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Review

ErbB/integrin signaling interactions in regulation of myocardial cell–cell and cell–matrix interactions☆

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ABSTRACT

Neuregulin (Nrg)/ErbB and integrin signaling pathways are critical for the normal function of the embryonic and adult heart. Both systems activate several downstream signaling pathways, with different physiological outputs: cell survival, fibrosis, excitation–contraction coupling, myofilament structure, cell–cell and cell–matrix interaction. Activation of ErbB2 by Nrg1β in cardiomyocytes or its overexpression in cancer cells induces phosphorylation of FAK (Focal Adhesion Kinase) at specific sites with modulation of survival, invasion and cell–cell contacts. FAK is also a critical mediator of integrin receptors, converting extracellular matrix alterations into intracellular signaling. Systemic FAK deletion is lethal and is associated with left ventricular non-compaction whereas cardiac restriction in adult hearts is well tolerated. Nevertheless, these hearts are more susceptible to stress conditions like trans-aortic constriction, hypertrophy, and ischemic injury. As FAK is both downstream and specifically activated by integrins and Nrg-1β, here we will explore the role of FAK in the heart as a protective factor and as possible mediator of the crosstalk between the ErbB and Integrin receptors. This article is part of a Special Issue entitled: Cardiomyocyte Biology: Cardiac Pathways of Differentiation, Metabolism and Contraction.

1. Introduction

In 1995 three articles were contemporaneously published in Nature describing the effect of systemic deletion of Neuregulin(Nrg)-1, epidermal growth factor receptors ErbB2 and ErbB4 in mice. These studies demonstrated that Nrg/ErbB signaling is needed for the correct development of heart trabeculae, a structure responsible for the normal function of the embryonic heart [1–3]. Since then our knowledge has greatly increased and it is now clear that this signaling system is also active in the adult heart and is critical for its maintenance under stressed conditions. Specific deletion of ErbB2 [4] and ErbB4 [5] leads to spontaneous dilated cardiomyopathy associated with higher susceptibility to aortic banding. Both cardiac and cancer research have connected directly and indirectly Nrg-1β/ErbB to several signaling pathway, such as Phosphatidylinositol 3-Kinase (PI3K)/Akt, Mitogen-Activated Protein Kinase (MAPK)/ Extracellular signal-Regulated Kinase (Erk) 1/2, and the non-receptor tyrosine kinase Src/Focal Adhesion Kinase (FAK), and demonstrated its involvement in a wide variety of physiological outputs, including cardiac cell survival, migration, angiogenesis, cytoskeleton, and excitation–contraction coupling(for a detailed review on these pathways in the heart see ref. [6]).

The primary role of integrins is to link the extracellular matrix (ECM) to the intracellular signaling. Deletion of β1 subunit, the most common in the heart, suggests that ECM is involved in the differentiation of cardiomyocytes during heart development [7]. Integrins are also critical for the maintenance of the adult heart both under normal and pathological conditions, as their deletion results in a spontaneous increase in fibrosis as well as induction of heart failure [8]. The non-receptor tyrosine kinase FAK is the main effector of integrins, converting changes in the extracellular matrix into intracellular signaling.

As FAK is both downstream and specifically activated by integrins and Nrg-1β, here we will explore the role of FAK in the heart as a protective factor and a possible mediator of the crosstalk between ErbB and Integrin receptors (Fig. 1).

2. Nrg-1β/ErbB2/ErbB4 signaling

2.1. Nrg-1β/ErbB dependent Akt and Erk1/2 signaling and their role in the heart

Both Erk1/2 and Akt signaling pathways have been extensively studied in the heart and we will just briefly summarize these studies here (for a detailed review on these pathways as NRG-1β downstream

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effectors please refers to Pentassuglia and Sawyer, 2009, Experimental Cell Research: The role of Neuregulin-1β/ErbB signaling in the heart [6]). Several studies conducted so far demonstrate that both Erk1/2 and Akt mediate Nrg1β-dependent cell survival, metabolism, and growth in the heart under normal and stressed conditions. Postnatal cardiac-specific deletion of ErbB2 leads to spontaneous dilated

