Seminars in Cell & Developmental Biology 64 (2017) 18–25

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Role of epigenetics in lung cancer heterogeneity and clinical implication

Nian Dong[a,1], Lin Shi[b,1], Diane C. Wang[a,1], Chengshui Chen (MD) (Prof.)[a,*], Xiangdong Wang (MD PhD) (Prof.)[a,b,**]

[a] Department of Pulmonary Medicine, The First affiliated Hospital, Wenzhou Medical University, Wenzhou, 325000, China
[b] Zhongshan Hospital, Shanghai Institute of Clinical Bioinformatics, Fudan University Center for Clinical Bioinformatics; Zhongshan Hospital Institute of Clinical Science of Fudan University, Shanghai, China

ARTICLE INFO

Article history:
Received 21 August 2016
Accepted 24 August 2016
Available online 26 August 2016

Keywords:
Epigenetics
Heterogeneity
Lung cancer
Clinical implication

ABSTRACT

Lung cancer, as a highly heterogeneous disease, can be initiated and progressed through the interaction between permanent genetic mutations and dynamic epigenetic alterations. However, the mediating mechanisms of epigenetics in cancer heterogeneity remain unclear. The evolution of cancer, the existence of cancer stem cells (CSCs) and the phenomenon of epithelial-mesenchymal transition (EMT) have been reported to be involved in lung cancer heterogeneity. In this review, we briefly recap the definition of heterogeneity and concept of epigenetics, highlight the potential roles and mechanisms of epigenetic regulation in heterogeneity of lung cancer, and summarize the diagnostic and therapeutic implications of epigenetic alterations in lung cancer, especially the role of DNA methylation and histone acetylation. Deep understanding of epigenetic regulation in cancer heterogeneity is instrumental to the design of novel therapeutic approaches that target lung cancer.

Contents

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide with 220,000 estimated new diagnosis and 160,000 estimated deaths per year [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers, including adenocarcinoma (AD), squamous cell carcinoma (SCC), and large cell carcinoma (LCC) subtypes [2]. NSCLC was considered as a heterogeneity disease due to histological and molecular heterogeneity. First-line treatment of advanced disease remains platinum-based doublet chemotherapy. Recently,

* Corresponding author.
** Corresponding author at: Zhongshan Hospital, Shanghai Institute of Clinical Bioinformatics, Fudan University Center for Clinical Bioinformatics; Zhongshan Hospital Institute of Clinical Science of Fudan University, Shanghai, China
E-mail addresses: wzchencs@163.com (C. Chen), xiangdong.wang@clintransmed.org (X. Wang).
[1] Authors contributed to this paper equally as the first authors.

http://dx.doi.org/10.1016/j.semcdb.2016.08.029
1084-9521/

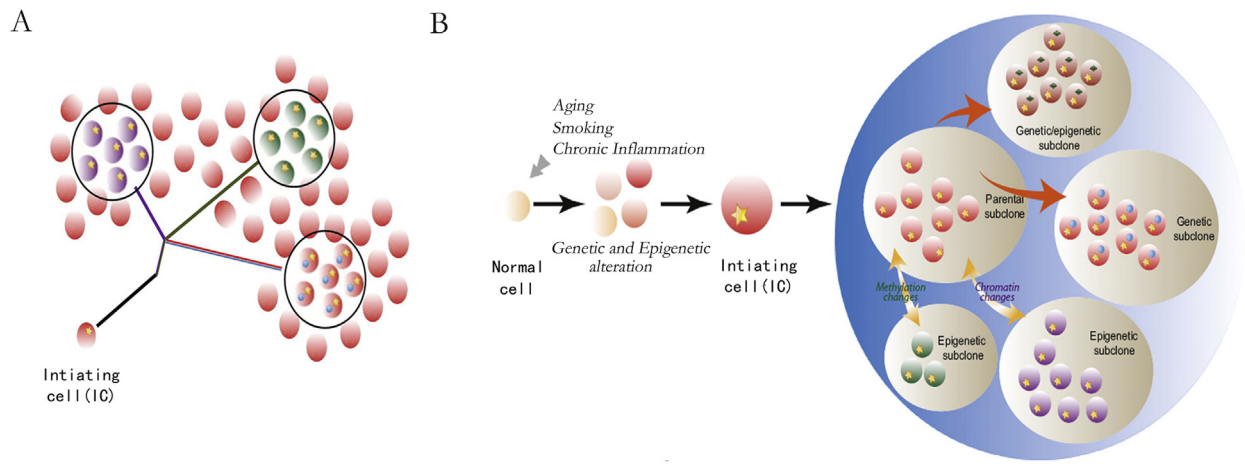

Fig. 1. Genetic and epigenetic contributions to the heterogeneity of lung cancer. (A) Intratumoral heterogeneity was observed in individual cell of lung cancer through biopsy at distinct regions. (B) During tumorigenesis of lung cancer, smoking, aging and so on may promote clonal expansion of founder tumor cells or initiate cells with permanent genetic or dynamic epigenetic abnormalities. The formation of cancer heterogeneity forms as lung cancer develops. In an established tumor, the parental subclone may acquire new driver or passenger mutations (genetic subclone) or undergo epigenetic alterations such as DNA methylation, histone modification or ncRNAs.

