Extracellular signal-regulated kinase 2 (ERK2) mediates phosphorylation and inactivation of nuclear interaction partner of anaplastic lymphoma kinase (NIPA) at G2/M.

NIPA is an F-box-like protein that contributes to the timing of mitotic entry. It targets nuclear cyclin B1 for ubiquitination in interphase, whereas in G(2)/M phase, NIPA is inactivated by phosphorylation to allow for cyclin B1 accumulation, a critical event for proper G(2)/M transition. We recently specified three serine residues of NIPA and demonstrated a sequential phosphorylation at G(2)/M, where initial Ser-354 and Ser-359 phosphorylation is most crucial for SCF(NIPA) inactivation. In this study, we identified ERK2 as the kinase responsible for this critical initial phosphorylation step. Using in vitro kinase assays, we found that both ERK1 and ERK2 phosphorylated NIPA with high efficiency. Mutation of either Ser-354 or Ser-359 abolished ERK-dependent NIPA phosphorylation. Pharmacologic inhibition of ERK1/2 in cell lines resulted in decreased NIPA phosphorylation at G(2)/M. By combining cell cycle synchronization with stable expression of shRNA targeting either ERK1 or ERK2, we showed that ERK2 but not ERK1 mediated NIPA inactivation at G(2)/M. ERK2 knockdown led to a delay at the G(2)/M transition, a phenotype also observed in cells expressing a phospho-deficient mutant of NIPA. Thus, our data add to the recently described divergent functions of ERK1 and ERK2 in cell cycle regulation.
which may be due in part to the differential ability of these kinases to phosphorylate and inactivate NIPA at G(2)/M.