Integrin signaling and lung cancer

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The poor prognosis of most non small cell lung carcinomas is due to their ability to efficiently invade surrounding tissues and blood vessels, finally metastasizing to distant organs. Integrin mediated adhesive interaction with the surrounding extracellular matrix is a key limiting step in the regulation of the invasive properties of several cancer cell types. Here, we examine the rising evidences about the role that integrins can play in the physiopathology of non small cell lung carcinomas by regulating cell adhesion as well as the activation of growth factors and the traffic of their cognate receptors. Modulation of the signaling pathways controlled by integrins in lung cancer cells might offer the opportunity to design and develop new drugs that might be successfully combined with conventional chemotherapy and radiotherapy.

Introduction

Colonization of distant organs by cancer cells moving out from primary tumors is the most life-threatening event in the oncogenic process and accounts for most human cancer deaths.1 In multicellular organisms both in physiological and pathological settings, e.g., tissue morphogenesis and metastatization, cells move by dynamically adhering on proteinaceous extracellular matrices (ECM) via heterodimeric αβ integrin receptors.2 In mammals, 18 α subunits and 8 β subunits of integrins assemble into 24 distinct receptors. On the cell surface, integrin heterodimers are present in either low or high affinity conformations depending on the balance between inhibiting and activating signal transduction pathways triggered by extracellular guidance cues, such as chemokines,3 growth factors4,5 and semaphorins.6 At the same time, the regulation in space and time of cell adhesion and migration on ECM proteins also depends on the modulation of the endo/exocytic shuttling of integrins back and forth from the plasma membrane.7 Thus, alterations in integrin expression levels,8 conformational activation9 and traffic10,11 can endow cancer cells with the abnormal and advantageous ability to cross the physiological barriers of the tissue of origin, invade and alter the functionality of vital organs. In addition to mediating mechanical interactions of cells with the surrounding environment, integrins can promote cancer cell proliferation, survival and differentiation by activating latent growth factors,12 regulating the traffic10,13 and the downstream signaling8 of tyrosine kinase receptors.

Lung epithelial cells adhere to a basement membrane of which laminin 332 (aka laminin 5, nicein, kalinin or epiligrin) is the major component.14 α5β4 integrin is the main epithelial laminin receptor that localizes at the basal epithelial cell surface, where it associates with intermediate filaments and plays a key role in the formation and maintenance of multirpote protein adhesion complexes known as hemidesmosomes.15 α3β1, which interacts with the actin cytoskeleton, is another laminin-binding integrin that, while not directly involved in the assembly of hemidesmosomes, exerts a crucial control in the deposition and organization of the laminin 32 containing basement membrane.16 Mice lacking the α3 integrin subunit die during the first twenty four hours after birth and display a severe decrease in bronchial branching as well as in the maturation of the distal bronchiolar epithelium.17 Other integrin heterodimers, such as α5β1, αvβ3 and αvβ6, bind to ECM ligands other than those normally present in the basement membrane, such as fibronectin (FN) and osteopontin (OPN), which are instead induced together with their receptors at sites of epithelial repair and tumor development. Because of its aggressive and highly metastatic potential, lung cancer is a major cause of cancer death worldwide.18 Here we will review experimental evidences supporting a role of integrins in lung cancer progression. In particular, we will focus on non-small cell lung cancer (NSCLC) since this is the histotype in which the potential role of integrin signaling has been better documented up to now.

