Computational and Structural Biotechnology Journal 16 (2018) 211–223

COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

journal homepage: www.elsevier.com/locate/csbj

Mini Review

Lung Cancer Therapy Targeting Histone Methylation: Opportunities and Challenges

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ARTICLE INFO

Article history:
Received 30 March 2018
Received in revised form 10 June 2018
Accepted 11 June 2018
Available online 20 June 2018

Keywords:
Histone methylation
Histone demethylation
Lung cancer
Histone methyltransferase
Histone demethylase
Inhibitors

ABSTRACT

Lung cancer is one of the most common malignancies. In spite of the progress made in past decades, further studies to improve current therapy for lung cancer are required. Dynamically controlled by methyltransferases and demethylases, methylation of lysine and arginine residues on histone proteins regulates chromatin organization and thereby gene transcription. Aberrant alterations of histone methylation have been demonstrated to be associated with the progress of multiple cancers including lung cancer. Inhibitors of methyltransferases and demethylases have exhibited anti-tumor activities in lung cancer, and multiple lead candidates are under clinical trials. Here, we summarize how histone methylation functions in lung cancer, highlighting most recent progresses in small molecular inhibitors for lung cancer treatment.

Contents

Abbreviations: ALK, anaplastic lymphoma kinase; DUSP3, dual-specificity phosphatase 3; Elk1, ETS-domain containing protein; EMT, epithelial-to-mesenchymal transition; HDAC, histone deacetylase; IHC, immunohistochemistry; KDMs, lysine demethylases; KLF2, Kruppel-like factor 2; KMTs, lysine methyltransferases; LSDs, lysine specific demethylases; MEP50, methylosome protein 50; NSCLC, non-small cell lung cancer; PAD4, peptidylarginine deiminase 4; PCNA, proliferating cell nuclear antigen; PDX, patient-derived xenografts; PRC2, polycomb repressive complex 2; PRMTs, protein arginine methyltrasferases; PTMs, posttranslational modifications; SAH, S-adenosyl-L-homocysteine; SAM, S-adenosyl-L-methionine; SCLC, small cell lung cancer; TIMP3, tissue inhibitor of metalloproteinase 3.

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https://doi.org/10.1016/j.csbj.2018.06.001

1. Introduction

Lung cancer is one of the most prevalent malignancies and the leading cause of cancer-related death in the US and in China [1, 2]. Among patients with lung cancer, non-small cell lung cancer (NSCLC) accounts for about 85% and small cell lung cancer (SCLC) accounts for the remaining 15% [3]. According to the pathological phenotypes, NSCLC includes adenocarcinoma, squamous cell carcinoma, and large cell lung carcinoma [4]. The past decades have witnessed the clinical introduction of several small molecular inhibitors, which significantly improved overall prognosis of lung cancer [5–7]. However, many patients still suffer from poor response to drug therapy due to individually differences in genetic, epigenetic, phenotypic or psychosocial features [8, 9]. Therefore, precision medicine aiming to provide personalized targeted treatment becomes an attractive strategy to improve the drug efficacy against lung cancer [10–12]. Epigenetic differences among patients have been considered as a critical factor in the development of precision medicine [13], and in various malignancies including lung cancer, epigenetic dysregulation has been identified to play a crucial role in the tumorigenicity and heterogeneity [14–17].

