Abstract Form

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Title:

EGFR AND EGFRVIII INDUCES EXPRESSION OF THE PROANGIOGENIC RECEPTOR EPHA2 IN CANCER CELLS

Corresponding and Presenting Author :Alice Bjerregaard Larsen[1]
Mikkel Wandahl Pedersen[1], Helle Broholm[2], Henning Laursen[2] and Hans Skovgaard Poulsen[1]

Affiliations

[1]Department of Radiation Biology, section 6321, The Finsencenter, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark
[2]Department of Neuropathology, section 6301, Copenhagen University Hospital, Denmark, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

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The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that plays an important role in the regulation of cell growth, proliferation, survival, and motility. EGFR and its ligands are involved in the development of tumors originating from the brain, lung, breast, colon, ovary, or head and neck. Recently, we have identified the receptor tyrosine kinase EphA2 in a search for EGFR regulated genes[1]. EphA2 belongs to the Eph receptor family, which is divided in two major classes (EphA and EphB) based on similarity of their extracellular domain sequences and their binding affinities for ephrin-A and ephrin-B ligands. The Eph family of receptors has mainly been associated with neuronal development. However, EphA2 is frequently overexpressed in advanced cancers, and increasing evidence suggests that EphA2 contributes to multiple aspects of the malignant character including angiogenesis and metastasis.

In this study, the role of ligand activated EGFR and constitutively activated EGFRvIII in the regulation of EphA2 expression, was investigated. Our results show that activated EGFR and EGFRvIII induces EphA2 mRNA and protein levels in a number of mammalian cell lines including the human cancer cell lines A431 and HN5. In addition, using luciferase reporter assay with a vector containing the EphA2 promoter (-4030 to +21), we show that the EGFR induced expression of EphA2 is via a direct effect on the EphA2 promoter. Using a panel of small molecular inhibitors is it shown that the EGFR induced expression of EphA2 is dependent on EGFR tyrosine kinase activity and on MEK activity.

To validate these findings, the level of EGFR and EphA2 was investigated in a panel of primary glioblastoma multiforme tissues. The results show frequent coexpression of EphA2 and EGFR in these tumors.

In summary, activated EGFR and EGFRvIII are able to induce expression of EphA2 through a pathway involving activation of MEK in human cancer cell lines. These results could have important implications for understanding the role of EGFR in cancer, as EphA2 might be a link between EGFR activity and EGFR mediated tumor angiogenesis and metastasis.