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Review

Alpha2beta1 integrin in cancer development and chemoresistance

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ABSTRACT

Extracellular matrix, via its receptors the integrins, has emerged as a crucial factor in cancer development. The α2β1 integrin is a major collagen receptor that is widely expressed and known to promote cell migration and control tissue homeostasis. Growing evidence suggests that it can be a key pathway in cancer. Recent studies have shown that α2β1 integrin is a regulator of cancer metastasis either by promoting or inhibiting the dissemination process of cancer cells. The α2β1 integrin signaling can also enhance tumor angiogenesis. Emerging evidence supports a role for α2β1 integrin in cancer chemoresistance especially in hematological malignancies originating from the T cell lineage. In addition, α2β1 integrin has been associated with cancer stem cells. In this review, we will discuss the complex role of α2β1 integrin in these processes. Collagen is a major matrix protein of the tumor microenvironment and thus, understanding how α2β1 integrin regulates cancer pathogenesis is likely to lead to new therapeutic approaches and agents for cancer treatment.

1. Introduction

Integrins are the major receptors for extracellular matrix (ECM) proteins. They are α/β heterodimeric membrane proteins that mediate cell adhesion to the surrounding ECM [1–3]. There are 18 different α chains and 8 different β subunits in humans, which associate in pairs to give rise to at least 24 distinct α/β integrin heterodimers. Upon ligand binding, integrins form clusters on the cell surface at sites termed focal adhesions that act not only as structural links between the ECM and the actin cytoskeleton but also as sites of signal transduction from the ECM to intracellular signaling pathways such as focal adhesion kinase (FAK), Src kinase, integrin-linked kinase (ILK), proline-rich tyrosine kinase (PYK-2), mitogen activated protein kinase (MAPK) including extracellular signal regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38, as well as phosphoinositide 3-kinase (PI 3-kinase) and protein kinase B (AKT) [4–8]. Integrins are the primary means by which cells sense and respond to their microenvironment and are now recognized as important receptors in regulating the hallmarks that characterize human cancers, which include proliferation, self-renewal, resistance to cell death and therapy, angiogenesis, immune evasion and metastasis.

The expression profile of integrins on cancer cells and the composition and organization of ECM of the tumor stroma are major factors in cancer development, metastasis and in therapy resistance [9–15]. Collagen is the most abundant ECM protein in vertebrate organisms, forming the framework of connective tissues and of soft interstitial matrices such as the bone marrow. It is also a critical matrix of the tumor microenvironment [12–15].

Cell attachment to collagen is principally mediated by collagen-binding integrins α1β1, α2β1, α10β1 and α11β1 [16,17] that generally recognize the triple helical GFOGER (O = hydroxyproline) sequences of collagen [18–21]. In addition, discoidin domain receptors, which are non-integrin transmembrane tyrosine kinase receptors and other membrane receptors can also serve as collagen receptors [22]. α2β1 integrin is a major receptor for fibrillar type I collagen but can also bind other types of collagens (III, IV, XI), laminins and some proteoglycans [16,23]. It is expressed on different cell types such as epithelial, fibroblast and endothelial cells as well as on immune cells and it is also found on many types of cancer cells [24,25]. In contrast to α1β1 integrin, α2β1 integrin is widely expressed on epithelial cells and its levels are increased in several carcinoma cells from the epithelial origin [24,26].

Growing evidence indicates that α2β1 integrin can be a key pathway in cancer pathogenesis. The structure and ligand binding regulation of α2β1 integrin have been elegantly reviewed

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Table 1
Role of α2β1 integrin in different types of cancer.

Cancer type	Function	References
MMTV-Neu-induced breast cancer	Suppression of hematogeneous metastasis	[72]
MDA-MB-231 breast cancer	Invasion and metastasis to the bone	[30,85]
	Resistance to paclitaxel and vincristine	[103]
HPV-induced squamous carcinoma	Tumor initiation and progression	[73]
Human melanoma and squamous carcinoma xenografts	Growth via promotion of angiogenesis	[55,56]
Pancreatic cancer	Local invasion but suppresses distant metastasis	[43,78,79]
	Promotion of EMT	[46–48]
	Resistance to 5-fluorouracil	[105]
	Resistance to gemcitabine	[112,113]
Prostate cancer	Invasion and metastasis to the bone	[80–82]
	Marker of prostate cancer stem cells	[166–170]
Colorectal cancer	Proliferation, invasion and metastasis to the liver	[45,87,88,90]
	Growth of human colorectal xenografts via angiogenesis	[60,62]
	Promotes stem cell-like phenotype	[172,173]
Gastric cancer	Peritoneal and liver metastasis	[91–93]
	Promotion of EMT	[49]
Small cell lung cancer	Resistance to chemotherapy and radiotherapy	[106,107]
	Growth of small lung cancer xenografts via angiogenesis	[61]
Lung cancer	Resistance to EGF receptor inhibitors	[114]
T-cell Acute Lymphoblastic Leukemia	Protection from death-receptor-mediated apoptosis	[123,124]
	Resistance to doxorubicin	[125,138]

MMTV; mouse mammary tumor virus, HPV; human papilloma virus.

