Review Article

Translational new frontiers in lung cancer research

Giulia Sedda[1], Roberto Gasparri[1], Lorenzo Spaggiari[1,2]

[1]Department of Thoracic Surgery, IEO, European Institute of Oncology IRCCS, Milan, Italy; [2]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

Contributions: (I) Conception and design: G Sedda; (II) Administrative support: None; (III) Provision of study materials or patients: G Sedda; (IV) Collection and assembly of data: G Sedda; (V) Data analysis and interpretation: G Sedda; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Giulia Sedda, PhD. Department of Thoracic Surgery, IEO, European Institute of Oncology IRCCS, Via Giuseppe Ripamonti 435, 20141 Milan, Italy. Email: giulia.sedda@ieo.it.

Abstract: Lung cancer (LC) accounts for 1.6 million death each year, remaining the leading cause of oncology-related death. This worst-case scenario is linked to poor survival associated with late diagnosis. This happens commonly in clinical practice, even in countries with strong and developed health systems, resulting in a lower chance of survival and a higher cost of treatment. Ideally, screening in an asymptomatic at-risk population could increase the chance of recognition cancerous cells, or even pre-cancerous conditions, in a majority of individuals who will results negative to the test. With this article, we aim to summarize the best new approach in LC research.

Keywords: Lung cancer (LC); early diagnosis; research

Received: 18 November 2019; Accepted: 30 November 2019; Published: 10 April 2020.

doi: 10.21037/shc.2019.11.15

View this article at: http://dx.doi.org/10.21037/shc.2019.11.15

Cancer is a chronic, heterogeneous and dynamic disease (1) characterized by an uncontrolled proliferation of cells (2). There are more than 200 different types of cancer, such as carcinoma, sarcoma, leukemia and lymphoma. The World Health Organization (WHO) has estimated for 2018, 9.6 million new death related to cancer, remaining the second cause of deceases worldwide and increasing each year (3). Among these, lung cancer (LC) is considered the "big killer", accounting for 1.6 million death. In Italy for 2019, 42,500 new LC diagnoses are expected (29,500 men and 13,000 women). LC remains the leading cause of death (12%) of all cancers in the Italian population, with a 5-year survival of 16% (4). This worst-case scenario is linked to poor late survival associated with late diagnosis, which is over 60% for early-stage whereas those with stage IIIA disease have survival of 36% (5,6). Undeniably, due to the fact that patients are mostly asymptomatic, the diagnosis is usually achieved when the disease is advanced or spread to the extrathoracic region when surgery is no longer an option. Other life-threatening tumors have much higher survival rates thanks to predictive tests, such as fecal occult blood testing for colon cancer and mammography for breast cancer (7). Goldberg *et al.* estimated that if all LC could be diagnosed at an early stage, deaths could be reduced by more than 70,000 per year (8).

LC etiology still lacks all mechanisms elucidation, but there are many known promoting cause understood, consumption of tobacco which has defined in the last decades the geographical and temporal patterns of LC incidence (9). Others factor known are exposition to chemical or toxic compounds and ionizing radiation. The main histological categories of LC are non-small-cell LC, which accounts for more than 80% of cases, and small-cell lung carcinoma (SCLC). Non-small-cell lung carcinoma (NSCLC) includes three main types: adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma. All the histotype carried the somatic mutations of *TP53* gene (i.e., the regulator of cell proliferation) and driver genetic alterations frequently funded are *EGFR* and *BRAF* mutations, *ALK* and *ROS1* rearrangements, with others less represented *MET*, *RET*, *NTRK*, *HER2* (10). Germline variations promoting LC have not been demonstrated yet,

even if an increased familiar risk has been studied (9).

