Review

CellPress

Special Issue: Cell Biology of Cancer

Integrins and cancer: regulators of cancer stemness, metastasis, and drug resistance

Laetitia Seguin, Jay S. Desgrosellier, Sara M. Weis, and David A. Cheresh

Department of Pathology and the Moores Cancer Center, University of California San Diego, La Jolla, CA 92093, USA

Interactions between cancer cells and their surroundings can trigger essential signaling cues that determine cell fate and influence the evolution of the malignant phenotype. As the primary receptors involved in cell–matrix adhesion, integrins present on the surface of tumor and stromal cells have a profound impact on the ability to survive in specific locations, but in some cases, these receptors can also function in the absence of ligand binding to promote stemness and survival in the presence of environmental and therapeutic stresses. Understanding how integrin expression and function is regulated in this context will enable the development of new therapeutic approaches to sensitize tumors to therapy and suppress their metastatic phenotype.

Integrin heterodimers and ligand specificity in cancer

When the extracellular matrix (ECM) is proteolytically degraded or deformed by mechanical forces, cells are prompted to undergo responsive changes that influence remodeling during physiological and pathological events. Integrins are a family of heterodimeric cell surface receptors that sense these changes and trigger a range of cellular responses by forming a physical connection between the inside and outside of a cell to allow the bidirectional 'integration' of signals to control cell adhesion, migration, proliferation, survival, and differentiation [1]. While integrins regulate processes important for a range of physiological functions, these receptors also play a crucial role in promoting a more malignant tumor cell phenotype in the setting of cancer [2].

The ability of integrins to dictate cellular responses to a variety of inputs stems from their capacity to differentially recognize distinct environments. To allow for this flexibility, integrins are comprised of 18 α subunits and eight β subunits that pair to form at least 24 different functional heterodimeric receptors that each bind to one or more ECM ligands. This specificity allows integrin–ligand binding events to enforce distinct niches or boundaries, so that cells expressing only certain integrin heterodimers can pass within an ECM containing specific components such as laminin, collagen, vitronectin, or fibronectin. Since a given integrin can bind to multiple ligands, and a single ligand can recognize multiple integrin heterodimers, spatio-temporal patterns of integrin versus ligand expression ultimately determine how a cell senses and responds to its environment. Integrin control of matrix metalloproteinases (MMPs) on the surface of cells is also a determining factor for invasive behavior [3]. In the context of cancer, this cell adhesion-dependent aspect of integrin function plays a critical role in determining the ability of a cell to break through a defined tumor margin in order to locally invade and ultimately metastasize. Ligand binding also controls whether a certain tumor cell can disseminate to a particular metastatic niche, such as bone, brain, or lung environments characterized by distinct ECM signatures.

Upon encountering a specific ligand, integrins undergo a conformational change that switches them from an inactive low avidity state to a high avidity state [4]. This change is based in part on the ability of ligated integrins to cluster in the plane of the membrane leading to 'outside-in' signaling via a physical linkage to the actin cytoskeleton (Box 1). Alternatively, intracellular signaling can also activate 'inside-out' signals that affect integrin affinity/avidity for extracellular ligands [5]. By selectively recruiting adapter or scaffolding proteins such as CRK-associated substrate (CAS), Src homology 2 domain containing transforming protein 1 (shc), and growth factor receptor-bound protein 2 (GRB2), integrins play an important role in potentiating the activity of receptor tyrosine kinases, including receptors for growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), or epidermal growth factor (EGF) [1,6–9]. Although these 'canonical' integrin signaling pathways have been extensively characterized, new specificities and signaling components are still being discovered [10].

Similar to growth factor receptors, integrin clustering within the plasma membrane is regulated by numerous direct or indirect integrin binding partners, and serves to amplify signal-generating capacity (Figure 1). Accordingly, integrin clustering could represent an Achilles' heel for integrin function that could be exploited therapeutically. Galectins, a family of β-galactoside-binding lectins recently associated with metastasis [11], influence tumor cell behavior by binding to carbohydrates on the extracellular

Corresponding author: Cheresh, D.A. (cheresh@scripps.edu, dcheresh@ucsd.edu).
Keywords: integrins; cancer; drug resistance; stemness.

0962-8924/
 http://dx.doi.org/10.1016/j.tcb.2014.12.006

Box 1. The canonical integrin signaling cascade

Integrins are the major cell surface receptors for ECM molecules, which play critical roles in a variety of biological processes. FAK is a key component of the signal transduction pathways triggered by integrins. When integrins interact with their specific ligands, they recruit FAK through their β subunit. FAK undergoes autophosphorylation that leads to its association with Src, resulting in activation of both kinases. Then, the active FAK/Src complex recruits p130CAS and paxillin that in turn recruit Crk leading to activation of Ras-related C3 botulinum toxin substrate 1 (RAC1), PAK, Jun amino-terminal kinase (JNK), and NFκB. Alternatively, the FAK/Src complex can recruit and activate Ras-proximate-1 (RAP1), which in turn activates ERK and MAPK through v-Raf murine sarcoma viral oncogene homolog B (BRAF). The FAK/Src complex may also lead to its association with GRB2, which in turn can activate RAS leading to the activation of the RAF–MEK–ERK pathway, and PI3K has also been shown to bind FAK leading to activation of PI3K and its downstream effectors.

domain of integrins and regulate clustering. Several galectins have recently been identified to play a role in tumor progression including Galectin-1, which promotes lung cancer metastasis by potentiating integrin α6β4 and Notch1/Jagged2 signaling [12], and Galectin-3, which induces integrin β3-mediated anchorage-independence and drug resistance [13]. Tetraspanins also play key roles in clustering integrins by regulating their trafficking and function [14,15]. The tetraspanin CD151 in particular shows promise as a diagnostic marker as well as a therapeutic target [16]. Thus, through their effects on integrin clustering, galectins and tetraspanins could provide a means to control integrin signaling independent of ligand binding and promote tumor cell dissemination and metastasis.