Epigenetic dysregulation is usually resulted from aberrant changes in DNA and histone modifications. In eukaryotic cell, genomic DNA is wrapped around a protein octamer which contains four core histones (H2A, H2B, H3, H4), forming the structure of the nucleosome [18]. Each of the histone proteins possesses a tail, which is a classic location where various posttranslational modifications (PTMs) function [19, 20]. Through changing the charge density between DNA and histones, DNA methylation and histone PTMs (acetylation, methylation, and phosphorylation) can regulate the loosening of the nucleosome, affecting the access of transcription factors and RNA polymerase to their target genes [21–24]. Currently, DNA methylation has been widely accepted as important biomarkers in the clinical management of lung cancer, since DNA methylation-based biomarkers provide useful information in distinct clinical questions about early diagnosis, staging, prognosis and therapy-response prediction [25]. However, questions about whether other epigenetic modifications can be explored as lung cancer therapeutic targets never stopped during the last decade. Histone acetylation has been demonstrated to play a vital role in lung cancer development by activating gene transcription [16]. Although some histone deacetylase (HDAC) inhibitors, such as Vorinostat and Panobinostat, have gained optimistic results in pre-clinical and clinical trials on NSCLC, further studies of HDAC inhibitors in lung cancer are necessary for evaluating their anti-tumor effect [16, 23]. Histone methylation, one of the most well studied patterns among histone modifications, can either promote or inhibit transcription at different gene loci, thus plays a rather complex role in lung cancer [21]. It is believed that the methylation of lysine (K) and arginine (R) residues on histone tails largely determines the chromatin configurations and, hence, biological outcomes [19]. Like other histone modifications, histone methylation is a dynamic process regulated by a series of 'eraser' and 'writer' enzymes. Methylation 'erasers' and 'writers' respectively remove and add specific methyl marks crucial for gene expression, genomic stability and cell fate [19]. Methyltransferase 'writers' and the corresponding demethylase 'erasers' for histone lysine residue are termed as histone lysine methyltransferases/demethylases (KMTs/KDMs for short respectively). For histone arginine residues, the 'writers' and 'erasers' are histone arginine methyltransferases and histone arginine demethylases respectively.

Some of these histone methylation modifiers have been identified in cancers with altered activities, suggesting their oncogenic or tumor-suppressor roles [19, 26]. Aberrations of histone methylation modifiers have been closely intertwined with lung cancers as well [14, 27]. Moreover, along with the deeper understanding of the patterns and functions of histone methylation in lung cancer, several inhibitors targeting histone methylation modifiers have entered clinical trials [22]. It may be a right time to review and rethink the potential of histone methylation for developing lung cancer therapy, however, there lacks a systematic review about this issue. Here, we discussed the functions and related structural foundations of histone methylation modifiers in lung cancer, and highlighted the most recent progresses in lung cancer therapy targeting histone methylation.

2. KMTs and their Roles in Lung Cancer

KMTs can remove methyl groups on lysine residues of histones or non-histone substrates [28, 29]. Based on the similarity of structural organization and catalytic domain, KMTs are divided into two categories, SET domain-containing KMTs and the only non-SET-domain-containing KMT DOT1L (Fig. 1A and B) [30, 31]. The first histone KMTs identified in human is the H3K9 methyltransferase SUV39H1, a mammalian homologue of *Drosophila* Su(var 3–9) [32]. Since then, more histone KMTs have been discovered, which target H3K4 [33], H3K9 [26, 34], H3K27 [35, 36], H3K36 [37], H3K79 [38, 39] or H4K20 [40]. In addition to their essential roles in physiologic activities, such methyltransferases are found to closely associate with variant cancers. Here, the structures and functions of representative histone methyltransferases and their therapeutic potentials for lung cancer are summarized (Table 1).

2.1. SET Domain-Containing KMTs

The SET domain comprises approximately 130 residues, and is regarded as the evolutionarily conserved catalytic motif of KMTs (Fig. 1A). It was originally identified from three *Drosophila* proteins, *i.e.* Suppressor of variegation 3–9 (Su(var) 3–9), Enhancer of zeste (E (z)) and Trithorax (Trx), which involve in epigenetic process [41]. The SET domains of most of histone KMTs bind to histones as well as methyl donors (S-adenosyl-L-methionine, also known as AdoMet or SAM) and reaction products (S-adenosyl-L-homocysteine, also known as AdoHcy or SAH) [42]. Most SET-containing histone KMTs function SAM-dependently or SAH-dependently. A knot-like structure within