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Mini review

Signalling pathways linking integrins with cell cycle progression ☆

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ABSTRACT

Integrins are adhesion receptors that allow cells to sense and respond to microenvironmental signals encoded by the extracellular matrix. They are crucial for the adhesion, survival, proliferation, differentiation and migration of most cell types. In cell cycle regulation, integrin-mediated signals from the local niche constitute a spatial checkpoint to allow cells to progress from G1 to S phase, and are as important as temporal growth factor signals. Proliferation is altered in diseases such as cancer and fibrosis, so understanding how integrins contribute to this process will provide novel strategies for therapy. Here we consider recent studies to elucidate mechanisms of integrin-dependent cell cycle progression and discuss perspectives for future study.

Contents

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1. Introduction

Integrins are widely expressed glycoprotein receptors that mediate cell adhesion and communication with the extracellular matrix (ECM). These receptors are composed of α and β subunits forming 24 heterodimers from a combination of 18 α and 8 β subunits. Integrins sense the composition and mechanical properties within the pericellular environment, and transmit this information intracellularly to both the cytoskeleton and to signals that modify cell behaviour. To achieve this, integrins recruit mediators to their cytoplasmic domains. More than 150 proteins have been identified to interact at integrin adhesion sites, forming an adhesion complex also known as the "adhesome" (Zaidel-Bar et al., 2007; Legate et al., 2009; Streuli, 2009). Adhesion complex proteins include cytoskeletal components, enzymes and adaptor proteins that collectively modulate cell shape, and control cell fate decisions including proliferation, differentiation and migration.

The cell cycle is tightly regulated by a series of cyclins and cyclin-dependent kinases (cdks) that coordinate checkpoints for progression through each stage of the cycle. The first checkpoint to commit to cell cycle takes place during G1 phase. Both mitogenic signals and ECM adhesion activate transcription factors such as AP-1, which control the expression of cyclin D1. Cyclin D1 binds cdk4 to phosphorylate the Retinoblastoma protein (Rb), which disassociates from E2F. Relief of E2F suppression permits cyclin E transcription, formation of a cdk2/cyclin E complex and further Rb phosphorylation, thereby amplifying the production of the complex. Once the levels of this complex are sufficient, the cell passes the restriction point and enters S phase. Mitogens simultaneously suppress negative regulators such as the cyclin-dependent kinase inhibitors (CKIs) p27 and p21, which inhibit the cdk4/cyclin D complex. Thus synchronised formation of cdk/cyclin complexes together with downregulated CKIs eventually allows assembly of a replication complex and subsequent proliferation.

Cell adhesion via integrins is crucial for progression through the G1/S checkpoint. Integrins indirectly recruit adaptor proteins such as talin and paxillin, and enzymes such as focal adhesion kinase (Fak) and small GTPases, which control downstream effectors in signalling cascades. These effectors regulate the levels of cyclins, CKIs, and the transcription of genes required for proliferation such as c-Jun and E2F (Walker and Assoian, 2005). Integrins also participate in mitotic spindle alignment (LaFlamme et al., 2008; Streuli, 2009). The role that integrins play in proliferation is so important that in the absence of integrin-mediated adhesion, metazoan cells do not commit to enter the cell cycle and thus do not proliferate.

Here, new studies on molecular mechanisms linking integrins to cell cycle entry will be discussed. We focus first on the general mechanisms of how integrins cooperate with growth factor receptors (GFRs) to control proliferation, and second on the mechanisms associated with specific integrin β subunits.

1.1. Cooperation between integrins and growth factor receptors in cell cycle regulation

The classical model of cell cycle regulation presented in textbooks highlights growth factors as the unique stimulus to trigger proliferation. However it is now established that integrin adhesion is also an essential requirement for proliferation in metazoan cells. Normal cells either detached from ECM substrata or genetically lacking integrin subunits cannot progress into cell cycle, even in the presence of growth factors (Nikolopoulos et al., 2005; Walker and Assoian, 2005; Streuli and Akhtar, 2009; Jeanes et al., 2012). Despite the major contribution of integrins to cell cycle progression, they cannot trigger proliferation independently of GFRs.

