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Full Length Article

Integrin-Linked Kinase, Snail and Multidrug Resistance Protein 1: Three concordant players in the progression of non-small cell lung cancer

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Abstract *Background:* Integrin Linked Kinase (ILK), Snail and Multidrug Resistance Protein 1 (MRP1) have been implicated in several cancers; however, their roles in non-small cell lung cancer (NSCLC) remain to be elucidated.
Aim: Investigation of their expression in NSCLC tissue. Relationships among these proteins and their association with clinicopathological parameters were studied.
Materials and methods: ILK, Snail and MRP1 expression were immunohistochemically assessed in 97 tumor tissues. Furthermore, western blot analysis for ILK, Snail and MRP1 in 6 cases of NSCLC was also performed.
Results: ILK overexpression, positive Snail and MRP1 expression were found in 46.4%, 36.1% and 49.5% of tumors respectively. ILK expression was significantly correlated with tumor grade ($p = 0.013$), lymph node (LN) metastases ($p = 0.001$) and stage ($p = 0.001$). Positive Snail and MRP1 expression were significantly associated with LN metastasis ($p = 0.004$ and 0.022, respectively) and advanced stage disease ($p = 0.018$ and 0.024, respectively). MRP1 expression was significantly higher among adenocarcinoma cases compared to other types ($p = 0.001$). ILK over-expression was significantly associated with up-regulation of Snail and MRP1 ($p < 0.001$ both). Significant association was also, found between Snail and MRP1 expression ($p = 0.005$). Moreover, the co-expression of two markers or more was significantly associated with less differentiation ($p = 0.011$), advanced tumor status ($p = 0.030$), LN metastasis ($p < 0.001$) and advanced stage ($p < 0.001$) disease. Western blot analysis validated immunohistochemical findings.

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Conclusion: ILK may have an important role in the progression of NSCLC, possibly through up-regulation of Snail and MRP1. ILK, Snail and MRP1 are important molecular markers for predicting carcinogenesis and progression of NSCLC.

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Introduction

Lung cancer, particularly non-small cell lung cancer (NSCLC), is one of the most common malignancies and the leading causes of cancer-related mortality worldwide [1].

The prognosis of NSCLC patients is generally poor especially in advanced stage disease, where less than 10% of patients survive beyond 5 years [2]. Tumor metastasis and therapeutic resistance are the major causes of the disease recurrence and treatment failure [3]. Acquisition of invasive and migratory abilities and the development of drug resistance in cancer cells result primarily from adopting an epithelial-mesenchymal transition (EMT) phenotype [4–6].

EMT is a complex molecular and cellular process of phenotypic switch of polarized epithelial cells into motile mesenchymal cells. Alterations in cellular adhesion, morphology, architecture and migration potential are the major events characterizing this process [6]. EMT was initially described during embryonic development and tissue repair and more recently in cancer progression, where it induces an invasion–metastasis cascade and confers multidrug resistance (MDR) phenotype on cancer cells [4–7]. MDR is a major obstacle on effective treatment of cancer. It participates in cancer metastasis and recurrence, resulting in a more aggressive tumor than that seen at the start of treatment [5]. Therefore, understanding of the molecular basis of these processes for identification of potential cancer-targeted therapeutic strategies is fundamental.

As a novel EMT regulator, ILK has attracted widespread attention. Its role in governing the metastatic ability in various cancers, predominantly by acquiring the mesenchymal phenotype has been documented [8–10].

ILK, an intracellular serine/threonine kinase protein, is a downstream substrate of the phosphoinositide 3-kinase (PI-3K) pathway. It interacts with cytoplasmic domains of β-integrin subunits and regulates integrin dependent functions. ILK plays an important role in transducing many of the signals that are initiated by cell–matrix interactions and that regulate many biological processes [11].

ILK overexpression was reported in many types of human cancers including NCSLC [8,9,12]. Its overexpression promotes oncogenic transformation of cancer cells via regulation of several downstream targets that promote cancer cell proliferation, survival, metastasis and angiogenesis. Recently, the development of ILK inhibitors has provided novel mechanisms for blocking ILK signaling aiming at controlling tumor metastasis and therapy resistance [8,11].

Snail (SNAI1) transcription factor which belongs to the Snail superfamily of zinc finger proteins has a central role in inducing the EMT process in physiologic and pathologic situations and triggering invasive activities of cancer cells [6]. This is partly mediated by controlling genes that regulate tight junction stability, epithelial cell polarity and morphology. It interacts with Smad3 and Smad4 to form a transcriptional repressor complex which targets the gene promoters of CAR (a tight-junction protein), occludin, claudin-3 as well as E-cadherin during EMT in cancer cells [13]. Snail has also been found to upregulate the expression of matrix metalloproteases (MMPs) such as MMP9 [14].

Development of MDR is a major deterrent in the effective treatment of cancers by chemotherapy. Multidrug resistance protein 1 (MRP1/ABCC1) is a key member of the ATP-binding cassette (ABC) transporter superfamily proteins. These proteins are involved in the trans-membrane efflux of a wide spectrum of anticancer drugs from the intracellular compartment to the extracellular one, thus decreasing their intracellular concentration thereby leading to MDR. Overexpression of MRP1 has been detected in a variety of tumors (15–17) and is associated with poor patient outcome in NSCLC (15, 17).

A growing body of evidence has demonstrated a close relationship connecting EMT, increased invasive and metastatic abilities as well as drug resistance in several cancers including NSCLC [4,5,9,18–20]. However, a comprehensive study of the molecular elements underlying EMT and their association with NSCLC progression and drug resistance has not been conducted, yet. The present study hypothesized that the expression of ILK, Snail and MRP1 might play an important role in NSCLC progression and assumed that ILK may be involved in acquiring the EMT and MDR phenotypes in NSCLC. In this series of NSCLC, the expression of ILK, Snail and MRP1 and their association with clinicopathological data were estimated using immunohistochemistry. The presence of possible associations among these proteins and the effect of their combined expression on NSCLC progression were also evaluated. In addition, western blot analysis for ILK, Snail and MRP1 in 6 cases of NSCLC was performed.

Materials and methods

Tissue specimens

The current work comprised 97 specimens of NSCLC. Cases were diagnosed between 2007 and 2014 in the Departments of Pathology, Minia University Hospital and Minia Oncology Centre, Egypt. The corresponding clinicopathological information was obtained from patients' medical records. Tumor histotype and tumor grade of differentiation were revised according to World Health Organization (WHO) criteria, 2004. Tumor staging was done according to Tumor, Node and Metastasis Classification System, AJCC Cancer Staging Manual, sixth edition [21].

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