Rapamycin-induced G1 arrest in cycling B-CLL cells is associated with reduced expression of cyclin D3, cyclin E, cyclin A, and survivin.

Abstract:

In B-cell chronic lymphocytic leukemia (B-CLL), malignant cells seem to be arrested in the G(0)/early G(1) phase of the cell cycle, and defective apoptosis might be involved in disease progression. However, increasing evidence exists that B-CLL is more than a disease consisting of slowly accumulating resting B cells: a proliferating pool of cells has been described in lymph nodes and bone marrow and might feed the accumulating pool in the blood. Rapamycin has been reported to inhibit cell cycle progression in a variety of cell types, including human B cells, and has shown activity against a broad range of human tumor cell lines. Therefore, we investigated the ability of rapamycin to block cell cycle progression in proliferating B-CLL cells. We have recently demonstrated that stimulation with CpG-oligonucleotides and interleukin-2 provides a valuable model for studying cell cycle regulation in malignant B cells. In our present study, we demonstrated that rapamycin induced cell cycle arrest in proliferating B-CLL cells and inhibited phosphorylation of p70s6 kinase (p70(s6k)). In contrast to previous reports on nonmalignant B cells, the expression of the cell cycle inhibitor p27 was not changed in rapamycin-treated leukemic cells. Treatment with rapamycin prevented retinoblastoma protein (RB) phosphorylation in B-CLL cells without...
affecting the expression of cyclin D2, but cyclin D3 was no longer detectable in rapamycin-treated B-CLL cells. In addition, rapamycin treatment inhibited cyclin-dependent kinase 2 activity by preventing up-regulation of cyclin E and cyclin A. Interestingly, survivin, which is expressed in the proliferation centers of B-CLL patients in vivo, is not up-regulated in rapamycin-treated cells. Therefore, rapamycin interferes with the expression of many critical molecules for cell cycle regulation in cycling B-CLL cells. We conclude from our study that rapamycin might be an attractive substance for therapy for B-CLL patients by inducing a G(1) arrest in proliferating tumor cells.