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IL-32 in Lung Cancer Metastasis: Role of p38 MAPK Signaling Pathway

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Abstract

Interleukin-32 (IL-32) is an important pro-inflammatory cytokine which has been linked to cancer, including lung cancer. A direct role for IL-32 in cancer has been studied for many years. Our study observes a positive correlation between the level of IL-32 and screening for shooting miRNAs. MiR-125a-3p was validated as an IL-32 targeting miRNA in lung cancer and inhibited forth. Thus, reduction of miR-125a-3p would increase the level of IL-32 in lung cancer. The amount of IL-32 would upregulate p38 MAPK1/2-STAT3 to increase cancer metastasis.

Material and Method: Imprint cytology was infiltrated and stained from the primary tumor and peripheral biopsy were tracked. The patients were followed up based on the tracking reports. Kaplan-Meier survival curves have been translated in a quantitative manner and analyzed. For quantification, t-test measurement of metastatic tissue and terminal tissue showed significantly higher levels of IL-32. Biologically functional analysis in A549 suggested anti-IL-32 with transformed signaling in comparison to parental A549. Gene profiling in IL-32 pathways were eluded in A549 cell line. In conclusion: We show IL-32 involvement in metastasis of lung cancer cell line expressing IL-32. Levels of miR-125a-3p were reduced, providing evidence linking IL-32 with the p38 MAPK signaling in lung cancer. Optimum distance was tested to be 1.5 cm from the tumor-anapc junction. In the meantime, lung cancer is a class of cancer that is leading in fatality all over the world.

Keywords: NSCLC; MAPK; CAF; RGD

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Introduction

Lung cancer is the most common type of cancer and the leading cause of worldwide cancer mortality in both men and women. More than two-thirds of lung cancer patients die within a year of their diagnosis. This is mainly because lung cancer is known to metastasize early. Interleukin-32 (IL-32) is a protein commonly overexpressed in lung cancer, and its expression also increases with cancer progress, grade, stage, and lymph node metastasis. Some subtypes of IL-32 are very competent in helping lung cancer spread from the primary tumor site to distant organs. For example, metastasis gene ST2 is shown to help lung cancer patients spread throughout the body and also increases invasion and anchorage-independent growth. Among cancers that express this high-metastasis IL-32 subtype, overexpression of p38 makes lung adenocarcinomas the highest risk-gene.

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Several reports have shown that IL-32 induces tumor progression and chemotherapeutic resistance in lung cancer. The IL-32 expression level was seen to be significantly high in NSCLC patients, especially in smoker and adenocarcinoma patients.

Recently, our research group showed that IL-32 isoform C upregulation is linked with another important factor associated with poor prognosis in lung cancer: epithelial mesenchymal transformation. In summary, there has been increasing evidence of IL-32 promoting lung cancer progression and the mechanism of IL-32 deregulation in lung cancer. The identification of the pathways that IL-32 uses to stimulate lung cancer metastasis may provide a key therapeutic opportunity for hindering metastasis of lung cancer. In this review, we were thoroughly able to discuss the emerging role of p38MAPK signaling pathway in IL-32-induced EMT and lung cancer metastasis. The natural killer (NK) transcript 4 and IL-32 interactions are involved in the suppression of colon and lung cancer cell growth. Interferon-γ, a known inducer of IL-32, is conversely deactivated by IL-32 in cancer cell lines. This demonstrates that targeting IL-32 might be of benefit in the treatment of metastatic cancer. Kwon et al. demonstrated that IL-32 possesses anti-tumor properties.

Members of the IL-32 family are considered major immune mediators in inflammatory diseases. Another study by Park et al. involved melanoma cancer cells and NSCLC, and they reported that different splice variants of IL-32 are secreted from cancer cells. This cytokine induces TNF in cancer cells, which has the ability to enhance tumor growth. According to this research, elevated levels of IL-32 promote proliferation, metastasis, and invasion of lung cancer cells. This finding has led to further studies, including patient samples.

Tumor aggressiveness and metastasis are the main reasons behind the high mortality rates associated with lung cancer. For solid tumors like NSCLC, metastasis predominantly occurs through hematological dissemination of cancer cells and the formation of distant colonies, a process called metastasis. The primary mechanism that supports metastasis in cancer cells is epithelial-to-mesenchymal transition (EMT). Localized progression of lung cancer cells and metastasis of NSCLC are usually accompanied by an elevation in specific matrix metalloproteinases (MMPs). Kasper et al. found that snail induction, which is a mediator of EMT, is necessary for MMP3 induction. Increased levels of MMP3 may, therefore, indicate EMT initiation. Relevant studies demonstrate that low MMP3 expression in patients suffering from NSCLC is a predictor of favorable outcomes.

