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Cell Surface Expression of Nucleolin Is Maintained by $\alpha_v\beta_3$ Integrin and is required for Pleiotrophin-induced Cell Migration

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SUMMARY

Pleiotrophin (PTN) is a secreted heparin-binding growth factor with roles in many different processes, such as cell growth and survival, neurite outgrowth, endothelial cell migration and angiogenesis, as well as tumour growth and metastasis. We have previously shown that PTN induces tumor and endothelial cell migration through its receptor protein tyrosine phosphatase β/ζ (RPTPβ/ζ) that forms a functional complex with $\alpha_v\beta_3$ integrin on the cell surface. The multifunctional protein nucleolin (NL) has been also mentioned to be a low affinity cell surface receptor for PTN. Nucleolin acts as a shuffle between cytoplasm and nucleolus, is increased on the surface of angiogenic endothelial cells and binds a variety of ligands that play critical role(s) in tumorigenesis and angiogenesis. In the present work, we studied whether NL plays a role in PTN-induced cell migration. Down-regulation of NL by siRNA or blockage of cell surface NL by its ligand 5(KPR)TASP in human endothelial cells completely abolished PTN-induced cell migration. NL was found to directly interact not only with PTN, but also with both RPTPβ/ζ and $\alpha_v\beta_3$ on the membrane of human endothelial and cancer cells. Interaction of both PTN and RPTPβ/ζ with NL was also observed inside the cell, while $\alpha_v\beta_3$ was only detected on the cell surface. Although NL was not detected on the surface of cells that do not express integrin $\alpha_v\beta_3$, both PTN and RPTPβ/ζ appeared in the nucleus of these cells, suggesting the existence of an alternative transport pathway. It seems that PTN is a casein kinase 2 (CK2) substrate, with CK2 being implicated in PTN and RPTPβ/ζ nuclear transport mechanism. Inhibition of CK2 activity did not influence the effects of PTN on cell migration, implying that nuclear translocation of PTN and RPTPβ/ζ does not affect cell migration and that cell surface NL participates in the transduction of a yet unknown signal that induces cell migration. Collectively, our data suggest that cell surface expression of NL is maintained by $\alpha_v\beta_3$ integrin and is required for PTN-induced cell migration.