Nevertheless, a person LC risk depends not only to exposure factors, but it is also influenced by other factors such as age. Indeed, the primary prevention (i.e., avoiding the risk factor) could prevent between 30% and 50% of cancer death. However, the remaining mortality is not avoidable considering that not all cancers are preventable and many cases are due to multifactorial factors, thus could be only reduced by early detection. In clinical practice, even in countries with strong and developed health systems, many patients are diagnosed at later-stage, resulting in a lower chance of survival and a higher cost of treatment. This is due to multiple barriers, which include people lack knowledge of how-to recognition symptomatic LC patients and early diagnosis approach missing for asymptomatic ones. Thus, improving these steps are pivotal to reduce the delays in cancer diagnosis and improve cure possibility. Ideally, screening in an asymptomatic at-risk population could increase the chance of recognition cancerous cells, or even pre-cancerous conditions, in a majority of individuals who will results negative to the test. This type of investigation should have five essential characteristics (11): reproducibility, high accuracy associated with real-time analysis, non-invasiveness and low cost of sample collection.

LC development has been associated with deregulated signal transduction and aberrant protein activity and/or function due to genomic aberrations. These metabolic changes resulting from cancer-promoting agents mentioned before determined the transformation of a normal cell into a malignant one. These alterations are progressive, can accumulate over time and are known as the "hallmarks of cancer". As described originally by Hanahan and Weinberg in 2000 (12) the complexities of cancer can be summarized into six major features: self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis. The updating review (13), a decade later, had added reprogramming energy metabolism and evading the immune response. These eight traits underline the complexity of cancer even though, some authors (14,15) reported that other properties, such as invasion or dissemination, should be considered in cancer description.

The research community has struggled to understand the early events leading to cancer development in order to block them at the beginning. In recent years, the focus on tumor–centric molecular profiling has greatly enhanced our understanding of the molecular basis of LC. For instance, the role of EGFR has been intensely studied and nowadays new therapy targeting driven mutation have been established in clinical practice with an extraordinary response. Other subtypes of LC have been characterized for program death receptor 1 (PD-1), which helps the tumor to evade immune checkpoints determined a poor prognosis, nowadays addressed with direct antibodies such as pembrolizumab (16). These discoveries have undoubtedly increased the precision oncology opportunity for patients and clinicians now have the ability to identify the appropriate targeted therapy given a tumor's molecular drivers with a personized attitude. However, tumor–based profiling approaches have only partially contributed to reduced LC death. In particular, resistance to treatment can be due to already present cancer mutations and *de novo* mutations emerged during time treatment. The first can be present in a minor subclone of cells, not sampled before therapy thus not be detectable, and became prominent during selective pressure of therapy (i.e., the death of non-mutated cells). Instead, the mutations developed during therapy can emerge in the long-period in tumor cells. Both clonal evolutions can influence a patient's outcome (17). For instance, the efficacy of EGFR inhibitors can be different into apparently homogeneous patients: this failure has been investigated and one of the major players is the aberrant epigenetic able to reprogramming cell phenotypes and promote intratumoral heterogeneity (18).

In the last decades, thanks to the advent of the next-generation sequencing, liquid biopsy analysis prices have been reduced. Still, genome sequencing for screening large cohort of asymptomatic patients is not applicable. For instance, circulating tumor DNA (ctDNA, i.e., tumor-derived free DNA fragmented in the bloodstream) has been evaluated as an emerged effective tool for LC detection. For instance, a promising test called CancerSEEK (19) was conceived with the idea of assessed mutations in cell-free DNA levels together with circulating proteins. Nevertheless, even if the test was able to distinguish the 70% of eight cancer types (i.e., ovary, liver, stomach, pancreas, esophagus, colon-rectum, lung, or breast) the distinct sensitivity for LC detection was relatively lower. Moreover, even though some study demonstrated that plasma ctDNA mutation can be detected through targeted sequencing, the results for a different stage of the disease is varied. One study (20) demonstrated that ctDNA was detectable in only 47% of patients with stage I disease compared to a more advanced stage of the disease up to 82% (i.e., metastatic patients).

Instead, the incidence of anomalous DNA methylations is higher and increases considering total DNA. This type of

modification is included in the epigenetic area, all chemical changes to the DNA and histones that can be transient or heritable (21). Epigenetic changes can promote the modification of the chromatin structure or the function of the gene without altering the genome directly (22). The epigenome has been considered as the interface between the environment and the genome. DNA methylation has been studied in different body fluids of LC patients, such as sputum, plasma or tissue biopsy (23). For instance, Diaz-Lagares and colleagues in 2016 (24), identified nine cancer-specific hypermethylated genes in formalin-fixed paraffin-embedded tissues, bronchial aspirates and sputum samples of early-stage LC patients. Four of them were used to develop a specific signature with an accuracy of 91%. These results were validated in multiple independent cohorts to maintain a high diagnostic accuracy.