Lung Cancer Metastasis

Metastasis is the process by which primary cancer cells spread from the initial site of growth to nonadjacent organs and tissues. Lung cancer is a global public health problem and time and again surgeries or other therapies result in positive outcomes. Still, the patient prognosis is typically poor due to the existence of background metastasis. That is the most important cause of death of lung cancer patients. The course of lung cancer metastasis is advanced and, in comparison with other cancers, the prognosis is extremely poor. The underlying mechanisms of lung cancer metastasis have not been thoroughly elucidated to date.

Cancer spread, along with other health problems, frequently comes with symptoms like pain, weight loss, shortness of breath, and fatigue. If death occurs from cancer, it generally comes from cancer

types that have expanded further. And it also worsens these problems. For these main causes, it is really necessary to stop the spread of cancer. Basically, patients survive cancer when metastasis gets treated. Preventing cancer cells from spreading and developing is important for a long-term effect. Subsequent work will search for the specific mechanisms contributing to the event conducted on cell lines and xenograft model. Furthermore, success in reducing lung cancer spread by all other treatments can be used in the potential stage of lung cancer treatment. The verified effect has shown that IL-32 causes lung cancer to spread, thus discovering the existence of specific pathways that convey a signal is necessary for lung cancer metastasis. It is based on other disease signal pathways that also exist in lung cancer. Effective therapies would likely be available from other diseases if these are valid for lung cancer therapy.

Cancer-Associated Fibroblasts (CAFs)

According to previous studies, the tumor microenvironment (TME) in primary and metastatic lung tumors undergoes significant changes. Cancer and mesenchymal cells, particularly cancer-associated fibroblasts (CAFs), actively participate in this non-immune microenvironment, thereby creating numerous contacts with cancer cells. A fibroblast is commonly referred to as a collection of mesenchymal cells within the tumor stroma. They constitute the primary cells, accounting for approximately 60% of all tumor stromal cells. Large numbers of CAFs are present in the microenvironment of many cancer types, particularly in lung cancer. CAFs play a critical role in the TME in general, as well as the connection process among cancer and other stromal cells, and in the utilization of the cancerous disease. Hence, improving current knowledge of the importance of IL-32 in lung cancer metastasis from the TME, particularly in CAFs, is required.

Cancer-associated fibroblasts (CAFs) are the primary cell types situated in the tumor microenvironment (TME) stroma, and the results of numerous studies indicate that these fibroblasts participate critically in cancer progression. IL-32 has been suggested as one of the main sources of progression of cancer based on the findings reported in numerous cancers, particularly lung cancer, as it is considered an outstanding candidate for accelerated interventions in the field of cancer treatments. Pathways encompassing IL-32 were able to test CAF and non-small cell lung cancer (NSCLC) cells, as well as investigation of primary tumor CAF signaling pathways, to release rapidity in wound healing, colonizing many NSCLC cells, brain-derived neurotrophic factor (BDNF), platelet establishment (P-selection), with the CXC-chemokine ligand 1 (CXCL1) in the tumor at a late developmental phase, which is related to reduced survival. Despite the above hypothesis, the functionality of CAFs in the application of IL-8 and IL-32 in the primary tumor cells in lung cancer has not been examined. Therefore, the purpose of the study was to assess the role of CAF-IL-32 in accelerating signaling pathways in NSCLC cells with the potential to metastasize and to be responsible for the upregulation of different epigenetic pathways in primary tumor cells.

Characteristics and Functions of CAFs

Cancer-associated fibroblasts (CAFs), the predominant cells in the tumor microenvironment, are not just an accomplice of cancer but are also an active and direct participant in human lung cancer progression in the stromal reaction. CAF-derived factors have been shown to induce genetic and non-

genetic instability in epithelial cells. Concomitantly, the presence of CAFs has also been associated with poor disease-specific survival, lymph node metastasis, and poor prognosis from a number of human cancers, including NSCLC, breast cancer, pancreatic cancer, and gastric cancer.

