Research

Tumor Evolution of Lung Cancer and Mortality

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Abstract: This article is committed to consider improvement of lung cancer mortality in the world. Through the previous two decades malignant growth was altogether expanding reason for mortality and real general medical issue in world. Lung disease remains the most continuous reason for passings among other type of harmful neoplasms. Mortality improvement from lung disease and other threatening neoplasms fundamentally separated among Western and previous socialist nations. Throughout the most recent two decades lung malignant growth mortality significantly diminished among guys, while in females it was quickly expanding. Older individuals over age 65 are the most various populaces experiencing lung disease. Everybody realizes that tobacco smoking is significant hazard factor which adds to lung disease, however by and by, individuals keep on smoking. In spite of the measures taken against tobacco, smoking predominance stays high in the different nations of Asia.

Keywords: lung, cancer, mortality

Introduction

A cancer cell can be characterized by the classic six hallmarks of cancer that enable the cell to proliferate, resist cell death, induce angiogenesis, evade growth suppressors, disseminate, invade and metastasize [1]. The understanding of the underlying genomic, epigenomic and proteomic diversity of a tumor cell behind these changes, has over the last few years increased considerably, through advanced sequencing technology. The genome of a cancer cell harbors several mutations and only a subset is thought to be causal and crucial for the cancer progression by contributing to clonal growth advantage. They are called drivers. The rest are called passengers and are defined as those that do not affect the fitness of the cell,
but are acquired during the progression through e.g. genomic instability which leads to increased mutation rates and chromosomal rearrangements [2, 3]. Furthermore, it has become evident that not only the cancer cell alone but also the surrounding tumormicroenvironment, is contributing to the hallmark properties. Another characteristics of cancer involves the inflammatory state that is driven by cells of the immune system, enabling tumor progression in various ways [4]. To understand the complexity of a tumor, the hallmarks of cancer proposed by Hanahan and Weinberg in 2000 and 2011, are valuable guidelines in the search for cancer risk factors, therapeutic targets or prognostic and diagnostic markers (Figure 1).

Figure 1. Hallmarks of cancer. (From the review by Hanahan and Weinberg: Hallmarks of cancer: next generation, 2011 [4]).

Lung cancer is the most predominant disease related passing with 1.37 million passings for every year [5]. Most of essential lung tumors are lung carcinomas and can be partitioned into two gatherings; Small cell lung carcinoma (SCLC) and Non-Small Cell Lung Carcinoma (NSCLC). SCLC is a forceful neuroendocrine tumor comprising of little tumor cells getting from epithelial and neuroendocrine cells. This sort of lung disease is firmly connected with smoking with a poor visualization. Because of quick spread of these tumors, patients with SCLC are once in a while worked [6]. NSCLC represents roughly 80% of all lung diseases and incorporates three histological subtypes; adenocarcinoma (AdC), squamous cell carcinoma (SCC), and substantial cell carcinoma (LCC)[7]. As of late, AdC of the lung has supplanted SCC as the most regular histologic subtype for the two people [8]. AdC emerges from cells with glandular or secretary properties in the fringe of the lung [9]. The movements in histologic kinds are identified with expanded rates of smoking in ladies and to present day.
cigarettes that contain higher convergences of specific cancer-causing agents [10]. Most AdC cases are connected to tobacco smoke and record for 20% of all lung malignancies. However, among non-smokers and ladies, AdC represents generally cases. SCC represents 30% of all lung diseases [11]. SCC begin from multilayered squamous cells, which are ordinarily not present in the respiratory epithelium, yet emerge from glandular or secretory cells by metaplastic change because of tobacco smoke [9, 12]. NSCLC is arranged from IA to IV, IA having the best guess and IV being the most noticeably awful, in view of the level of spreading from the essential tumor [13].

Figure 1: Different subtypes of lung cancer. Formalin fixed paraffin embedded (FFPE) tissues stained by standard hematoxylin and eosin protocol. Magnification: 20x. A) Adeno B) Squamous cell C) Large cell D) Small cell carcinoma.

Tumor evolution and heterogeneity

Cancer is a complex disease that is initiated by acquiring and accumulation of mutations in a single cell through time resulting in a cancerous cell population42. It is a genetically heterogeneous disease and several subpopulations coexist in a single tumor43. In 1976, cancer has been defined as an evolutionary process which is driven by somatic mutations and selection pressures that help
outgrowth of some clones over others. This definition led to two different concepts of evolution, i.e. linear versus branched. In the first model, cancer cells contain all driving mutations that accumulate during evolution, while in the branched model each tumor cell can acquire different mutations and multiple subclones can grow out within a tumor. A branched evolution can result in extensive intra-tumor heterogeneity and this can affect clinical outcome of targeted therapy. Intra-tumor heterogeneity has been shown in different cancer types including NSCLC, clear cell renal carcinoma and pancreatic cancer. Genomic analysis using multiple samples of a patient and analysis at single cell level can improve our understanding about this complex disease and help to further optimize treatment strategies.

**Targeted therapy in lung cancer**

Utilizing WGS and/or WES provided detailed information about genomic aberrations in lung cancer and this approach has led to identification of potential new targets for therapy. These NGS developments were introduced at the same time frame as the development of novel chemical compounds that can target proteins derived from oncogenic driver mutations. New technologies enhanced generation of structurally adapted compounds to optimally inhibit specific target kinase receptors. Discovery of EGFR mutations and their predictive value on tumor response to targeted TKI treatment in lung cancer patients is a revolution in so called “personalized therapy”, i.e. specific drugs targeting these drivers of lung cancer (targeted therapy). Despite prolonged survival of lung cancer patients with these targeted drugs, tumor cells develop resistance. This indicates the need for novel targeted drugs to treat patients with resistant tumors. This resistance might occur due to intra-tumor heterogeneity and emergence of resistant minor subpopulations via selective pressure applied by treatment. Several promising phase I and II studies are currently being executed that will improve treatment results of lung cancer patients. One can envisage that more driver mutations will be detected in tumor cells and that new or combinations of drugs will enhance treatment outcome in the future. Of course, toxicity and induced resistance may still limit their efficiency. Currently there is a growing number of targeted treatments available for NSCLC patients in clinical setting such as gefitinib, erlotinib and afatinib for activating EGFR mutations, rociletinib and AZD9291 for resistant EGFR T790M mutations, crizotinib, ceritinib, brigatinib and alectinib for EML4-ALK fusion proteins and combination of dabrafenib and trametinib for BRAF mutations.
Conclusion

Lung cancer is the main cause of cancer-related death worldwide and conventional treatment strategies must be improved. In addition to mutations in several well-known cancer-associated genes, recent advances in sequencing technology have led to the discovery of numerous novel gene mutations and translocations. Some of these genomic aberrations occur at similar frequencies in all lung cancer subtypes, whereas others appear to be specific for adenocarcinoma or squamous cell lung cancer. High frequency mutations or recurrent translocations support involvement of the affected genes in the pathogenesis of lung cancer. The presence of activating aberrations is indicative for putative driver genes that might be essential for tumor cell growth and survival. These driver genes are potential targets for developing new treatments for lung cancer patients. Indeed, multiple tyrosine kinase inhibitors (TKIs) are currently used to treat lung cancer patients based on the presence of activating mutations, and novel drugs are under investigation. Patients benefit for about one
year from current targeted treatments, but progression of disease inevitably occurs and resistance of the tumor to the TKI used can be observed in re-biopsied tumor samples. The aim of this review is to provide an overview of mutated genes in non-small cell lung cancer, an overview of targeted treatment strategies that are currently applied, and the known resistance mechanisms.

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