Review

The opposing roles of laminin-binding integrins in cancer

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Abstract

Integrins play an important role in cell adhesion by linking the cytoskeleton of cells to components in the extracellular matrix. In this capacity, integrins cooperate with different cell surface receptors, including growth factor receptors and G-protein coupled receptors, to regulate intracellular signaling pathways that control cell polarization, spreading, migration, survival, and gene expression. A distinct subfamily of molecules in the integrin family of adhesion receptors is formed by receptors that mediate cell adhesion to laminins, major components of the basement membrane that lie under clusters of cells or surround them, separating them from other cells and/or adjacent connective tissue. During the past decades, many studies have provided evidence for a role of laminin-binding integrins in tumorigenesis, and both tumor-promoting and suppressive activities have been identified. In this review we discuss the dual role of the laminin-binding integrins α3β1 and α6β4 in tumor development and progression, and examine the factors and mechanisms involved in these opposing effects.

Laminin-binding integrins, what they are and what they do

Laminins are large heterotrimeric extracellular matrix (ECM) glycoproteins that contain an α, a β, and a γ chain. They are major components of the basement membrane (BM) that separates the nervous system, epithelial, endothelial, fat and muscle cells from adjacent connective tissue [1]. The BM, however, is not just a physical barrier; it also contributes to the adhesion, proliferation, migration and survival of cells. Integrins are heterodimeric transmembrane glycoproteins that function as adhesion receptors for ligands in the extracellular matrix (ECM) and transduce mechanical signals from the ECM into biochemical signals within the cell. Four integrins recognize laminins as their extracellular ligands: α3β1, α6β1, α7β1 and α6β4 (reviewed in [2]). Their specificity and affinity for binding to various laminin isoforms differ considerably [3–5] (Table 1). Alternative mRNAs splicing of the α3, α6 and α7 subunits further increases the functional diversity of these laminin-binding integrins by generating evolutionary conserved isoforms with different affinities for ligand binding and signaling activities [6]. The α6 and α7 subunits have distinct isoforms that differ in both their extracellular (X1 and X2) and cytoplasmic domains (A and B), while the α3 subunit only exists as two distinct cytoplasmic variants [7–14]. The expression of these isoforms is tissue specific and developmentally regulated [15–18], however a full understanding of their role is still lacking.

Integrin α6β4 is expressed at the base of most epithelial cells, but also by a subset of endothelial cells [19] and by perineural fibroblasts and Schwann cells in peripheral nerves [20,21]. It mediates cell adhesion to laminins and plays a crucial role in the formation of specific cell-matrix complexes, i.e. hemidesmosomes (HDs) [22]. Hemidesmosomal dysfunction is associated with a group of inherited disorders called epidermolysis bullosa, symptoms of which are severe blistering of the skin and mucosal membranes [23]. Mice lacking either the integrin α6 or β4 subunit display very similar defects in skin and mucosal membranes, and die perinatally [24–26].

Table I. The ligand-binding specificity of the laminin-binding integrins (bold printed – laminin isoforms reported to bind with the highest affinity) and reported phenotypes of mice and human diseases linked to non-functional integrins.

LAMININ ISOFORM SPECIFICITY		GENE		MOUSE PHENOTYPE	HUMAN DISEASE
-332 -511/521	α6β4	*Itgb4*	LETHAL, Perinatal	Severe skin blistering	Epidermolysis bullosa
-111, -332, -511/521 -211/221, -411	α6β1	*Itga6*	LETHAL Birth	Severe skin blistering, defects in cerebral cortex and retina	Epidermolysis bullosa
		Itgb1	LETHAL E 5.5	Inner cell mass deterioration	Lethal
-511/521, -332 -211/221	α3β1	*Itga3*	LETHAL Birth	Defects in kidneys, lungs, skin, and cerebral cortex. Disorganization of the BM	Congenital nephrotic syndrome, interstitial lung disease, and epidermolysis bullosa
-211/221 -111, -511/521	α7β1	*Itga7*	VIABLE Fertile	Muscular dystrophy	Congenital myopathy

Despite sharing the common β1 subunit, the integrins α3β1, α7β1 and α6β1 have unique functions and distinct distribution patterns. Integrin α3β1 is most abundant in skin, kidneys, lungs, intestine, bladder and stomach. In these tissues, it mediates adhesion of epithelial cells to laminin-332 and -511 in the BM, and plays a role in the maintenance of cell–cell contacts. Recently, mutations in the gene encoding the α3 subunit (*ITGA3*) have been identified in patients suffering from a congenital nephrotic syndrome, interstitial lung disease and a mild form of epidermolysis bullosa [27–29]. Similar symptoms have been previously described in genetically engineered mice lacking α3β1 [30]. Notably, the skin defects observed in the absence of α3β1 occur early in life and are associated with micro-blisters and a disorganized BM. Later in life, these defects are no longer observed [31,32].

Integrin α7β1 is most prominently expressed in cardiac and skeletal muscles, where it connects muscle fibers to laminin-211/221 in the BM of the myotendinous junction. In line with its function, patients with a loss-of-function mutation in the gene encoding the α7 subunit (*ITGA7*) suffer from congenital myopathy [33], and mice lacking α7β1 develop muscular dystrophy [34].

Finally, integrin α6β1 is expressed on platelets, leukocytes, gametes and some epithelia. It binds to a wide range of laminin isoforms, with the highest affinity to laminin-111, -511 and -332 [5]. Apart from a defect in laminar organization of the developing cerebral cortex and retina, seen in the α6-deficient mice (but not in β4-deficient mice), no other defects are associated with the absence of this integrin α subunit in mice [26,35]. The β1 subunit is ubiquitously expressed and can bind to as many as 12 different α subunits (reviewed in [2]). Therefore, it is not surprising that its depletion causes a failure of embryonic development [36].

Laminin-binding integrins can be found in two different adhesion complexes, focal adhesions (FAs) and HDs. FAs are dynamic protein complexes that form mechanical links between the ECM and the actomyosin cytoskeleton [37]. The dynamic regulation of FAs and the reorganization of the associated actin cytoskeleton are important determinants for cell migration. HDs are more stable adhesion structures that act as anchoring sites for intermediate filaments (reviewed in [38–41]). These adhesions need to be disassembled during migration and several mechanisms have been suggested to contribute to the disassembly of HDs, including endocytosis of HD proteins [42,43], laminin chain processing [44], cleavage of the β4 subunit by calpain or caspases [45,46], and phosphorylation of HD proteins [47–52]. Upon dissociation of HDs, α6β4 has been reported to be redistributed to actin-rich filopodia and lamellae [53,54], where it plays a role in the regulation of cell migration. However, the mechanism responsible is poorly understood.

In addition to their role in maintaining structural integrity of tissues, the laminin-binding β1 integrins also function as bidirectional signaling molecules. “Inside-out” signaling regulates the binding affinity and/or avidity of the integrin to its ECM ligand, while “outside-in” signaling is triggered upon adhesion and results in the transduction of signals into the cell (reviewed in [55–58]). As integrins lack intrinsic enzymatic activity, they signal through direct or