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Review

Tomorrow's genome medicine in lung cancer

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ABSTRACT

Tomorrow's genome medicine in lung cancer should focus more on the homogeneity and heterogeneity of lung cancer which play an important role in the development of drug resistance, genetic complexity, as well as confusion and difficulty of early diagnosis and therapy. Chromosome positioning and repositioning may contribute to the sensitivity of lung cancer cells to therapy, the heterogeneity associated with drug resistance, and the mechanism of lung carcinogenesis. The CCCTC-binding factor plays critical roles in genome topology and function, increased risk of carcinogenicity, and potential of lung cancer-specific mediations. Chromosome reposition in lung cancer can be regulated by CCCTC binding factor. Single-cell gene sequencing, as part of genome medicine, was paid special attention in lung cancer to understand mechanical phenotypes, single-cell biology, heterogeneity, and chromosome positioning and function of single lung cancer cells. We at first propose to develop an intelligent single-cell robot of human cells to integrate together systems information of molecules, genes, proteins, organelles, membranes, architectures, signals, and functions. It can be a powerful automatic system to assist clinicians in the decision-making, molecular understanding, risk analyzing, and prognosis predicting.

Contents

1. Introduction

Genome medicine is a revolutionary discipline of clinical understanding, definition, category, diagnostics, monitoring, and therapy based on genome pathology and pathophysiology, e.g. alterations of DNA with or without coding, RNA, or genomes of the nucleus, mitochondria and chloroplasts. Lung cancer is one of the most explored diseases in genome medicine and was early considered for precision medicine with a number of developed targeted therapies, such as inhibition of the epidermal growth factor receptor (EGFR) tyrosine kinase for non-small cell lung cancer (NSCLC). A number of genome-based biomarkers were discovered and developed in lung cancer, including the expression, sequencing, or epigenetics of DNA, element networks, or chromosome positioning [1–3]. The present issue with a special focus on genome medicine in lung cancer will overview the most important topics on TGFbeta-induced transcription in cancer [4], genetic modification of lung cancer subtypes [5], ALK mutation and inhibition in lung cancer [6], the genetic mechanism of COPD-lung cancer transformation [7], Smyd3-associated transcriptional pathways in cancer [8], heterogeneity and drug efficacy in lung cancer [9], new strategies of targeted drug combinations for mutation-driven drug resistance [10], global view of regulatory networks in lung cancer as an approach to understand

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homogeneity and heterogeneity [11], and regulatory roles of epigenetic modulators, modifiers and mediators in lung cancer [12].

The present review aims to headline and overview the understanding of chromosome positioning and repositioning in the sensitivity of lung cancer cells to therapy, the heterogeneity associated with drug resistance, and the mechanism of lung carcinogenesis. We discuss the critical roles of CCCTC-binding factor in genome topology and function, increased risk of carcinogenicity, and potential of lung cancer-specific mediations. Single-cell gene sequencing, as part of genome medicine, was paid a special attention in lung cancer to understand mechanical phenotypes, single-cell biology, heterogeneity, and chromosome positioning and function of single lung cancer cells. We at first propose to develop an intelligent single-cell robot of human cells to integrate systems information of molecules, genes, proteins, organelles, membranes, architectures, signals, and functions together. It can be a powerful automatic system to assist clinicians in decision-making, molecular understanding, risk analyzing, and prognosis predicting.

2. Understanding of chromosome positioning and repositioning

The chromosome repositioning may be associated with the sensitivity of lung cancer cells to therapy. The haploid/diploid genome, as part of chromosome compositions, was found to play a critical role in the stability of allodiploid genome and the differentiation of stem cells [13]. The alterations of haploid or diploid may be one of important regulatory mechanisms of X chromosome inactivation and are used to define regulating phenotypic differences of activated genes. The number of circulating tumor cells (CTC) correlated with the number of metastatic nodules in lung, the growth of primary cancer, the cutting edge of removed tumor from the normal tissue, and the prognosis of patients with cancer. The chromosome repositioning in CTCS reflected by phenotyping of cytokeratin 18 and karyotyping of chromosome 8 was furthermore noticed to be involved in the mechanism by which the cancer cell sensitivity can be changed. The cytokeratin 18-negative diploid and majority of cytokeratin 18-potive diploid CTC subtypes were sensitive to chemotherapy, while the cytokeratin 18-positive multiploid CTC subtype were insensitive to Cisplatin [14].

