Crosstalk between integrin and receptor tyrosine kinase signaling in breast carcinoma progression

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This review explored the mechanism of breast carcinoma progression by focusing on integrins and receptor tyrosine kinases (or growth factor receptors). While the primary role of integrins was previously thought to be solely as mediators of adhesive interactions between cells and extracellular matrices, it is now believed that integrins also regulate signaling pathways that control cancer cell growth, survival, and invasion. A large body of evidence suggests that the cooperation between integrin and receptor tyrosine kinase signaling regulates certain signaling functions that are important for cancer progression. Recent developments on the crosstalk between integrins and receptor tyrosine kinases, and its implication in mammalian tumour progression, are discussed. [BMB reports 2010; 43(5): 311-318]

INTRODUCTION

Cancer progression is a multi-step process that enables tumor cells to invade through extracellular tissues and metastasize to distal organs (1). Compelling recent evidence demonstrates that cooperation between signals from the extracellular matrix (ECM) and growth factors enhances malignant behaviors of aggressive cancer cells, such as proliferation, migration, survival, and invasion (2). Intracellular signals generated by growth factors and their receptor tyrosine kinases (RTKs) are generated independently from those produced by interaction between the ECM and integrin, and the synergy between these signals plays an important role in tumor growth and metastasis (3). Therefore, defining the mechanism by which these two signaling pathways cooperate is essential for understanding cancer progression.

This review focuses on the evidence for crosstalk between integrin and RTKs in breast carcinoma progression. Breast cancer originates from breast epithelial cells that are transformed into metastatic carcinomas. Metastatic potential and responsiveness to treatment vary depending on the expression of hormone receptors such as estrogen receptor and progesterone receptor (5), RTKs such as ErbB-2, epidermal growth factor receptor (EGFR), and hepatocyte growth factor receptor, c-Met (6), and integrins (7). Major integrins expressed on breast epithelial cells include \( \alpha_2\beta_1 \), \( \alpha_3\beta_1 \), \( \alpha_\text{v}\beta_3 \), \( \alpha_\text{v}\beta_5 \), \( \alpha_5\beta_1 \), \( \alpha_6\beta_1 \), and \( \alpha_6\beta_4 \) (7). Among these, this review focuses on \( \alpha_\text{v}\beta_3 \), \( \alpha_3\beta_1 \), and \( \alpha_6\beta_4 \) all of which are upregulated in invasive breast carcinoma and have well established relationships with RTKs (8). These integrins serve as receptors for vitronectin, fibronectin, and laminin, respectively (9), and contribute to the survival and invasion of mammary tumors. Model systems describing the mechanisms and relevance of these integrin-RTK interactions will be discussed.

Integrin interaction with ECM

Integrins represent a major family of receptors that mediate cell adhesion to the ECM. To date, at least 18 \( \alpha \) and 8 \( \beta \) integrin subunits have been discovered (10). These non-homologous, transmembrane \( \alpha \) and \( \beta \) subunits dimerize to form 24 different integrins, each with distinct and sometimes overlapping specificities for various ECM proteins. While the primary role of integrins was thought to be as mediators of adhesive function, integrins also regulate cellular biological processes related to cell morphology, proliferation, survival, migration, and invasion (11). In other words, integrins relay cues from the ECM to intracellular signaling machinery upon ligand binding, a process called "Outside-in Signaling" (9). On the other hand, intracellular signaling activated by other receptors could induce conformational changes in integrins, thus altering their functional activity, a process called "Inside-out Signaling" (12). Therefore, integrins and RTKs can exchange or amplify their signaling pathways via both "Outside-in" and "Inside-out" signaling.

Downstream signaling events induced by integrin-ECM interactions include Ras, Phosphop-inositol-3-kinase (PI3 Kinase), MAP kinase, focal adhesion kinase (FAK), Src, Akt, integrin-linked kinase (ILK), Abl and Rac, Rho, and cdc42 small GTPases (13-16). In addition, integrin-ECM interactions induce the phosphorylation of key tyrosine residues of integrin sub-
units such as β3 and β4, which results in recruitment of signaling adaptor molecules such as Shc, Shp-2, and Crk (17-19). These adaptor molecules not only transmit integrin-dependent signals, but also contribute to crosstalk with other signaling receptors including RTKs (20-22). It is interesting to note that intracellular signaling events activated by integrin ligation are also influenced by growth factor stimulation. Indeed, integrin-ECM interactions significantly amplify growth factor-mediated signaling events (23), which suggests that synergy between integrin and RTK signaling could maximize biochemical responses.

Evidence for integrin and RTK crosstalk

Considering that neither α nor β integrin subunits possess catalytic activity, it is possible that multiple mechanisms may regulate crosstalk between integrins and RTKs. The most compelling evidence comes from direct, physical association between integrins and RTKs. Co-immunoprecipitation assays have been used to identify biochemical interactions between these receptors. For example, αvβ3 integrin associates with insulin-like growth factor receptor (IGFR-1), platelet-derived growth factor receptor (PDGFR) (24, 25), and vascular endothelial growth factor receptor-2 (VEGFR2) (26). Additionally, α6β4 integrin has been shown to associate with ErbB2 (27), c-Met (28), EGFR (20), and Ron (29). These associations suggest that signaling cooperation between integrins and RTKs may be the result of receptor co-clustering upon cell adhesion or growth factor stimulation. Growth factor stimulation of RTKs or ECM-integrin interactions induces an increase in the local concentration of integrins and RTKs at focal adhesions and at leading edges of carcinoma cells, such that crosstalk could occur even without direct physical association by alteration of the intracellular localization of integrins (30).

The mode of signaling cooperation between integrins and RTKs could be reciprocal as well as uni-directional. Bi-directional cooperation between the two signaling systems was demonstrated for the αvβ3-IGF receptor (31) and αvβ3-PDGF-α complex (32), whereupon signaling pathways activated by both integrin engagement and growth factors converge down-

Fig. 1. Signaling pathways mediated by α6β4 integrin-RTK crosstalk. α6β4 integrin in Hemidesmosomes (HDs) has no signaling function but does provide structural support to the epithelia. The tumor microenvironment induces PKC-α-dependent phosphorylation of key Ser residues in the β4 integrin cytoplasmic tail, resulting in HD disassembly. Mobilization of α6β4 from HDs allows association of α6β4 with actin filament-rich sub domains of membrane structures in which functional interactions with RTKs occur, such as lipid rafts. Several examples in which α6β4 associates with RTKs are shown. (A) α6β4 is physically and functionally associated with ErbB2 and EGFR. The association of EGFR with α6β4 is mediated by SFKs (Fyn) activation. (B) MSP induces association of α6β4 with Ron through 14-3-3, which acts as a linker molecule. (C) Cooperative signaling between α6β4 and c-Met is responsible for various aspects of breast cancer progression, although the constitutive and physical interaction between c-Met and α6β4 remains controversial. PI-3K/Ras are major downstream signaling pathways mediated by α6β4-RTK crosstalk.