the recognition of tumor-driven genetic mutations led to the development of molecule-targeted drugs, including those targeting epidermal growth factor receptor (EGF), vascular endothelial growth factor, insulin-like growth factor I signaling and others [3–6]. However, the majority of NSCLC are diagnosed at a late stage resulting in a poor prognosis with the 5-year survival for localized, regional and widely disseminated NSCLC being 55%, 27 and 4% respectively [7], also due to the lack of early detection and disease-specific biomarkers [8]. The initiation and progression of lung cancer is a result of the combination of permanent genetic mutations as well as dynamic epigenetic alterations [9], which exhibits intertumoralorintratumoral heterogeneity [10] (Fig. 1).

Intertumoral heterogeneity, based on the genetic mutations, commonly refers to the heterogeneity among different cases [11–14]. In the past decade, there is sound data and compelling evidence for intertumoral heterogeneity with clinical implication. For example, the efficacy of EGFR inhibitors is different because of the different cases with or without EGFR mutations [15]. Although such molecule-targeted drugs on the basis of intertumoral heterogeneity together with the traditionally histologic-guided chemotherapy provides more therapeutic choices for clinicians. However, lung cancer has a high incidence coupled with poor a 5-year survival rate of less than 17%, which is partly influenced by intratumoral heterogeneity in an individual case or in an individual tumor [11,16–18]. It has been reported that epigenetic modulators indirectly contribute to the unscheduled expression of epigenetic mediators, facilitate the mediator-induced reprogramming of cell phenotypes of intratumoral heterogeneity, or transduce signals from internal or external stimuli [19]. Such intratumoral heterogeneity can be observed in distinct regions or individual cells of solid tumors. An increasing number of studies have demonstrated that aberrant epigenetics lead to cell-to-cell variability, which is thought to be responsible for treatment failure for cancer [20].

As mentioned above, epigenetics mainly contribute to the intratumoral heterogeneity. Several epigenetic defects, such as NSD1 and SETD2, are also associated with genetic mutations, which further induce intertumoral heterogeneity [21]. The present review will overview recent discoveries in the field of epigenetics in tumor heterogeneity, and summarize the potential diagnostic and therapeutic implications of epigenetic alterations in lung cancer. With the advent of the era of precision medicine, elucidating tumor heterogeneity as well as its potential regulatory mechanism will benefit the discovery and development of new diagnostics and therapies for lung cancer.

2. Roles of epigenetics in lung cancer development and metastasis

Cancer development and metastasis are the major cause of mortality and morbidity in lung cancer. A growing body of evidence suggests that the epithelial-to-mesenchymal transition (EMT) plays a central role in lung cancer development and metastasisas early changes in cell morphology occur with epithelial cells losing their polarity (e.g. E-cadherin) and acquiring new features of mesenchyme (e.g. Vimentin, N-cadherin). The induction of EMT is accompanied by a dynamic reprogramming of the epigenome involving changes in histone modification and ncRNAs [22]. The loss of E-cadherin expression or function by genetic or epigenetic aberrations is a common phenomenon in lung cancer [23]. Smoking may induce EMT by HDAC-mediated downregulation of E-cadherinin NSCLC, and HDAC inhibitor MS-275 may reverse the CSC-induced EMT[24]. Recently, numerous HDAC-containing complexes appear to play distinct roles in the regulation of E-cadherin during EMT, including the Mi2/nucleosome remodeling and deacetylase (Mi2/NuRD) complex, which is identified to interact with Twist, a major regulator in EMT [25]. TGF-β1 acts as a critical switch in the induction of EMT, which is also influenced by histone acetylation. The Smad complex, directly downstream of TGF-β, translocated into the nucleus and regulated the transcription by directly binding to the promoter of its downstream and the specific transcriptional co-activators or co-repressors, such as p300/CBP and HDAC [23]. Some epigenetic regulatory mechanisms of EMT and CSC of lung cancer are listed in Table 1.

Additionally, the HDACs may regulate the E-cadherin expression through ncRNAs. MiRNAs are involved in the regulation of EMT of lung cancer through regulation of various signaling pathways, such as TGF-β, EGF, and HGF signaling pathway (Fig. 2). Of those, MiR200b and miR200c were reported to have an effect on H3 acetylation at E-cadherin promoter site [26]. The miR-200 plays an essential role in EMT suppression through targeting Zeb, which is linked to lung cancer [27]. Gregory et al. have reported low miR-200 levelsin cells that had undergone EMT in response to TGF-β, while enforced miR-200 expression was justified to prevent TGF-β-induced EMT. Moreover, the lack of miR-200 expression was positively correlated with absent E-cadherin [28]. The metastasis suppressive role of the miR-200 was observed in NSCLC cell lines with mutant K-ras and p53 as well. The TGF-β-induced EMT of NSCLC cell lines were entirely miR-200 dependent [29]. The re-expression of miR-200 also downregulated genes that are involved