REVIEW ARTICLE

Translating cancer epigenomics into the clinic: focus on lung cancer

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Epigenetic deregulation is increasingly being recognized as a hallmark of cancer. Recent studies have identified many new epigenetic biomarkers, some of which are being introduced into clinical practice for diagnosis, molecular classification, prognosis or prediction of response to therapies. O-6-methylguanine-DNA methyltransferase gene is the most clinically advanced epigenetic biomarker as it predicts the response to temozolomide and carmustine in gliomas. Therefore, epigenomics may represent a novel and promising tool for precision medicine, and in particular, the detection of epigenomic biomarkers in liquid biopsies will be of great interest for monitoring diseases in patients. Of particular relevance is the identification of epigenetic biomarkers in lung cancer, one of the most prevalent and deadly types of cancer. DNA methylation of SHOX2 and RASSF1A could be used as diagnostic markers to differentiate between normal and tumor samples. MicroRNA and long noncoding RNA signatures associated with lung cancer development or tobacco smoke have also been identified. In addition to the field of biomarkers, therapeutic approaches using DNA methylation and histone deacetylation inhibitors are being tested in clinical trials for several cancer types. Moreover, new DNA editing techniques based on zinc finger and CRISPR/Cas9 technologies allow specific modification of aberrant methylation found in oncogenes or tumor suppressor genes. We envision that epigenomics will translate into the clinical field and will have an impact on lung cancer diagnosis/prognosis and treatment. (Translational Research 2017;■:1–17)

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Abbreviations: BAL = bronchoalveolar lavage; ChIA-PET = chromatin interaction analysis with paired-end tag; ChIP-seq = chromatin inmunoprecipitation and massively parallel sequencing; circ-ncRNA = circulating noncoding RNA; CRC = colorectal cancer; CRISPR-Cas9 = clustered, regularly-interspaced short palindromic repeats-associated protein 9; CSC = cigarette smoke condensate; ddPCR = droplet digital PCR; DNMT = DNA methyltransferase; DNMTI = DNA methyltransferase inhibitor; EMT = epithelial-to-mesenchymal transition; HDAC = histone deacetylase; HDACI = histone deacetylase inhibitor; HMA = hypomethylation agents; HMT = histone methyltransferase; lncRNA = long noncoding RNA; miRNA = microRNA; MGMT = O-6-methylguanine-DNA methyltransferase; ncRNA = non-coding RNA; NGS = next generation sequencing; NSCLC = non-smallcell lung cancer; PAM = protospacer adjacent motif; PCa = prostate cancer; PTM = post-translational modifications; SCC = squamous cell carcinomas; SCLC = small-cell lung cancer; sncRNA = short noncoding RNA; THU = tetrahydrouridine; TSG = tumor supresor gene; VEGF-A = vascular endothelial growth factor A; ZFP = zinc finger proteins

INTRODUCTION

It is currently acknowledged that epigenetic alterations play a crucial role in cancer development. Initially proposed by Riggs et al in 1996, the term epigenetics describes "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence." A decade later, Bird proposed a refined definition of epigenetics as "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states."[1] Epigenetic mechanisms include DNA methylation/demethylation, histone modifications, chromatin remodeling, and expression of noncoding RNAs (ncRNAs). Although these changes have been traditionally identified in one-at-a-time experiments, the implementation of novel genome-wide technologies are now producing massive amounts of data that will improve our understanding of tumor development and progression. Moreover, analysis of epigenetic changes in single genes and gene signatures either in tumor specimens or liquid biopsy can be useful in clinical settings for the molecular subclassification of tumors, prognosis, prediction of response to therapy, and follow-up of the patients after therapy.[2] Of particular interest is the detection of epigenomic biomarkers in liquid biopsy using novel ultrasensitive techniques, since this would allow the minimally invasive monitoring of the patients. In addition, recent studies have shown that epigenetic alterations can be targeted not only in hematological malignancies, but also in solid tumors. This review focuses on lung cancer, a type of malignancy that causes the highest number of cancer-related deaths worldwide.[3] Since lung tumors in advanced stages are rarely cured, early detection is critical to improving survival. In the last decade, several clinical trials of annual screening with low-dose computerized tomography have shown a reduction in cancer mortality.[4,5] However, several potential harms have been shown such as the risk of irradiation and overdiagnosis which could affect patients' quality of life, increase patient anxiety, and costs.[6] There is an urgent need to identify and validate biomarkers able to select individuals with a high risk for developing lung cancer. Furthermore, in recent years, targeted therapies and immunotherapy have improved the prognosis of patients with advanced non-small cell lung cancer (NSCLC), even though not all patients respond and those ultimately progress because of the development of resistances. Biomarkers to predict those patients with a higher probability of responding to therapy and those who will develop early resistance are clearly needed. Epigenetic biomarkers, either in combination with genetic biomarkers or alone, may offer a great opportunity for better monitoring and managing of patients.

EPIGENETIC PLAYERS: DNA METHYLATION, HISTONE MODIFICATIONS, AND NONCODING RNAS

DNA methylation. Among epigenetic marks, DNA methylation is by far the most widely studied. It is a covalent modification at the 5' carbon of cytosines catalyzed by a family of enzymes: the DNA methyltransferases (DNMTs). Whereas DNMT1 recognizes hemimethylated DNA and is classified as maintenance methyltransferase, DNMT3a and DNMT3b can introduce methylation marks without a template and are therefore termed de novo methyltransferases. Deviations in DNA methylation patterns can occur via gain (hypermethylation) or loss (hypomethylation) of methylation marks with respect to methylomes defined as normal.[7] In a cancer context, hypermethylation at CpG islands of gene promoters is associated with the repression of tumor suppressor gene (TSGs) expression.[8,9] Conversely, genome-wide hypomethylation in cancer cells has been linked to expression of proto-oncogenes, genomic instability,[10] and malignant transformation of tumors; a feature that increases with cancer progression.[11]