Emerging mechanisms in the chromatin-remodeling complex in pulmonary carcinoids: novel opportunities for the discovery of biomarkers and therapeutics tools.

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Pulmonary carcinoids comprise a heterogeneous group of rare tumors that entail complex management and treatment, mainly due to their difficult and late diagnosis. In the last years, the incidence of these tumors has increased worldwide. Despite the recent advances in defining the genomic and transcriptomic landscape of lung carcinoids, the molecular underpinnings behind their development and clinical behavior await elucidation. Interestingly, known components of the chromatin-remodeling pathway, such as MEN1, PSIP1 and ARID1A, comprise the most frequently mutated genes in pulmonary carcinoids. Chromatin remodeling is a key molecular process that, by opening and closing the chromatin structure, regulates gene expression, by allowing or preventing the binding of proteins responsible for DNA transcription. It has been suggested that inactivation of chromatin-remodeling is sufficient to drive transformation; however, the precise mechanisms that link mutations in those genes with the development of pulmonary carcinoids are not known. In particular, the potential role of posttranscriptional, downstream mechanisms involving RNA regulation in this context are largely unexplored. Therefore, the main objective of this work was to further explore the role of chromatin-remodeling regulation in lung carcinoids, focusing particularly on gene mutations and RNA processing.

To pursue our objective, we have analyzed RNAseq data from two cohorts, the first cohort comprised 20 lung atypical carcinoids (EGAS00001003699) and the second cohort integrated 30 typical and atypical carcinoids (SRP156394). We applied a biocomputational approach to interrogate the potential influence of the dysregulation of the selected genes on global transcriptomics patterns using Tuxedo pipeline. Additionally, we explored the potential associations between the genes that are likely dysregulated by mutations and other factors that contribute to RNA processing; specifically, we used SUPPA2 to interrogate the potential influence of the dysregulation of the selected factors on global splicing patterns.

We observed a clear dysregulation in the pattern of expression of genes related with chromatin-remodeling pathways in the tumor samples from patients harboring mutations in genes that belong to those complexes. Then, mutations in specific genes (e.g., ARID1A) may exert an influence in the expression of a discrete set of components of their related chromatin-remodeling pathway. Moreover, by analyzing the relationship of the altered genes with specific changes in functional categories and gene enrichment, we discovered that the mutations studied likely impact on cell homeostasis by modulating the function of the specific machinery comprised by those complexes, and thereby altering key peripheral regulatory systems targeting previously unrelated mechanisms such as metabolic balance. Furthermore,

samples harboring mutations in chromatin-remodeling pathway components displayed altered patterns of splicing and pointed to dysfunctional RNA processing machinery as a novel target potentially mediating the oncogenic actions of alterations of this pathway.

In conclusion, this work demonstrates the ability and suitability of biocomputational approaches for the identification of alterations and associations in key cellular machineries that hold potential for the discovery of novel diagnostic and/or therapeutic tools in pulmonary carcinoids. Ongoing efforts are aimed at validating the results unveiled by computational techniques through functional studies.