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Glial Cell-derived Neurotrophic Factor Increases Migration of Human Chondrosarcoma Cells Via ERK and NF-κB Pathways

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Abstract

Invasion of tumor cells is the primary cause of therapeutic failure in the treatment of malignant chondrosarcomas. Glial cell-derived neurotrophic factor (GDNF) plays a crucial role in migration and metastasis of human cancer cells. Integrins are the major adhesive molecules in mammalian cells. Here we found that GDNF directed the migration and increased cell surface expression of alphav and beta3 integrin in human chondrosarcoma cells. Pretreated of JJ012 cells with MAPK kinase (MEK) inhibitors PD98059 or U0126 inhibited the GDNF-mediated migration and integrin expression. Stimulation of cells with GDNF increased the phosphorylation of MEK and extracellular signal-regulating kinase (ERK). In addition, NF-kappaB inhibitor (PDTC) or IkappaB protease inhibitor (TPCK) also inhibited GDNF-mediated cells migration and integrin up-regulation. Stimulation of cells with GDNF induced IkappaB kinase (IKKalpha/beta) phosphorylation, IkappaB phosphorylation, p65 Ser(536) phosphorylation, and kappaB-luciferase activity. Furthermore, the GDNF-mediated increasing of kappaB-luciferase activity was inhibited by PD98059, U0126, PDTC and TPCK or MEK, ERK, IKKalpha, and IKKbeta mutants. Taken together, these results suggest that the GDNF acts through MEK/ERK, which in turn activates IKKalpha/beta and NF-kappaB, resulting in the activations of alphavbeta3 integrin and contributing the migration of human chondrosarcoma cells.