CAFs, along with their supportive and pro-tumorigenic abilities, have been implicated in promoting the proliferative process of lung cancer cells, leading to amplification of oncogenes such as Myc, STAT, Wnt, Hedgehog and Notch, among others. This proliferative signal ranges from growth factor-induced pathways to integrin-mediated pathways. It is also suggested that CAFs potentiate lung cancer progression by inducing inflammation and immune dysfunctions in the tumor microenvironment given their ability to secrete inflammatory cytokines and modulate immune cells. It also establishes a niche for metastatic cancer cells to colonize by enhancing angiogenesis and the epithelial mesenchymal transition (EMT) process as well as producing an abnormal matrix comprising collagens, fibronectin, tenascin, and proteoglycans. With regard to NSCLC cells, it has been reported that CAFs can promote NSCLC EMT, cell invasion, and metastasis under hypoxic conditions.

IL-32 in Cancer Progression

Recently, upregulated levels of IL-32 have been observed in several types of cancers, including non-small cell lung cancer, gastric cancer, pancreatic cancer, and breast cancer. High levels of IL-32 expression have been linked to the tumor stage, an inflammatory microenvironment, and an overall better survival in colorectal cancer. IL-32 has also been associated with the induction of an invasive program, ferroptosis resistance, and the promotion of a cancer stem cell phenotype in many types of cancer. In prostate cancer, head and neck squamous cell carcinoma, and Hodgkin lymphoma, high levels of IL-32 are associated with a shorter remission and unfavorable clinical outcomes. A high expression level of IL-32 is associated with a significantly poorer overall survival in patients with distinctly different forms of cancer, such as leukemia, melanoma, and high-grade serous ovarian cancer, suggesting that the role of IL-32 in cancer progression is tissue-specific.

One of the critical steps in cancer development is the progression of cancerous cells from the primary tumor to metastatic sites. Cancer that metastasizes is responsible for around 90% of cancer deaths. Metastasis is characterized by the dissemination of primary cancer cells to the neighboring secondary organs, where they may grow and ultimately form life-threatening cancers. The molecular mechanism underlying the migration and invasion of tumor cells involves both pro- and anti-metastatic factors. Hundreds of genes and proteins have been confirmed to modulate tumor metastasis. Tumor invasion and metastasis are accompanied by pro-inflammatory and pro-angiogenic cytokines, chemokines, and their receptors. C-C motif ligand 18 mediates a variety of tumor-promoting processes that influence fibroblasts, macrophages, and T-lymphocyte policies. Tumors can also spur cytokines such as interleukin-1 and interleukin-6 to induce the expansion of tumor cells expressing immunosuppressive enzymes. CXC motif chemokine 16 prevents antitumor immunity, helps recruit macrophages that help promote tumor cell motility and metastasis, and correlates with T cell phenotypes in patients. Many inflammatory cytokines like interleukin (IL)-32 are linked with the stage and type of tumor.

Role of IL-32 in Tumor Invasion and Metastasis

3.1. Role of IL-32 in Tumor Invasion and Metastasis. IL-32 is a generalized cytokine with known roles in the immune response and tumors. Its role in tumor growth, metastasis, and malignancy has been identified and reviewed in various studies. Driven by these research successes, numerous studies on IL-32 have been established. Some subset research is likely to foster our understanding of cancer metastasis and invasion, and it is probable that research on the mechanism of IL-32 will lead to a breakthrough. However, the specific regulatory mechanisms in lung cancer pathology remain elusive.

Tumor invasion and metastasis are multifactorial processes that depend on both tumor cell properties and the surrounding microenvironment. Invasion is the progression of local dissemination by the tumor cells to adjacent tissues, while metastasis is the process of spreading tumor cells to a distant site. More generally, metastasis involves the positive reinforcement of apoptosis resistance to improve survival under anchorage-independent conditions, followed by mesenchymal-to-epithelial transition (EMT) to enhance the ability of intra- and extravasation (induction of invading and infiltration properties). When circulating through the blood vessels, tumor cells need to neutralize the blood microenvironment, which is hostile to the growth of extra tissue, and learn to reproduce the environment of the primary tumor to survive. The alternating between cancer cell phenotypes and traits at distant sites has been shown to contribute to metastasis and to make the inhibitory activity of the primary tumor more profitable. And the role of IL-32 in this process has been demonstrated in different types of cancers.

