallmark of mantle cell lymphoma (MCL). However, the importance of cyclin D1 in the maintenance and progression of the disease remains to be defined. The aim of this study was to elucidate the role of cyclin D1 overexpression using an efficient cyclin D1-shRNA and a lentiviral system in well-characterized MCL cell lines. Surprisingly, the knockdown of cyclin D1 led to a moderate retardation in growth, without induction of apoptosis. The cyclin D1-shRNA-transduced MCL cells showed a 15% shift from S phase to G(1) phase of the cell cycle, a weak induction of p27(Kip1), decreased Rb (Ser807/811) phosphorylation, and a consistent upregulation of cyclin D2 mRNA and protein expression. However, double knockdown of cyclins D1 and D2 did not intensify the effects observed with cyclin D1 knockdown alone. These data suggest that the moderate effects of cyclin D1 downregulation on survival and proliferation are likely the result of compensatory cyclin-independent mechanisms governing proliferation or alternatively, secondary genetic events that make cyclin D1 dispensable. These findings have important implications for MCL therapy, as strategies targeting only cyclin D1 function might be hampered by compensatory regulatory mechanisms, resulting in a low
probability of treatment response.