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A novel role of the natriuretic peptide/cGMP/cGKI pathway in melanoma cells

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Background

The cGMP/cGMP-dependent protein kinase type I (cGKI) signaling pathway is activated by nitric oxide (NO), natriuretic peptides (ANP, BNP & CNP), and cGMP-elevating drugs. It regulates important physiological functions such as platelet aggregation, smooth muscle tonus, and cell growth and survival. Recent reports indicate that cGMP might also play a role in tumorigenesis. In the present study we found that cGKI is expressed in melanoma cells of murine and human origin.

Results

Treatment of intact mouse B16 melanoma cells with the membrane-permeable cGMP analog 8-Br-cGMP induced phosphorylation of the cGKI substrates, vasodilator-stimulated phosphoprotein and phosphodiesterase 5. ANP and CNP, ligands of the membrane-bound guanylyl cyclase GC-A and GC-B, respectively, activated the endogenous cGMP/cGKI pathway. CNP-induced cGMP signals were detected in cell extracts by ELISA and in living cells by a FRET-based cGMP sensor [1]. DEA/NO, which stimulates NO-sensitive soluble guanylyl cyclase, did not increase cGMP signaling in B16 cells. Interestingly, activation of cGMP/cGKI signal transduction was associated with an increase in ERK1/2 and p38 phosphorylation, growth and migration of B16 melanoma cells. Similar results were obtained with WM1205 human melanoma cells.

Conclusion

We have identified a natriuretic peptide/cGMP/cGKI pathway in melanoma cells, which stimulates tumor cell growth and migration in vitro. Pharmacologic inhibition of cGMP signaling may offer a promising strategy for the treatment of melanoma.

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