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Research Progress of Transcription Factor KLF4 in Lung Cancer

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Abstract

Lung cancer is the leading cause of cancer mortality worldwide. While our understanding of the molecular events in the lung cancers are poor. In this report, we reviewed the current studies on a transcription factor named Krüppel-like Factor 4(KLF4) in lung cancer. Tissue studies showed that KLF4 expression was significantly decreased in non-small-cell lung cancer (NSCLC), while significant over expression in small-cell lung cancer (SCLC). On the cellular level of lung cancer, KLF4 regulate p21, SPARC, vimentin, b-catenin, VEGF-A, and cyclin D1, and it may enhance the lung tumor formation combined with K-ras mutation. Moreover, Numbl, NLK, Interleukin-27, miR-7, miR-10b, and miR-29, HOTAIR and HIF were able to regulate the KLF4 expression. We suggest that more understanding of the mode of KLF4 actions and its functional networks may lead to the development of novel therapeutics to improve current prospects for lung cancer prevention and cure.

Keywords: KLF4; Lung cancer; Embryonic Stem Cells; Malignancy

Abbreviations: NSCLC: Non Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; KLF4: KRÜPPEL Like Factor 4; SPARC: The Secreted Protein Acidic and Rich in Cysteine; HIF: Hypoxia Inducible Factor; HESC: Human Embryonic Stem Cells

Introduction

Lung cancer is the most common malignancy involving both genders and remains the main cause of cancer-related mortality worldwide. The two main histological groups are non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). Approximately 85% of lung cancers are NSCLCs, which includes three major histological subtypes: Adenocarcinoma, squamous cell carcinoma and large-cell carcinoma. Despite the improving therapeutic approaches, the overall survival of lung cancer patients remains low. The 5-year survival for SCLC is lower compared with that of NSCLC (about 6% vs. 18%, respectively). Therefore, a better understanding of biomarkers associated with lung cancer may have clinical value in improving treatment selection and prediction, and may even set the base for the development of future novel targeted therapies.

Krüppel-like Factor 4 (KLF4) was initially identified as a zinc-finger transcription factor enriched in the epithelium of intestine and skin [1,2] Later, it was detected in a variety of other tissues, such as thymus, cardiac myocytes and lymphocytes [3-5] KLF4 plays an important role in the development and cell differentiation [6-8] In normal lung tissues, KLF4 is expressed in fibroblasts and airway epithelial cells, and was found to be the most significantly altered lung gene at birth [9]. As one of the four factors that induce pluripotent stem cells, KLF4 has a role in cell fate reprogramming and self-renewal of embryonic stem cells [10,11] KLF4 is implicated as a tumor suppressor gene in the gastrointestinal tract epithelium [12,13], Bladder cancer [14] and medulloblastoma [15], but it may function as a transforming oncogene in breast cancer [16] and skin cancer [17]. In this article, we review the current understanding of the behavior of KLF4 in lung cancer.

The KLF4 expression in lung cancer tissue

The KLF4 expression level differs in present studies. Hu et al. [18] were the first to report the down regulation of KLF4 protein and mRNA in primary lung tumor tissues using western blot and real-time PCR, involving 25 non-small cell carcinoma

[18]. Later, Naranjo Gómez et al. [19] reported high expression of KLF4 in neuroendocrine lung carcinomas, where KLF4 was positive in 23 of 35 large-cell neuroendocrine carcinomas, 10 of 10 tumor lets, 15 of 47 typical carcinoids and 18 of 18 SCLCs [19]. Then, Fadous-Khalife MC et al. [20] reported that a significant decrease in KLF4 expression was observed in non-small-cell lung cancer (NSCLC) compared with that in normal tissue, while significant over expression was detected in small-cell lung cancer. Furthermore, a higher rate of expression was observed in stage II, III and IV disease compared with stage I disease in NSCLC tissues [20]. Although the data is limited, it is more accepted that KLF4 is down-regulated in NSCLC and up-regulated in SCLC. And because the NSCLCs are the absolute majority, most of the researches on the mechanisms of how KLF4 works in lung cancer used NSCLC models.

The KLF4 associated network in Lung cancer

Regulation by KLF4

Down regulation of KLF4 in primary tumor tissues was associated with either down-regulating of p21, up-regulation of cyclin D1, or both. This is consistent with other studies indicating that KLF4 plays important roles in regulating p21 and cyclin D1 expression in cancer cells, which may contribute to its role in regulating cell cycle progression [21,22].

