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Cyclin-dependent Kinase 5 Interacts with RPTPβ/ζ and Mediates Pleiotrophin-induced Endothelial Cell Migration

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SUMMARY

Cyclin-dependent kinase 5 (cdk5), a proline-directed serine/threonine kinase, belongs to the cyclin-dependent kinase (CDK) family. Unlike other members of this group, cdk5 does not have a known role in cell-cycle progression and requires the regulatory subunits p35 or p39 for activation. Cdk5 is primarily expressed in neuronal cells and plays an important role in processes like neuronal migration and neurite outgrowth, but its functions in non-neuronal cells are unclear. There are a growing number of molecules that exhibit the capacity to interact with cdk5. Pleiotrophin (PTN), also known as heparin affin regulatory peptide or heparin-binding growth-associated molecule is an 18-kDa secreted growth factor that has high affinity for heparin. PTN is expressed in various cancer cell lines, takes part in many different processes, such as cell growth and survival, cell migration and angiogenesis, exerting diverse functions in different cell lines. We have previously shown that PTN induces migration of endothelial cells through binding to its receptor protein tyrosine phosphatase β/ζ (RPTP_/__ and $\alpha_v\beta_3$ integrin. In the present study, we investigated the role of cdk5 in PTN-induced human endothelial cell migration. Roscovitine, a synthetic inhibitor of cdks with selectivity towards cdk2 and cdk5, as well as down-regulation of cdk5 by siRNA completely attenuated PTN-induced migration of endothelial cells. PTN increased cdk5 kinase activity with the maximum increase observed within 5 min after stimulation of cells with PTN. Interestingly, by immunoprecipitations followed by Western blot or mass spectroscopy analyses, cdk5 was found to directly interact with RPTPβ/ζ. Similar results were obtained in human glioblastoma U87MG cells, which are known to express both RPTPβ/ζ and $\alpha_v\beta_3$ and migrate in response to PTN. These data suggest that cdk5 is a significant regulator of the PTN/RPTPβ/ζ/$\alpha_v\beta_3$ signaling pathway that leads to increased cell migration.