MED28 regulates MEK1-dependent cellular migration in human breast cancer cells

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Abstract

MED28, a mammalian Mediator subunit, exhibits several cellular roles, including a merlin, Grb2, and cytoskeleton-associated protein (magicin), a repressor of smooth muscle cell differentiation, and an endothelial-derived gene (EG-1). Overexpression of MED28 may stimulate cell proliferation which presumably results from the transcriptional activation of the Mediator function. Additionally, several tumors, including breast cancer, highly express MED28. We have found recently that MED28 potentiated epidermal growth factor (EGF)-induced migration in human breast cancer cells. Therefore, the objective of this study is to identify the role of MED28 in the aspect of cellular migration and invasion in human breast cancer cells. Suppression of MED28 blocked cellular migration and invasion with concomitant reduced expression levels of matrix metalloproteinase-2 (MMP2) and mitogen-activated protein kinase kinase 1 (MAP2K1; MEK1); overexpression of MED28 enhanced cellular migration and upregulated MMP2 and MEK1 expression. Moreover, suppression of MEK1, by dominant-negative, kinase-dead MEK1 cDNA construct or MEK1-specific small interfering RNA (siRNA) as well as MEK1 inhibitors, blocked MED28-induced MMP2 activation, cellular migration, and invasion in breast cancer cells. Furthermore, ectopic expression of MEK1 rescued the inhibitory effect of MED28 knockdown on invasion, and exogenous MMP2 recombinant protein recovered the suppression on invasion upon MED28 or MEK1 knockdown. Our data indicate that MED28 regulates cellular migration in a MEK1-dependent manner in human breast cancer cells, reinforcing the important cellular roles of MED28.