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Role of CDK4 and p16INK4A in interleukin-6-mediated growth of multiple myeloma.

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Interleukin-6 (IL-6) promotes growth of human multiple myeloma (MM) cells via phosphorylation of retinoblastoma protein (pRB). We therefore examined the kinetics of cyclin-dependent kinase 4 (CDK4), p16INK4A, and pRB activation during IL-6-mediated patient MM cell growth compared with growth of IL-6 unresponsive patient plasma cell leukemia (PCL) cells. CDK4 protein was more strongly expressed in PCL cells than in MM cells. On the other hand, p16 protein was present in MM cells but undetectable in PCL cells. Interestingly, IL-6 induced peak proliferation of MM cells at days 1-3, with a return to baseline levels of DNA synthesis by days 6-9 in spite of replenishing IL-6. In these cells, IL-6 triggered a sustained increase in CDK4 by day 1 and a gradual increase in p16 to day 9. The progressive increase in p16 without further increments in CDK4 resulted in a shift from cyclin D2-CDK4/CDK6 binding at days 1-3 to p16-CDK4/CDK6 complex formation at days 6-9. Both phosphorylated pRB and dephosphorylated pRB were present initially in patient MM cells; IL-6 triggered a shift to phosphorylated pRB and G1 to S transition at days 1-3, with return to baseline levels of dephosphorylated pRB and related G1 growth arrest by day 9. No similar changes in CDK4, p16, or cell cycle profile were observed in IL-6 nonresponsive PCL cells. Our data therefore suggest a feedback mechanism in IL-6-mediated MM cell growth which is absent in IL-6 nonresponsive PCL cells.