PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

RAFTK/Pyk2-mediated signaling in breast cancer cells

ArticleInfo		
ArticleID	:	3702
ArticleDOI	:	10.1186/bcr-2000-66665
ArticleCitationID	:	66665
ArticleSequenceNumber	:	68
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2000–3–30 OnlineDate : 2000–3–30
ArticleCopyright	:	Current Science Ltd2000
ArticleGrants	:	
ArticleContext	:	1305822

Chris Jones,[Aff1]

Aff1 Royal Free and University College London, UK

Keywords

ErbB-2, invasion, RAFTK, RasGAP, RhoGAP

Introduction

The erbB-2 type I tyrosine kinase receptor is involved in cell differentiation, proliferation, migration and carcinogenesis, although its precise biological functions remain unclear. Heregulin (HRG) can activate ErbB-2 receptors as a result of ErbB-2/ErbB-3 or ErbB-2/ErbB-4 heterodimeric interactions. HRG can induce either a growth arrest or a mitogenic response, and may be associated with regulation of cytoskeleton reorganization and cell migration. Mitogen-induced changes in the actin cytoskeleton are accompanied by changes in the tyrosine phosphorylation of several focal adhesion proteins. The gene encoding a novel human cytoplasmic tyrosine kinase termed RAFTK, which is related to focal adhesion kinase (FAK), has been cloned and the product subsequently shown to interact with different protein tyrosine kinases such as Src, as well as focal adhesion molecules such as paxillin and HAF1.

Aims

To investigate the role of RAFTK in HRG-mediated signaling in breast cancer cells.

Comments

Overexpression of ErbB-2 is reported in 25-30% of breast cancers, correlates with poor prognosis, and is a novel target for therapy. A number of recent reports have demonstrated the ability of ErbB-2 to confer invasion capacity on breast cancer cells, via phosphatidylinositol (PI) 3'-kinase and extracellular regulated kinase (ERK) pathways. This paper presents evidence for involvement of a novel tyrosine kinase, related adhesion focal tyrosine kinase (RAFTK), in mediating ErbB-2-regulated invasion/ migration, acting via the mitogen-activated protein (MAP) kinase pathways. An association with key regulators of the actin cytoskeleton is also presented, further strengthening the case for ErbB-2 as a critical component of the migration/invasion machinery of carcinoma cells.

Methods

The breast cancer cell lines T47D, MCF-7 and MDA-MB-435 were used in this study. Protein analysis was carried out by immunoprecipitation and immunoblotting. Invasion was measured by the Matrigel invasion assay.

Results

HRG stimulation of the T47D breast cancer cell line induced the tyrosine phosphorylation of RAFTK and the formation of a multiprotein complex. The proteins participating in this complex were found to be p190 RhoGAP (GTPase-activating protein), RasGAP, and an unidentified 160 kDa protein. Both p190 RhoGAP and RasGAP were found to associate with RAFTK in an independent manner, and RAFTK mediated the tyrosine phosphorylation of p190 Rho by Src. RAFTK binding to ErbB-2 was mediated by Src. Furthermore, RAFTK mediated the activation of MAP kinase by HRG, and this pathway involves ras molecules, but not Src. Breast carcinoma cell invasion was promoted by RAFTK, and this required the kinase activity of the enzyme as well as its ability to bind and activate Src.

Discussion

The data presented here demonstrate the involvement of RAFTK in regulating breast cancer cell invasion. RAFTK appears to mediate activation of MAP kinase by HRG as well as the interaction of RhoGAP - RasGAP. This suggests that RAFTK acts as a point of integration between the GAP proteins and HRG-mediated signaling, and thereby is associated with HRG-initiated cytoskeletal changes through the ErbB-2 receptor in breast cancer cells.

References

1. Zrihan-Licht S, Fu Y, Settleman J, Schinkmann K, Shaw L, Keydar I, Avraham S, Avraham H: RAFTK/Pyk2 tyrosine kinase mediates the association of p190 RhoGAP with RasGAP and is involved in breast cancer cell invasion. Oncogene. 2000, 19: 1318-1328.