

HMGB1: A Potential Therapeutic Target for Non-Small Cell Lung Cancer

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Citation: Tu, Z., et al. HMGB1: A Potential Therapeutic Target for Non-Small Cell Lung Cancer. (2016) Lett Health Biol Sci 1(2): 28- 29.

Abstract

Recent studies have found HMGB1 as a potential and valuable bio-marker for NSCLC. Many targeted therapies have been developed with effective clinical proofs; however treatment responses are typically short-lived because of the frequent mutation of target genes. HMGB1 which has been targeted in several cancer therapies for its conservative feature would possess a potential clinical value for NSCLC treatment.

Received Date: August 25, 2016

Accepted Date: Sept 1, 2016

Published Date: Sept 5, 2016

DOI: 10.15436/2475-6245.16.008

Keywords: HMGB1; NSCLC; Target therapy



Introduction

Lung cancer, as the leading cause of cancer-related death worldwide, is a malignant lung cancer categorized by uncontrolled cell growth in the lung tissues. The two main histological types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for nearly 80% among all histological types of lung cancer, and it can also be divided into two major histological types: adeno carcinoma (ADC) and squamous cell carcinoma (SCC). However, the mechanism of pathogenesis of NSCLC is still unclear, and the early detection bio-markers were lack in the diagnosis and prognosis of NSCLC. So the main task is to explore the molecular mechanisms of pathogenesis of NSCLC, and find effective markers for early diagnosis of NSCLC.

As a potential bio-marker for many cancers, high mobility group box 1 (HMGB1) performs dual functions according to its location in cancer cells. In the nucleus, HMGB1 functions as a gene transcription regulator increasing the binding affinity of many transcription factors to their cognate DNA, such as p53 and NF- κ B^[1]. It could be an alarm molecule after being secreted by immune or cancer cells through negative secretory pathway. A major part of researches have revealed that over expression of HMGB1 triggers cell differentiation, cell migration and cancer metastasis after being release into the extracellular space, thus it could promote cancer development and resistance^[2]. Our previous study has already showed that HMGB1 over expressed in NSCLC and intensely affect the survival of NSCLC patients^[3], so this review focused on the therapeutic target value of HMGB1 for NSCLC in current researches.



Targeted Therapies for NSCLC

Targeting tyrosine kinase (TK) like epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and anaplastic lymphoma kinase (ALK) are their receptors has play a significant role in NSCLC treatment and research in recent years^[4,5]. Some of monoclonal antibodies (mAbs) and small molecules targeting tyrosine kinase like Erlotinib^[6] and Gefitinib^[7] were approved for treatment in NSCLC clinical therapy. Unfortunately, drug resistance develops after initial benefit through a variety of mechanisms. Patients with EGFR mutations or ALK rearrangements could occur tyrosine kinase inhibitor (TKI) resistance, so the search for new drugs and therapies is to be considered to be important for the development of outcomes in the treatment of NSCLC patients.

Targeting HMGB1 therapies for various cancer treatment

Besides of genetic suppress of HMGB1 expression in cancer cells, several targeting-HMGB1 agents have been used in experimental cancer research (see Table 1). Release of HMGB1 from cancer cells and necrotic cells during the progress of anti-cancer therapy has negative effects, so these agents include HMGB1 neutralizing antibody^[8] quercetin^[9], glycyrrhizin^[10], ethylpyruvate^[11] and oxaliplatin^[12,13] may be conducive toward better outcomes in the treatment of cancer patients. Anti-HMGB1 antibody can inhibit the activity of extracellular HMGB1 in serum and tissues. Small molecules like glycyrrhizin and quercetin which could directly bind to HMGB1 which are used as potential HMGB1 inhibitors to enhance the effectiveness of anti-cancer drugs in several cancer models^[9,14]. Meanwhile, oxaliplatin have the capacity to reduce the release of HMGB1 by retaining HMGB1 within the nucleus^[12,13]. Further investigations are needed to value these target therapies and their possible usage in clinical therapies.

Table 1: Targeting-HMGB1 Agents for Cancer Therapies

Agents	Targeting-HMGB1 Location	Tumor Types	References
Anti-HMGB1 Antibody	Extracellular HMGB1	Leukemia	[8]
Ethyl Pyruvate	Extracellular HMGB1	Hepatocarcinoma	[11]
Glycyrrhizin	Extracellular HMGB1	Meloma	[8]
Oxaliplatin	Intracellular HMGB1	Colon Carcinoma	[12,13]
Quercetin	Extracellular HMGB1	Breast Cancer	[9]

HMGB1 in NSCLC

As the previous studies showed, HMGB1 over expressed in NSCLC and affected the prognosis and development of NSCLC patients. Because of the rare mutation of HMGB1 in NSCLC patients^[3], we considered HMGB1 as a better targeting bio-marker for NSCLC than TKs. However, there's no research target HMGB1 as a therapy strategy for treatment of NSCLC patients. So we think that further basic and clinical studies are warranted to confirm the significant role played by HMGB1 in NSCLC and to identify means to exploit this therapeutically.

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