Sequestration of p27Kip1 protein by cyclin D1 in typical and blastic variants of mantle cell lymphoma (MCL): implications for pathogenesis.

Abstract:
p27 is a cyclin-dependent kinase inhibitor that plays a critical role in regulating G(1)/S progression, and whose activity is, in part, regulated through interactions with D-type cyclins. Mantle cell lymphoma (MCL) is characterized by the t(11; 14) translocation resulting in deregulated cyclin D1. We previously showed that p27 expression in MCL, as assessed by immunohistochemistry (IHC), does not show the usual inverse relationship to proliferate seen in most other lymphomas that do not overexpress cyclin D1. This suggested that the normal expression or control of p27 activity on cell growth might be altered through potential interactions with cyclin D1. Using Western blot and coimmunoprecipitation studies, we assessed the interrelationship between cyclin D1 and p27 in several cyclin D1(+) cell lines and primary MCL cases. Similar to our previous results by IHC, typical MCLs showed lower expression of p27 when compared to the more highly proliferative blastic cases or cell lines (mean arbitrary units: 58 versus 236 versus 120). Cyclin D1 was expressed at variable levels in both typical and blastic MCLs. p27 protein could be consistently coimmunoprecipitated with cyclin D1 from both cell lines and cases. Using techniques of exhaustive immunoprecipitation, we could demonstrate that most p27 protein was sequestered into complexes containing cyclin D1. We hypothesize
that mantle cell lymphomagenesis results not only from direct consequences of inappropriate cyclin D1 expression, but also from the ability of overexpressed cyclin D1 to buffer physiologic changes in p27 levels, thereby rendering p27 ineffective as an inhibitor of cellular growth.