Fibronectin and α5β1 Integrin Regulate Invasion and EGF Receptor Signaling

FN is a large disulfide-linked dimeric glycoprotein, implicated in cell adhesion, migration and differentiation.19 FN is deposited as an insoluble cross-linked multimeric fibrillar network by many cell types and exists as soluble plasma FN as well. Each FN subunit contains several homologous modules displaying binding sites for integrins and for other ECM proteins, such as type I collagen or proteoglycans.20 During normal wound healing damaged blood vessels transiently release fibrin and plasma FN that polymerize in a matrix scaffold allowing the migration of repair cells.21 Many cancers behave as wounds that do not heal, in which chronically leaky vessels cause the formation of a fibrin/FN fibrillar network around the tumoral lesion; moreover, cancer cells themselves secrete FN.22 Hence, to grow and invade neo-plastic cells have to deal with a FN-containing matrix.
Tobacco is the major risk factor for lung cancer. Recently, genome-wide association studies identified an association between single nucleotide polymorphism in nicotinic acetylcholine receptor subunit genes and susceptibility to lung cancer. Of note, the main tobacco alkaloid nicotine stimulates lung cancer cell growth by inducing FN synthesis. Indeed, through the α7 nicotinic acetylcholine receptor nicotine stimulates FN mRNA and protein synthesis. Moreover, silencing or functionally blocking α5β1 integrin, the major FN receptor, impairs the mitogenic effect of nicotine on lung cancer cells. Increased α5β1 levels significantly correlate with lymph node metastasis of NSCLCs. In addition, 40% of the NSCLC patients with a lymph node negative status die because of tumor recurrences. The 5-year survival rate of node-negative NSCLC patients that overexpress α5β1 integrin is significantly worse than that of individuals with NSCLC displaying normal α5β1 expression. Thus, it is conceivable that α5β1 integrin participates in promoting both NSCLC proliferation and metastatic dissemination.

The natural history of the metastatic process implies that carcinoma cells need to disassemble the tight junctions that keep them firmly connected to neighboring epithelial cells and then exploit their integrin-mediated adhesion to migrate and colonize distant tissues and organs. In this respect, it is particularly relevant that the enzymatic activation of members of the protein kinase C (PKC) family can both trigger the disruption of tight junctions, e.g., by phosphorylating the zona occludens-1 (ZO-1) protein, and promote cell directed motility through the control of integrin traffic. Moreover, a constitutively active version of PKCε has been detected in lung cancer cells. Notably, Tuomi and colleagues recently identified PKCε as a master regulator of a new molecular network controlling the migration of NSCLC cells via ZO-1 and α5β1 integrin. Indeed, in motile NCI-H460 cells α5β1 integrin is required for the formation of the leading edge lamella, where it colocalizes with ZO-1 (Fig. 1). Here, the small GTPase Rac is known to signal the generation of new peripheral adhesive contacts (focal complexes), whereas Rho favors their maturation in focal adhesions localized under the cell body. Interestingly, ZO-1 silencing, while increasing Rac activation and the development of multiple protrusions containing focal complexes, significantly impairs the persistence, i.e., the straightness, of the migratory path of NSCLC cells. In migrating NCI-H460 cells, the PKCε-driven phosphorylation of ZO-1 on Serε68 allows its interaction with a noncanonical PSD-95-Dlg-ZO-1 (PDZ) motif in the ε5 integrin cytoplasmic tail and localization at the lamella (Fig. 1). In addition, in situ proximity ligation revealed the presence of a ZO-1-α5β1 complex in histological samples of NSCLC patients with metastatic disease.
αvβ6 Integrin Controls TGFβ Activity

αvβ6 integrin, which is synthesized by epithelial cells mainly during development, in the adult organism is re-expressed together with its ligand FN during wound healing and inflammation. In addition, Kaplan-Meyer survival analysis indicates that the neo-synthesis of αvβ6 integrin in carcinoma cells is also a negative prognostic factor for the survival of NSCLC patients. Since this integrin is an efficient FN receptor, it is likely that expression of αvβ6, similarly to that of α5β1, endows lung tumor cells with an enhanced ability to adhere, migrate, and invade the FN-rich matrix that surrounds NSCLCs. However, an additional mechanism by which αvβ6 integrin can promote lung carcinoma progression and invasion is represented by its ability to activate the release of the ECM associated transforming growth factor β (TGFβ) in its bioactive form (Fig. 3).

TGFβ is synthesized as a large disulphide-linked homodimeric precursor that is then cleaved in the endoplasmic reticulum by furin proteases, giving rise to a small C-terminal dimer (bioactive TGFβ) and a large N-terminal latency associated peptide (LAP; Fig. 3). Bioactive TGFβ non-covalently associates with the LAP giving rise to the so called small latent complex (SLC). The latter is then covalently linked to the latent TGFβ-binding protein...
Furthermore, myofibroblast-generated biomechanical forces have been recently shown to cause the translocation of existing vascular loops into contracting tissues, a phenomenon very similar to the vessel co-option strategy adopted by cancers for being vascularized.