There are different mechanisms by which integrins cooperate with GFRs (Fig. 1A). One is that integrins and GFRs activate the same pathways (signal crosstalk). For proliferative responses, the major pathways regulated by GFRs and integrins are the PI3K/Akt, Mek/Erk, and small GTPase (Rho and Rac) pathways. Integrins also control the expression of GFRs at the transcriptional level. For example, Epidermal Growth Factor Receptor (EGFR) protein levels are decreased in human epithelial cells cultured in suspension, and the downregulation of EGFR reduces β1-integrin levels (Grassian et al., 2011). Integrins also cooperate with GFRs through physical association. Mechanisms include: activation of integrins by GFRs to enhance the mitogenic signals; activation of GFRs by integrins in the absence of GFR ligand; increased internalisation and endocytic trafficking of GFRs by integrins. However, GFR phosphorylation by integrins is only transient and less effective than that mediated by growth factors. Thus, a sustained activation of Erk mediated by GFRs and integrins together is required for the synthesis of cyclin D1. This has been discussed more in detail previously (Walker and Assoian, 2005; Streuli and Akhtar, 2009).

1.1.1. Perspectives

Although the basis of the synergistic relationship between integrins and GFRs in cell cycle control has been established, there are still major questions remaining. For example, what are the precise molecular connections within the adhesome that link integrin cytoplasmic tails to downstream proliferation signalling pathways? Which integrins are required for proliferation in different cell types? Are the signalling pathways downstream GFRs and integrins the same in all cell types? What adhesion complex proteins are phosphorylated or turned over by GFRs and are these GFR-specific? Are the same mechanisms activated in 2D vs 3D cultures and in vivo?

1.2. Integrins control Akt and Erk signalling

Akt signalling is adhesion-dependent in many cell types. This pathway can be activated by integrins via Fak, which binds to the p85 subunit of PI3K, or through a Src–vinculin complex. The Akt pathway is essential for proliferation because a dominant negative mutant of PI3K prevents cyclin D1 expression. However proliferation also requires Erk signalling. An inducible activated Mek transfected into suspended fibroblasts rescues the proliferation defect arising from ECM detachment, but when treated with a specific PI3K inhibitor the transfected cells fail to enter S phase (Walker and Assoian, 2005). Both Akt and Erk phosphorylation are required to induce cell growth when stimulated with mitogens (Dellinger and Brekken, 2011; Fournier et al., 2012; Zhang et al., 2013). Moreover, some studies suggest that Akt and Erk both regulate Elk1 activity (Mut et al., 2012). Thus, adhesion-activated Akt and Erk pathways contribute to cyclin D1 induction via different mechanisms, which complement each other to allow transition through G1/S (Fig. 1B).

Besides regulating Elk1, Akt controls Foxo3a transcriptional activity by phosphorylating three of its Ser/Thr residues (Zhang et al., 2013). FoxO3a normally induces transcription of the CKIs p27 and p21. When phosphorylated by Akt, FoxO3a becomes inactive and is translocated to the cytosol. Akt also activates the mammalian target of rapamycin complex 2 (mTorc2), a kinase which stimulates the expression of Skp2, forming part the ubiquitin ligase complex (Shanmugasundaram et al., 2013). Together, these Akt-regulated events lead to p27 and FoxO3a degradation, thereby permitting cell cycle progression. Integrins also cooperate with EGFR to suppress FoxO1 via Akt signalling, thereby promoting transcription of the early response gene, Egr-1 (Cabodi et al., 2009).

The CKIs are regulated by other mechanisms that permit integration of cell cycle control by GF and adhesion signals. On the GF arm, Erk can also phosphorylate Foxo3a at S294, S344 and S425, causing Foxo3a cytoplasmic localization and degradation via the E3 ubiquitin ligase MDM2 (Yang et al., 2008). In the absence of degradation, nuclear Foxo represses cyclin D1 expression in the absence of p27. Additionally, β1 integrins are required to maintain low levels of p27 or p21 in neurons and epithelial cells, respectively (Blaess et al., 2004; Li et al., 2005).

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