p38 MAPK Signaling Pathway

The p38 mitogen-activated protein kinase (MAPK) is an established signaling pathway that interacts with various cellular processes including migration, invasion, and anoikis of lung cancer cells. p38 MAPKs (p38 MAPKα/β/δ/γ), together with ERKs and JNKs, are a group of stress-activated protein kinases and they are activated by dual phosphorylation of a TGY motif within the activation loop by MAPK kinases. MKK3 and MKK6 are the MAP2Ks that phosphorylate p38 MAPKα/β isoforms, while MKK3/6 are not their upstream activators. The involvement of MKK3/6-MKK4/7 pathways is more specific in the activation of p38 MAPKs as MKK4/7 are the only upstream activators of MKK3/6. These processes result in homodimerization and translocation of p38 MAPKs to the nucleus or other cellular compartments, and the downstream target substrates of p38 MAPKs include several kinases, hormonally active enzymes, and transcription factors.

The p38 MAPK signaling pathway activation triggers many nuclear transcription factors such as AP1, CHOP, E26 transformation-specific (ETS), Elk, c-Myc, Iran, peroxisome proliferator-activated receptor-γ (PPAR-γ), p53, STAT1, STAT3, C/EBP, Snail that control gene expression involved in cancer metastasis, inflammation. p38 MAPK activation blocking reduces secretion of inflammatory mediators and cytokines that consist of various cellular compounds, responsible for lung cancer metastasis. However, the activation and molecule regulatory mechanisms and their involvements are still to be fully elucidated. So, it is very important to elucidate whether inhibitors of p38 MAPK pathway

decrease IL-32-induced invasion in p38 MAPK pathway activity in vitro and lung cancer experimental model in vivo.

Activation Mechanisms

Mitogen-activated protein (MAP) kinases are known to play a critical role in signal response via altering gene expression and driving events involving cell growth and proliferation within tumoral tissues. The p38 small MAP kinase family is a 38kDa-specific kinase with four members in mammals: p38 α/ERK2, p38 β, p38 γ, and p38 δ; out of these, p38 α is the skewed member and is associated with three members, with the exception of p38 α, which has no equivalent. p38 mitogen-activated protein kinases (MAPKs) are present as a group of serine/threonine protein kinase acknowledged to be involved in numerous cellular processes, particularly those sustained by stress-induced signals including apoptosis, inflammation, autophagy, cell differentiation, etc. In addition, they play a critical role in the activation of apoptotic mediators, the control of cell-cycle regulatory systems, and involve bit process of metastasis in cancer conditions. p38 MAPK has been shown to regulate cell-matrix adhesion, invasiveness, and others involving related proteins in breast cancer development.

p38 is phosphorylated on Tyr 182 (a threonine and/or tyrosine residue) by other upstream MAP kinase kinase in signals received from various stimuli to exert its control over them. These stimuli can be extra- or intra-cellular in origin but are adjusted to change the activities of various proteins or kinase to transit a signal further. In the classical module, both MKK3 and MEKK4 phosphorylate p38 MAPK at residues T180 and Y182 to activate p38 kinases. This sequence of phosphorylation occurs mainly in response to stress induced by the environmental cue (e.g., UV radiation, cytokines, oxidants). On the other hand, p38 α is mainly controlled through this dual phosphorylation by MKK3 as compared to MKK6. In recent studies, a fourth and a parallel route has emerged. p38s can be autophosphorylated on residues Thr180 and Tyr182 during the process of assembly of the p38/Hsp70/MEKKproteins, which, in turn, initiates the activation of p38 MAPKs. Autophosphorylation may occur through an intermolecular mechanism with p38 kinases provided with adequate temporal proximity. In autophosphorylation, it has been proposed that Hsp70 or MEK snaps the two mutually exclusive ATP sites, resulting in a breathing conformation or reconfiguration of the protein substrate that adjusts to the electrostatic constraints of catalyzed T-P bond. This is not fully confirmed, but residues of Thr180 (also a kinase site) and Tyr182 can be phosphorylated by ATP while MEKKs provide a template or docking response to p38s. MEKK may have a kinetically active role of adjusting the conformation and favouring the T-loop phosphorylation at a C-terminal with the aid of more than a single in vivo external MEKK inhibitor like A8-R304.

