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The Cancer Control Challenge:
Better Understanding It to Better Face It

OVERVIEW OF lncRNA EXPRESSION IN NON-SMALL CELL LUNG CANCER REVEALS PATHWAYS FAVORABLE TO ADVANCE THE FIELD CANCERIZATION

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Introduction: Lung cancer, especially non-small cell lung cancer (NSCLC), is a major public health concern and the leading cause of cancer-related mortality worldwide. Dysregulated long non-coding RNAs (lncRNAs) can influence gene signaling networks, contributing to tumorigenesis. Recent research in LC has increasingly focused on lncRNAs as promising candidates for biomarker identification. Objectives: to identify potential lncRNAs as biomarkers and pathways involved in the cancerization field of NSCLC. **Objectives:** to identify potential lncRNAs as biomarkers and pathways involved in the cancerization field of NSCLC. **Methods:** Samples from lung cancer patients treated at reference hospital were divided into two groups: Tumoral (n=18) and adjacent (n=9), with sample collection approved by Ethics and Research Committee (CAAE_41667021.4.3001.0017). Total RNA was extracted using the Biospin Total RNA Extraction II kit (BioFlux), and library preparation for sequencing was performed with the TruSeq Stranded Total with Ribozero (Illumina) kit. The NGS platform used was the Nextseq 500/550 (paired-end, Illumina). Read quality assessment was conducted using the Fastp software (Minimum QV > 15). Transcript reads were aligned using the Salmon program, utilizing the "gencode.43.complete" index for human coding and non-coding transcript information. Data manipulation, statistical analysis, differential expression (DE), and generation of graphs were performed using the RStudio software with packages including tximport, DESeq2, ggplot2, and ComplexHeatmap. To select the best biomarkers, pROC (AUC > 0.9) was used. Functional enrichment of lncRNAs was generated through the ClusterProfiler package (GSEA), with "Hallmarks" category. **Results:** 1,147 DE lncRNAs were identified, of which 447 were down-regulated and 700 were up-regulated. PCoA analysis showed that the groups have significantly different expression profiles (PERMANOVA; p-value = 0.001). Of the total DE transcripts, the ROC curve classified 58 DE transcripts, which formed three clusters in a heat map and were

used in subsequent analyses. Cluster 1: containing 30 lncRNAs (such as *SFTA1P*, *FENDRR*) down-regulated in the tumor and up-regulated in the adjacent tissue, being involved in gene regulation processes, response to oxidative stress and inflammation; Cluster 2 and 3: having 12 (such as *CASC19*, *DDX11-AS1*) and 16 transcripts (such as *ZFPM2-AS1*), respectively, in which both are hyperregulated in the tumor and low, in the adjacent region, whose functionalities are linked to cell proliferation/metastasis promotion (cluster 1) and modulation of miRNAs, metastasis, epigenetic control, and modulation of inflammation (cluster 2). Furthermore, among the most expressive biological pathways in the transcriptomic data are: TNFA/NFKB, comprising the majority of non-coding transcripts; inflammatory response; IL6/JAK-STAT3 signaling; IFN Gamma; EMT process; KRAS signaling. **Conclusion:** The results of this study reveal the central role of lncRNAs in the regulation of critical pathways associated with inflammation, cell proliferation, epigenetic control and miRNA modulation in tumor and adjacent tissues, evidencing their active participation in the cancerization process. The functional distinction between the identified clusters suggests that changes in the expression profile of lncRNAs are not restricted to the tumor, but also affect adjacent regions, contributing to a microenvironment conducive to tumor progression. These findings expand the understanding of the molecular mechanisms involved in the initiation and progression of lung cancer, positioning lncRNAs as potential biomarkers and promising therapeutic targets in oncology.

Keywords: lung cancer; transcriptomics; lncRNA; biomarkers; biological pathways.