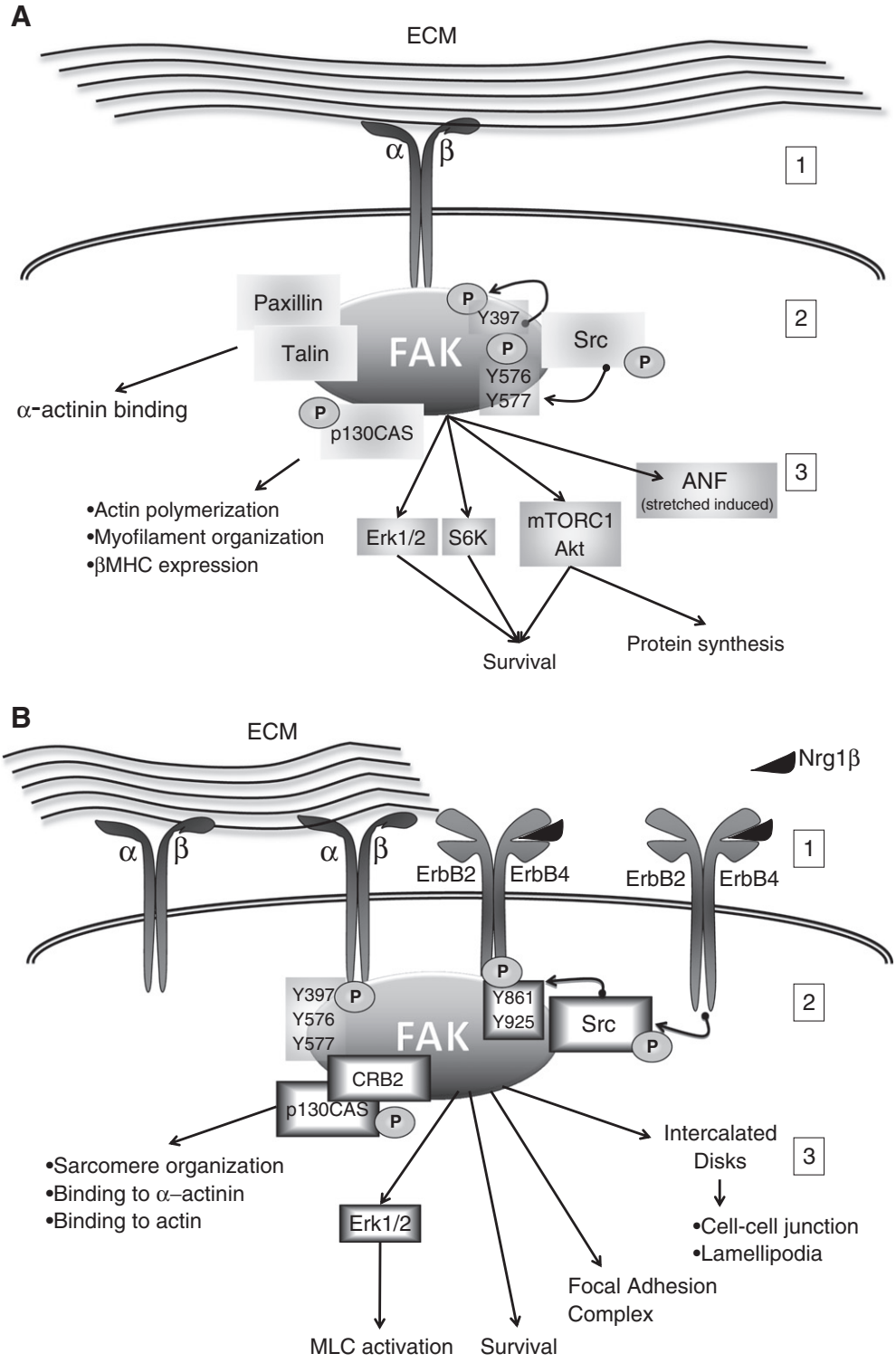

Fig. 1. FAK activation and role in cardiomyocytes. A. Integrin-dependent activation of FAK. Binding to the extracellular matrix (ECM) and mechanical stretch activates integrin receptors at the cell surface (1). To initiate intracellular signaling integrin dimer induces conformational changes in FAK and auto-phosphorylation on tyrosine (Y) 397. Src can then phosphorylate FAK at Y576 and Y577 in the activation loop (2). Activated FAK can then: interact with Paxillin and Talin to bind α-actinin; induce actin polymerization, myofilament organization, and expression of β Myosine Heavy Chain (MHC) via p130CAS; and promote survival via Erk1/2, S6K, mTORC1, and Akt, protein synthesis via mTORC1 and Akt, and stretch induced expression of ANF (3). B. Nrg1β-specific phosphorylation of FAK and its role in cardiomyocytes. Upon binding to Nrg1β (1), the ErbB2/ErbB4 heterodimer induces phosphorylation of FAK at Y861 and Y925 via Src (2). Phosphorylated FAK: is involved in sarcomere organization and binding to actin and α-actinin via interaction with p130CAS and CRB adaptor proteins; induces activation of Myosin Light Chain (MLC) via Erk1/2; promotes myocyte survival and focal adhesion complex formation; and migrates to the intercalated disks where it promotes cell–cell interaction and lamellipodia formation (3).