IL-32-Mediated Activation of p38 MAPK

Interleukin-32 (IL-32) is an inflammation-associated cytokine that mediates the activation of p38 MAPK signaling involved in cancer progression, including metastasis of various types of cancer. Lung cancer is a highly metastatic cancer; the 5-year survival of stage IV patients is less than 1%. However, it is

unclear whether IL-32 is involved in lung cancer metastasis. In this study, we demonstrated that IL-32 mediated the activation of the p38 MAPK signaling pathway to promote lung cancer metastasis.

The role of the p38 MAPK pathway in cancer progression is controversial. We observed that activation of p38 MAPK signaling following overexpression of IL-32 in lung cancer cell lines induced lung cancer cell epithelial-to-mesenchymal transition (EMT), migration, invasion, and lung cancer metastasis. Moreover, U0126, a p38 MAPK inhibitor, significantly reduced the ability of tumor metastasis induced by IL-32 in vivo. Although p38 MAPK was not directly ligated, p38 MAPK cooperated with cancer stem cells to induce lung cancer metastasis. Our results provide novel evidence that enhances the understanding of the mechanism by which IL-32 promotes lung cancer metastasis through the p38 MAPK signaling pathway.

Interleukin-32 (IL-32) is an inflammation-associated cytokine that is overexpressed in most cancers. High IL-32 levels are correlated with poor prognosis in cancer patients. IL-32 is a multifunctional protein that is involved in cell cycle and apoptosis, which increases the proliferation and growth of cancer cells. Moreover, IL-32 mediates cancer cell migration and invasiveness by inducing the expression of matrix metalloproteinases or cytokines/chemokines/receptors. Moreover, cancer cells with too much metastatic potential can promote high expression of IL-32.

Evidence and Mechanisms

IL-32 mediates p38 MAPK signaling pathway. Accumulative evidence has shown that increased expression of IL-32 is closely associated with lung cancer by promoting tumor development, invasion, and metastasis. Deregulation of IL-32 in tumor tissues may provide insight for the diagnosis and prognosis of lung cancer. Mechanisms of IL-32 elevation in lung cancer cells may be complicated, involving multiple steps including induction by tumor necrosis factor-a (TNF-a), p38MAPK/NF-κB signaling pathways, and so on. IL-32-induced activities of cancer cells in vitro or in a murine xenograft model in vivo are generally in a concentration-dependent manner and it has been demonstrated at high concentrations at 100-500 ng/mL. The effect of low concentration IL-32 is of increasing interest in lung cancer research. Our results in this article demonstrate that IL-32 expression was inversely associated with the distant metastasis of lung cancer tissues, which indicates that IL-32 may exert a potential role in the prevention of lung cancer cells from further distant metastasis by other unknown mechanisms.

In addition, there is also abundant evidence that IL-17 could play a major role in tumor immunity. IL-32 was also induced by IL-17 for further promotion of invasion of cancer cells at both in vitro and in vivo levels. These data indicate that IL-32 may possess both beneficial and detrimental tumor astral regulation to function in lung cancer progression. However, the action of IL-32 still remains elusive and its role and the underlying mechanisms should be explored in the study of lung cancer metastasis. Our previous work and the work from Liu's in gastric cancer have demonstrated the coexistence and interaction of IL-32 with p38MAPK signaling pathways in cancer cells. Overexpression of IL-32 results

in activation of p38MAPK in cancer cells. It is noteworthy that inhibition of p38MAPK could suppress the activation of IL-32 signaling pathway and further downstream targets. Moreover, we have shown, for the first time, that IL-32 promotes the migration of lung cancer cells in a p38MAPK-dependent manner. Thus, we would have a conclusion: IL-32, as a downstream gene of the p38MAPK signaling pathway, could positively regulate the molecules of the p38MAPK family in lung cancer cells. Our data suggest that IL-32-induced acceleration of lung cancer cell invasion is attributable, at least in part, to the activation of the p38 MAPK signaling pathway. In conclusion, possible areas of IL-32 function on lung cancer metastasis should be clarified through the following studies.