The Integrin-Linked Kinase Signaling in Lung Cancer

Integrin-linked kinase (ILK) is a multifunctional protein, which participates in integrin biochemical signaling by acting both as an adaptor and a serine-threonine kinase enzyme. ILK consists of an N-terminal domain containing four ankyrin repeats, a central phosphatidylinositol 3 phosphate (PIP3) binding pleckstrin homology (PH) domain and a C-terminal kinase domain that interacts directly with several β subunit of integrins and the focal adhesion proteins paxillin and parvins. Once freed from the tumor ECM, bioactive TGFβ can diffuse and foster carcinoma progression by binding to surface receptors of either tumor cells themselves or host stroma fibroblasts. Indeed, on the one hand, by promoting epithelial-mesenchymal transition (EMT), TGFβ can favor the invasive behavior of carcinoma cells. On the other hand, the αβ6-mediated released of TGFβ can drive the differentiation of peri-tumoral stromal fibroblasts into α-smooth muscle actin (αSMA)-containing myofibroblasts, aka carcinoma associated fibroblasts (Fig. 3). In turn, peri-tumoral myofibroblasts secrete chemokines, such as SDF-1, or growth factors, such as VEGF, that can stimulate tumor growth and angiogenesis (Fig. 3). Furthermore, de novo expression of αSMA significantly enhances myofibroblast contractility and ECM stiffness. In cancer cells, increased matrix rigidity can trigger the integrin-mediated activation of both Erk mitogenic signaling and Rho-mediated contractility. The latter, by further augmenting the tissue stiffness, can give rise to a mechanical positive feed-back loop that contributes to malignant progression.

Inhibition of GSK-3β by ILK causes instead the accumulation of latent TGFβ-1, -3 or -4 to form the large latent complex (LLC). Once secreted, LTBP allows the binding of LLC first to FN fibrils and then to microfibril scaffolds formed by the assembly of fibrillins on the FN network. The interaction of αβ6 integrin with the microfibril-bound RGD motif of LAP allows the application of the cytoskeleton contractile force of lung epithelial cells to the LLC, likely causing its conformational modification, and the ensuing release of the sequestered TGFβ (Fig. 3).

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of β-catenin and the consequent activation of the T cell factor (TCF)/lymphoid enhancer factor (LEF) transcription factors, which by stimulating the expression of cyclin D1 support cell cycle progression and proliferation. GSK-3β inhibition results in the upregulation of NFκB-dependent of the transcriptional repressor Snail36 that suppresses E-cadherin expression and promotes EMT.37

Two independent histopathological studies demonstrated that a strong cytoplasmic staining of ILK is a poor prognostic factor in NSCLC,66,67 and increased phosphorylation in Ser 473 of the ILK effector Akt is an additional independent predictor of unfavorable prognosis as well.68 While the molecular mechanism responsible for ILK overexpression in several NSCLC is still undefined, it is conceivable that the activation of the integrin-ILK-Akt signaling pathway provides a significant advantage for NSCLC cell proliferation, survival, and invasion. Hence, the inhibition of ILK signaling could represent a new avenue to feed in NSCLC treatment. Up to now four generations of small molecule inhibitors of ILK have been developed and one of them, KP-392, was tested alone or in combination with cisplatin in a pre-clinical model of NSCLC.48 KP-392 was as effective as cisplatin in enhancing survival and the combination of the two drugs was significantly more effective than the single agents alone. Moreover, the combination KP-392/cisplatin inhibited NSCLC metastatization to kidney, bone and contralateral lung.68

The high mortality rate of NSCLC demands a likewise effective search for molecular mechanisms and new pharmacological targets to begin to alleviate the particular aggressiveness of this cancer histotype. The signaling pathways by which integrins and their ligands control the adhesion, migration, proliferation and survival of lung cancer cells might represent new therapeutic opportunities to develop drugs that might be successfully combined with chemotherapy and/or radiotherapy.

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