The secreted protein acidic and rich in cysteine (SPARC) over expression may play an important role in the initiation and development of NSCLC, whereas KLF4 inhibits this process [23]. Forced KLF4 expression inhibited cell growth and induced apoptosis. It is conceivable that KLF4 is able to enhance the sensitivity of cisplatin to lung cancer cells and the direct transcriptional targets of KLF4 also included vimentin, b-catenin, and VEGF-A [24]. K-ras mutation combined with Klf4 deletion significantly enhanced lung tumor formation. What's more, Klf4 deletion in conjunction with K-ras activation caused lung inflammation, which is partly responsible for the lung tumor formation. Class I histone deacetylases (HDACs) are over expressed in lung cancer and that HDAC inhibitors induced expression of KLF4 and inhibited proliferation of lung cancer cells, suggesting that KLF4 is probably repressed by histone acetylation [25].

Regulation of KLF4

Numbl-mediated tumorigenesis involved suppression of KLF4 "stemness" transcriptional program, thereby preserving a pool of progenitor-like cells in lung cancer and Numbl-Klf4 signaling is critical to maintain multiple nodes of metastatic progression, including persistence of cancer-initiating cells [26]. Both NLK knockdown and metformin treatment decreased the expressions of KLF4, Nanog, and c-Myc significantly, leading to the decrease of cancer stem cell stemness [27]. Elevated HOTAIR expression upregulated expression of the tumor stem cell related biomarkers KLF4, Nanog, Oct3/4, Sox2, c-Myc, and β-catenin [28]. What's more, Interleukin-27 down-regulated stemness-related genes including KLF4, and inhibited EMT of lung cancer cells [29]. Many aggressive tumors, including lung cancer, have been shown to display gene expression signatures characteristic of human embryonic stem cells (hESC). Hypoxia, through hypoxia-inducible factor (HIF), can induce an hESC-like transcriptional program, including the induced pluripotent stem cell inducers, KLF4, OCT4, NANOG, SOX2, cMYC, and microRNA-302 in lung cancer and other 10 cancer cell lines [30].

In distal lung vascular smooth muscle cells (VSMCs), miR-29 promotes the differentiation of VSMCs by targeting KLF4 and the PDGF pathway [31]. In addition, miR-10b [32,33] and miR-7 [34] may promote proliferation and invasiveness of lung cancer cells by down regulating the expression of KLF4 protein. Hypermethylation of the KLF4 promoter was thought to be associated with its transcriptional repression in a study, while some other researchers did not agree with that. Further study is needed to find whether hypermethylation of KLF4 promoter contribute to the process.

Conclusion

KLF4 is a transcription factor expressed in a wide variety of tissues in humans and is important in many different physiologic processes, including development, proliferation, differentiation, and apoptosis [35]. KLF4 can either activate or repress transcription depending on the target gene by utilizing different mechanisms. The expression of KLF4 appears to exert a dual effect on lung cancer, depending on the cell context and gene network.

The identification of proteins or transcription factors with altered expression as a manifestation of human lung carcinogenesis is important in the discovery of biomarkers for early detection of lung cancer. More data supported that the protein level of KLF4 expression was significantly decreased in NSCLC compared with that in normal tissue, while significant over expression was detected in SCLC, which represents the fast-growing nature of this type of lung cancer that is considered highly lethal. These findings suggest that KLF4 may play a role in the carcinogenic process. Advanced lung adenocarcinom as exhibited significantly higher rates of KLF4 expression compared with stage I disease, where the expression of KLF4 was absent.

Many factors are involved in the network of KLF4 in lung cancer. So far, we have limited data on the research of KLF4 in lung cancer: KLF4 has been demonstrated to down-regulate p21, SPARC, vimentin, b-catenin, and VEGF-A, but to up-regulate cyclin D1, and it may enhance the lung tumor formation combined with K-ras mutation. Moreover, Numbl, NLK, Interleukin-27, miR-7, miR-10b, and miR-29 decreased the expressions of KLF4, while HOTAIR and HIF elevated the expression of KLF4. Looking at the whole research concerning KLF4, it is known that more than 65 factors regulate KLF4 expression and more than 65 factors or pathways are regulated by KLF4 [36], so we still have a lot to know about the function of KLF4 in lung cancer.

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In clinical trials and practice, several drugs targeting the microenvironment have been tested including targets such as VEGF and its receptors on NSCLC-associated endothelial cells [37] and some of the drugs have brought clinical benefit for lung cancer patients. As KLF4 has been continuingly studied in lung cancer, there is hope that in the near future, we could know more about the prognostic and therapeutic value of KLF4 in lung cancer.

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