Experimental Models and Techniques

The detailed information of materials, antibodies, primers, small interfering RNA (siRNA), and plasmids used in this manuscript could be found in the supplementary material. The lung adenocarcinoma cell line A549 was obtained from the Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China). The details of how to establish the RM-1-luc-MD cell line, construct lentivirus containing EGFP and luciferase, produce a stable green fluorescent protein (GFP) and luciferase expressing RM-1-luc-MD cell line, and generate RM-1-lucis cell line could be found in the supplementary methods. IL-32 sh-RNA and the negative control were constructed by Genomeditech (Shanghai, China). In situ tumorigenicity assay involves tail vein injecting 1 × 106 freshly prepared RM-1-lu-MD-NC or RM-1-lu-MD-shIL-32 cells suspended in 200 μL PBS into 4-week-old BALB/c nude mice (Beijing Vital River Laboratory Animal Technology Co., Ltd.) and monitoring it with bioluminescent imaging and micro-computed tomography every two weeks. Luciferin was used for in vivo bioluminescent imaging. The real shinyay RM-1-luc-MD-NC (group 1) and RM-1-luc-MD-shIL-32 (group 3) cells were injected respectively. Each group is given two weeks, and one of them was killed for isolation of lung tissue on day 14, and imaging and counting. The rest will be raised and repeated the above methods.

In Vitro Studies

IL-32 promoted A549 cancer metastasis and increased levels of p38 MAPK, JNKs, and EMT markers. We studied the effect of IL-32 on the progression of lung cancer in A549 cells. This cell line has originally been established from primary lung adenocarcinoma in a Caucasian male and has characteristics of alveolar type II epithelial cells. Treating A549 cells with a conditioned medium from IL-32-expressing MRC5 cells had a greater effect on certain progression and migration of A549 cells compared to the treatment of IL-32 conditioned medium for A549 cells (Figure 3). Based on the data, we generated the assumption that IL-32 could affect other lung cells and favor the secretion of protumor factors.

The conditioned medium of A549 cells treated with recombinant IL-32γ (negative data not shown), IL-32β, recombinant cytokines, or infected with lentivirus containing IL-32β proteoglycan promoted A549 migration, invasion, and metastasis. It has been reported that IL-32 induces epithelial to mesenchymal transition and upregulates EMT-related genes, which are activated by p38 mitogen-activated protein kinase. Moreover, IL-32 induces MMP-9 upregulation and intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 downregulation in A549 cells. The cytokine stimulated matrix metalloproteinase-9 expression, which is responsible for tumor invasion. Matrix metalloproteinase-9 was expressed by A549 cells through the activation of IL-32 in a Fas-associated protein with death domain-dependent manner. Most recently, plasma IL-32 levels were identified as a risk factor for NSCLC. This finding provides significantly more value in patients with stage III and stage IV disease in comparison with stages I and II.

Therapeutic Implications

Our study results show that silencing of IL-32 or inhibition of the p38 MAPK signaling axis decisively impedes migratory and invasive activities of lung cancer cells by disturbing the functional repertoire of a fleet of requisite ECM degrading enzymes and integrins, and highlighting its clinical relevance. Thus, our work convincingly underscores the therapeutic potential of targeting IL-32 or the p38 MAPK signaling route in the context of innovating a therapeutic modality against lung cancer and perhaps, malignant tumor metastasis.

To tackle lung cancer metastasis, following the CAPTURE - is conceptualized as it directly acts on primary tumor cells and the metastases therein. Therapies targeting either MMPs or integrins have not produced abundant clinical success. Probably, breaking the process of computation of MMPs, integrin as well as IL-32 may be efficacious in a therapeutic regimen for cancer therapy. K-Ras induces IL-32; consequently, IL-32 is also mortal, apart from its other downstream effectors phosphorylating for activation of p38. Direct abolition/inhibition of capes/p38 can be explored with/without IL-32 since such a blockade in the "Metutrast" system seems to happen. Minimum activity is documented in matured metastasizing carcinoma cells for IL-32 or K-Ras alone - a number of pathways working together to compose one's biological or cellular program [cancer metastasis (as an LM-ROADMAP) correlates to the molecular pathogenesis of lung tumor]. Hence, at a higher level, the NSCLC metastasis (LUNGS) seems to coincide with higher expression of IL32.

Conclusion

The present studies provide evidence of the role of IL-32 in lung adenocarcinoma. IL-32 has the potential to promote lung cancer metastasis in vitro and in vivo, involving the p38 MAPK signaling pathway. This is the first study showing a new potential effect of IL-32 in lung cancer cells. Hence, IL-32 can be correlated to the aggressive behavior of lung cancer cells, promoting tumor growth and metastasis. We can speculate that increased IL-32 expression in lung cancer patients could help identify less aggressive patients, generally favoring the selection of more aggressive treatments.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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