Another type of epigenetics character considered in LC study is microRNA (miRNA), small non-coding RNA of 19 to 24 nucleotides that influence gene activity together with important regulatory roles identifiably inside serum or as exosomes' cargo. Since 2002, miRNAs have been associated with most type of cancer. Tumor cells can release miRNAs inside urine and saliva and serum, as free nucleotides or into vesicles. Classically when detected by imaging examination, tumor lesions already consist of more than 10^9 tumor cells by the time they can be detected by imaging examination, still, their products might be detected earlier. miRNAs have been studied also as potential prognostic and predictive markers (25) and their role in lung development and health have been well summarized recently (26-28).

In conclusion, in the last years, we have witnessed to a shift in global healthcare priorities toward shortening and improving the effectiveness of medical care, from diagnosis to cure. Great advances in translational and preclinical research are being made in molecular profiling of LC development and progression, which have been demonstrated to be useful for new approaches and cure discovery. A multilevel strategy which includes identifying highest–risk subjects considering their profiling characteristics together with understanding cancer etiologies and progression of single individuals are the focused of the next decades. This approach could also find the base of LC patients' heterogeneity could be linked to the multiple signaling events supposed to act at various stages along the carcinogenesis process. Accumulation of genetic alterations (e.g., point mutations, deletions, translocation, and/or amplification) as well as dynamic epigenetic alterations are at the base of LC development growth and spread (29) and new methods able to detect these alterations could allow distinguishing also the pre-malignancy conditions, which can perhaps have only a part of these modifications (30). Even though some promising studies have been recently published (10,31-34), the molecular alterations that occur before cancer manifestation still need to be investigated. The potential diagnostic implications of a deep characterization are tremendous. Understanding of the genetic, epigenetic, signaling, microenvironment, and immune factors that drive the development of cancer, starting through pre-malignancy to invasive cancer, will help to improve early discovery of disease clues and successful treatment.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Shanghai Chest* for the series "A New Era in Lung Cancer Care: from Early Diagnosis to Personalized Treatment". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/shc.2019.11.15). The series "A New Era in Lung Cancer Care: from Early Diagnosis to Personalized Treatment" was commissioned by the editorial office without any funding or sponsorship. GS and RG served as the unpaid Guest Editors of the series. LS serves as an unpaid editorial board member of *Shanghai Chest* from Aug 2019 to Jul 2021. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Li Y, Wu S, Bai F. Molecular characterization of circulating tumor cells-from bench to bedside. Semin Cell Dev Biol 2018;75:88-97.
2. Cancer Research UK. Worldwide cancer statistics. Available online: https://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer
3. Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2016 with focus on leukaemias. Ann Oncol 2016;27:725-31.
4. Aiom. I numeri del cancro in Italia 2019. 1st ed. 2019. Available online: https://www.aiom.it/wp-content/uploads/2019/09/2019_Numeri_Cancro-operatori-web.pdf
5. Hoffman PC, Mauer AM, Vokes EE. Lung cancer. Lancet 2000;355:479-85.
6. Spaggiari L, Casiraghi M, Guarize J, et al. Outcome of patients with pN2 "potentially resectable" nonsmall cell lung cancer who underwent surgery after induction chemotherapy. Semin Thorac Cardiovasc Surg 2016;28:593-602.
