D125 Involvement of ERK in Induction of Differentiation not of Apoptosis by Vitamin E-succinate in HL-60 Cells

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Mitogen-activated protein kinase (MAPK) signaling cascades are involved in the cellular response to extracellular stimuli. Specifically, extracellular signal-regulated kinases (ERKs) have been associated with proliferation and differentiation, whereas the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPKs) have been implicated in cell arrest and death. Vitamin E succinate (VES) induced monocytic differentiation of HL-60 cells (75% at 24 hr) followed by apoptosis (95% at 72). Phosphorylation of ERK was induced by treatment of VES before causing differentiation and cell cycle arrest associated with hypophosphorylation of the retinoblastoma (RB) tumor suppressor protein. ERK activation by MAP/ERK kinase (MEK) was necessary for VES induced differentiation in studies using PD08059 to block MEK phosphorylation. However, PD08059 has no effect on VES-induced apoptosis. The results suggest that ERK activation is required for induction of HL-60 cell differentiation and growth arrest by VES but is not needed for induction of apopotosis.

D126 Overexpressed Akt Blocks NGF-induced Neuronal Differentiation of PC12 cells by Inhibiting Growth Arrest Effect of NGF

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To investigate the role of Akt in NGF-induced neuronal differentiation, PC12 cells expressing the kinase-dead mutant or the wild type of Akt were analyzed. Compared to that in parental PC12 cells, NGF-induced neurite outgrowth was greatly accelerated in mutant cells, however, drastically blocked in wild-type cells. Wild-type cells were not susceptible to the growth-arresting effect of NGF unlike parental PC12 and mutant cells, which had decreased populations in S phase in response to NGF. Consistent with this, the levels and/or the activity of proteins regulating cell cycle progression such as CDK2, CDC2 and $p21^{WAF1}$ were not much changed in wild-type cells, while down-regulation of CDK2 as well as upregulation of $p21^{WAF1}$ by NGF were observed in parental and in mutant PC12 cells. Furthermore, when treated with anti-proliferative agents, wild-type cells regained the responsiveness to the differentiative action of NGF. Taken together, these data suggest that Akt function as a signaling molecule capable of overriding growth arrest and thus negatively regulating neuronal differentiation by NGF in PC12 cells.