[16,27,28]. Herein, we will discuss the major findings regarding its function in cancer, which are summarized in Table 1.

2. Regulation of cancer cell invasion and proliferation by α2β1 integrin

Integrin-mediated attachment to ECM is a critical step in determining the capacity of cancer cells to invade locally and ultimately to form distant metastases. The α2β1 integrin plays an important role in cancer cell migration and invasion into collagen. It can promote cell motility and enhance the production of matrix metalloproteinases (MMP), which are necessary to the proteolysis of matrix proteins. Along with α1β1 integrin, it mediates invasion of mouse carcinoma mammary cells through the production of stromelysin-1 (MMP-3) [29]. Migration of human MDA-MB-231 breast cancer cells and skin fibroblasts in collagen depends on α2β1 integrin-mediated activation of p38 MAPK, which upregulates the production of MMP-13 [30,31]. α2β1 integrin also promotes ovarian carcinoma cell invasion by increasing MMP-2/MMP-9 activation and through the disaggregation of tumor cell spheroids [32,33]. A proteomic/mass spectrometry approach has shown that in human HT-1080 fibrosarcoma cells, α2β1 integrin associates with 70 proteins among which adhesion and signaling molecules and membrane-type (MT)-MMP-1 [34]; a potent invasion-promoting protease that localizes to invadopodia membrane structures, and which has been associated with α2β1-mediated invasion of cancer cells [35,36]. A recent study showed that glycosylation of α2 integrin subunit is important for higher phosphorylation of FAK tyrosine 397 and for migratory capacities of pancreatic cancer cells into collagen [37].

In addition to matrix invasion, α2β1 integrin can also favor vascular extravasation of tumor cells such as PC-3 prostate, MDA-MB-231 breast and SKOV3 ovarian cancer cell lines by inducing disruption of endothelial cell adherens junctions via tyrosine phosphorylation of vascular endothelial cadherin [38].

The α2β1 integrin has also the ability of enhancing cell proliferation depending on the type and physical state of the collagenous matrix. When cells such as fibroblasts [39,40] and M24met melanoma cells [41] or primary uterine leiomyomas [42] are placed in collagen gels (polymerized fibrillar collagen type I), they become growth arrested at the G1/S checkpoint due to the accumulation of the cyclin-dependent kinase inhibitors p27Kip1 and p21Cip1. In contrast, monomeric collagen decreases the levels of the cyclin inhibitors and these cells enter the cell cycle. Similarly, monomeric collagen also triggers proliferation of pancreatic cancer cells [43]. These studies suggest that proteolytic degradation of collagen fibrils can promote α2β1 integrin-dependent tumor growth and that α2β1 integrin can have important implications in the regulation of tumor dormancy *vs* growth.

Similar to monomeric collagen type I, the binding of collagen type IV, a non-fibrillar form of collagen, to α2β1 integrin triggers proliferation of pancreatic cancer cells [44] and of colorectal cancer lines where it induces G1/S transition through FAK and MAPK/ERK activation and cyclin D1 upregulation [45]. This suggests that α2β1 integrin can be important for the growth of tumor cells in tissues rich in collagen type IV such as the liver.

In addition, α2β1 integrin has been associated with the promotion of epithelial-mesenchymal transition (EMT), which is an essential process triggered during invasion and metastasis. Collagen type I induces EMT of pancreatic cancer cells, leading to enhanced cell migration and proliferation, through JNK-mediated N-cadherin upregulation [46] and by disrupting E-cadherin-mediated cell–cell contacts [47]. The effect of collagen is transduced through α2β1 integrin and discoidin domain receptor 1 (DDR1), which increased FAK and PYK2 signaling respectively [47,48]. Similarly, α2β1 integrin enhances gastric cancer cell migration and proliferation by inducing disassembly of the E-cadherin-β catenin complex [49]. However, it is not clear from these studies if α2β1 integrin signaling regulates the transcriptional factors associated with EMT [50,51].

3. α2β1 integrin promotes tumor angiogenesis

Besides its direct role in cancer cells, α2β1 integrin also promotes endothelial cell function. Angiogenesis is a key process in tumor growth and consists on the formation of new blood vessels from pre-existing ones and involves endothelial cell migration and proliferation in a collagen-rich matrix. This process occurs at an uncontrolled rate in cancers and is tightly dependent on integrin signaling [52]. The expression and activity of the collagen-binding integrins α1β1 and α2β1 are highly upregulated in cultured endothelial cells by the proangiogenic growth factor VEGF, which enhances their attachment and spreading to collagen and to laminin-1 [53]. In turn, activated α1β1 and α2β1 integrins potentiate endothelial cell response to VEGF by enhancing MAPK/ERK activation leading to increased endothelial cell proliferation and chemotaxis towards collagen type I [54–56]. Moreover, α2β1 integrin promotes endothelial cell migration by activating p38 MAPK, enhancing focal adhesion disassembly and inhibiting

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