7. Gasparri R, Romano R, Sedda G, et al. Diagnostic biomarkers for lung cancer prevention. J Breath Res 2018;12:027111.
8. Goldberg SW, Mulshine JL, Hagstrom D, et al. An actuarial approach to comparing early stage and late stage lung cancer mortality and survival. Popul Health Manag 2010;13:33-46.
9. Brennan P, Hainaut P, Boffetta P. Genetics of lung-cancer susceptibility. Lancet Oncol 2011;12:399-408.
10. Beane JE, Mazzilli SA, Campbell JD, et al. Molecular subtyping reveals immune alterations associated with progression of bronchial premalignant lesions. Nat Commun 2019;10:1856.
11. Mazzone PJ. Obstacles to and solutions for a successful lung cancer screening program. Semin Respir Crit Care Med 2016;37:659-69.
12. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70.
13. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
14. Cantor JR, Sabatini DM. Cancer cell metabolism: one hallmark, many faces. Cancer Discov 2012;2:881-98.
15. Fouad YA, Aanei C. Revisiting the hallmarks of cancer. Am J Cancer Res 2017;7:1016-36.
16. Chargin A, Morgan R, Sundram U, et al. Quantification of PD-L1 and PD-1 expression on tumor and immune cells in non-small cell lung cancer (NSCLC) using non-enzymatic tissue dissociation and flow cytometry. Cancer Immunol Immunother 2016;65:1317-23.
17. Turajlic S, Sottoriva A, Graham T, et al. Resolving genetic heterogeneity in cancer. Nat Rev Genet 2019;20:404-16.
18. Dong N, Shi L, Wang DC, et al. Role of epigenetics in lung cancer heterogeneity and clinical implication. Semin Cell Dev Biol 2017;64:18-25.
19. Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science 2018;359:926-30.
20. Bettegowda C, Sausen M, Leary RJ, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. Sci Transl Med 2014;6:224ra24.
21. Ocak S, Sos ML, Thomas RK, et al. High-throughput molecular analysis in lung cancer: insights into biology and potential clinical applications. Eur Respir J 2009;34:489-506.
22. Quintanal-Villalonga Á, Molina-Pinelo S. Epigenetics of lung cancer: a translational perspective. Cell Oncol (Dordr) 2019;42:739-56.
23. Nunes SP, Diniz F, Moreira-Barbosa C, et al. Subtyping lung cancer using dna methylation in liquid biopsies. J Clin Med 2019. doi: 10.3390/jcm8091500.
24. Diaz-Lagares A, Mendez-Gonzalez J, Hervas D, et al. A novel epigenetic signature for early diagnosis in lung cancer. Clin Cancer Res 2016;22:3361-71.
25. Xu-Welliver M, Carbone DP. Blood-based biomarkers in lung cancer: prognosis and treatment decisions. Transl Lung Cancer Res 2017;6:708-12.
26. Dutta RK, Chinnapaiyan S, Unwalla H. Aberrant microRNAomics in pulmonary complications: implications in lung health and diseases. Mol Ther Nucleic Acids 2019;18:413-31.
27. Bottani M, Banfi G, Lombardi G. Circulating miRNAs as diagnostic and prognostic biomarkers in common solid tumors: focus on lung, breast, prostate cancers, and osteosarcoma. J Clin Med 2019. doi: 10.3390/jcm8101661.
28. Wu KL, Tsai YM, Lien CT, et al. The roles of microRNA in lung cancer. Int J Mol Sci 2019. doi: 10.3390/ijms20071611.
29. Mehta A, Dobersch S, Romero-Olmedo AJ, et al. Epigenetics in lung cancer diagnosis and therapy. Cancer Metastasis Rev 2015;34:229-41.
30. Devarakonda S, Govindan R. Untangling the evolutionary roots of lung cancer. Nat Commun 2019;10:2979.

31. Teixeira VH, Pipinikas CP, Pennycuick A, et al. Deciphering the genomic, epigenomic, and transcriptomic landscapes of pre-invasive lung cancer lesions. Nat Med 2019;25:517-25.
32. Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. Clin Cancer Res 2019;25:4691-700.
33. Kossenkov AV, Qureshi R, Dawany NB, et al. A Gene expression classifier from whole blood distinguishes benign from malignant lung nodules detected by low-dose CT. Cancer Res 2019;79:263-73.
34. Hu X, Fujimoto J, Ying L, et al. Multi-region exome sequencing reveals genomic evolution from preneoplasia to lung adenocarcinoma. Nat Commun 2019;10:2978.

doi: 10.21037/shc.2019.11.15
Cite this article as: Sedda G, Gasparri R, Spaggiari L. Translational new frontiers in lung cancer research. Shanghai Chest 2020;4:16.