Not only can integrin function be suppressed by competitively blocking integrin-ligand binding events, but it is also possible to suppress ligand-independent integrin clustering by manipulating the function of proteins such as galectins or tetraspanins that can cluster and promote integrin activity in the absence of cell adhesion in a permissive microenvironment. In fact, combining these strategies could provide therapeutic opportunities to short circuit the ability of integrins to generate signals across distinct environments. Developing such an approach will require a better understanding of the cues and responses that are spatially and temporally distinct during the course of cancer progression. This review is therefore focused on highlighting newly appreciated roles of integrins in driving a stem phenotype, drug resistance, and metastasis.

Dissecting integrin-dependent regulation of stem cells

Although epithelial stem cells play a critical role in the physiological development, maintenance, and remodeling of organs and tissues [17], their properties are also associated with the initiation and progression of carcinomas [18]. Since the stem cell niche is tightly regulated by signals from the local microenvironment including the ECM, certain integrins may be critical for the ability of stem cells to sense and respond to these cues in both normal tissues and cancer. Indeed, a number of integrins have recently been highlighted as important markers and functional regulators of stem cells, suggesting that additional insight into how integrins contribute to the stem cell phenotype will allow the development of therapeutic approaches to modulate stemness in aggressive cancers.

Integrin regulation of stem cells during development and physiological remodeling

Recent studies have identified specific integrins that are enriched in epithelial stem cells and critical for their behavior. Integrin β1 (CD29) is highly expressed in normal stem cells and regulates their biology in various organs. Stem cells are typically associated with a particular local microenvironment or niche that provides critical signals to direct their self-renewal and pluripotency. For example, ECM proteins such as periostin and tenascin-C are found in stem cell niches [19,20]. Increasing evidence demonstrates that

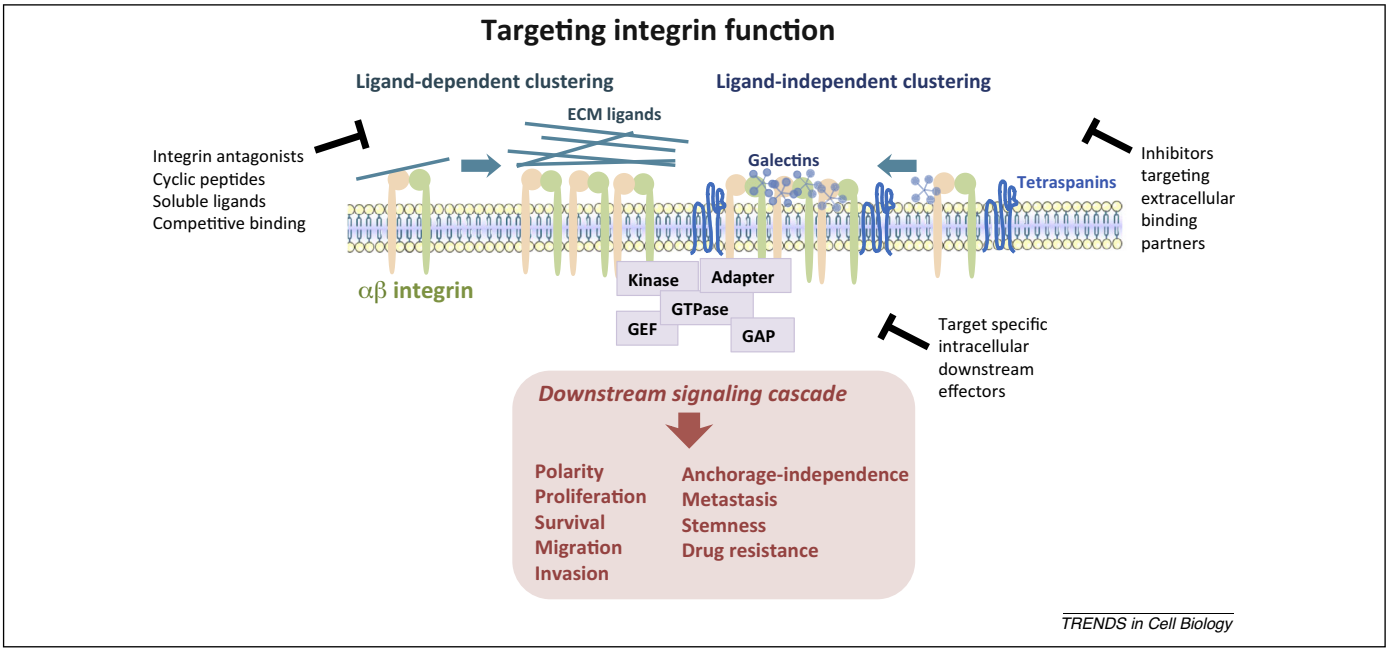

Figure 1. Integrin clustering is critical for generation of downstream signals. Integrin function can be blocked upstream by preventing ligand binding or ligand-independent clustering, or by targeting specific downstream integrin effectors.