It is possible that the chromosome repositioning may be a critical mechanism of lung cancer cell homogeneity and heterogeneity responsible for the development of drug insensitivity and resistance. A number of targeted therapies have been discovered and developed for lung cancer to increase the accuracy and efficacy of therapy, minimize the toxicity of drugs, and overcome insensitivities and side effects of chemotherapy. Clinical trials demonstrate that subtypes or subgroups of lung cancer cells with certain genetic characters, e.g. gene mutations are sensitive to targeted therapy. The mutation number and copy number variations of targeted genes were applied to select the sensitive population of patients with lung cancer for targeted therapy. The drug resistance developed after targeted therapy is a rising challenge to improve the efficacy of targeting drugs. The heterogeneity of lung cancer cells has been proposed as one of the important factors responsible for the development of drug resistance. The heterogeneity, or variability, exists among species, populations, patients, inter-organs/tissues, intra-tumor locations, or cells within a location [15]. It was found that insensitive cancer cells due to genetic heterogeneity could become a majority of regenerated cancer after the therapy and develop the resistance. It should be further clarified that the heterogeneity of lung cancer cells may result from the non-randomness of chromosome territory organization within an interphase nucleus, since the re-arrangement of chromosome territories can regulate genome functions during cell differentiation, quiescence and senescence [16]. The decisive role of chromosome positioning in the heterogeneity of lung cancer cells can be evidenced by the fact that the position of whole chromosomes or chromosomal domains can modulate transcriptional function, and chromatin architecture, gene-rich or gene-poor chromosomes are located in the nuclear interior or the periphery respectively, DNA within the nuclear interior has higher transcriptional activity and local chromatin structure affects the damage frequency and repair mechanisms. Chromosome repositioning can alter the sensitivity of chromosomal domains to damages, while DNA damage may increase the sensitivity of chromosomes to repositioning. For example, DNA damage induced the repositioning of some gene-rich chromosomes, such as chromosomes 17, 19 and 20, in a dose- and time-dependent manner, more than the others [17]. The expression of genes in chromosomes 1, 7 and 19 was found to be associated with genotypes and phenotypes of lung cancer subtypes [18–20]. It was suspected that chromosome repositioning may vary between lung cancer subtypes and lead to the heterogeneity of gene expression and transcriptional function among subtypes.

The chromosome repositioning is a new approach to understand molecular mechanisms of lung carcinogenicity, formation of heterogeneity within lung cancer, and lung cancer subtype-specific gene activity and genome stability. A number of questions on biological mechanisms and clinical significance of chromosome repositioning in lung cancer are raised with the development of biotechnologies on molecular imaging, genome architecture, and spatial position. The chromosome conformation capture techniques, e.g. 3C, 4C, and Hi-C, make it possible to map intra- and inter-chromosomal interactions and positions. It also allows measurement of the homogeneity and heterogeneity of chromosome positioning which exists between lung cancer and other origin cancers, between lung cancer subtypes, between lung cancer and chronic lung inflammation, between therapies, or between prognoses. Shachar et al. recently developed a high-precision, high-throughput, automated fluorescent in situ hybridization imaging pipeline to map the spatial location of genome regions on large scales [21]. This new approach makes it practical to quantitatively determine the position of multiple endogenous loci in the nucleus of lung cancer cells with high accuracy and high throughput and discover human genome positioning factors in an unbiased, large-scale fashion in combination with siRNA. We should understand the mechanism by which genes are positioned in the cell nucleus when lung cancer cells grow and metastasize in diverse responses to macro- or micro-environmental challenges or to different therapies, how intracellular factors may regulate repositioning of functionally diverse genomic loci, how repositioning of genes and chromosomes of lung cancer cells may be determined, or how repositioning patterns of chromosomes or chromosomal domains of lung cancer cells can be altered in responses to target therapy or chemotherapy. The understanding of chromosome repositioning will provide a new alternative to discover and develop molecular diagnosis and therapies for lung cancer.

3. Critical roles of CCCTC-binding factor (CTCF)

CTCF acts as an insulator protein mainly responsible for mediating the process between nuclear organization and gene expression, a transcription factor for activating or repressing gene expression, an insulator for communicating with enhancer-promoter or buffering transgenes from chromosomal position effects, and as an architectural protein for contributing to the establishment of genome topology [22]. CTCF can mediate the interaction with other architectural proteins to form topologically associating domains with which CTCF regulates the processes of gene expression

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