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

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INTRODUCTION

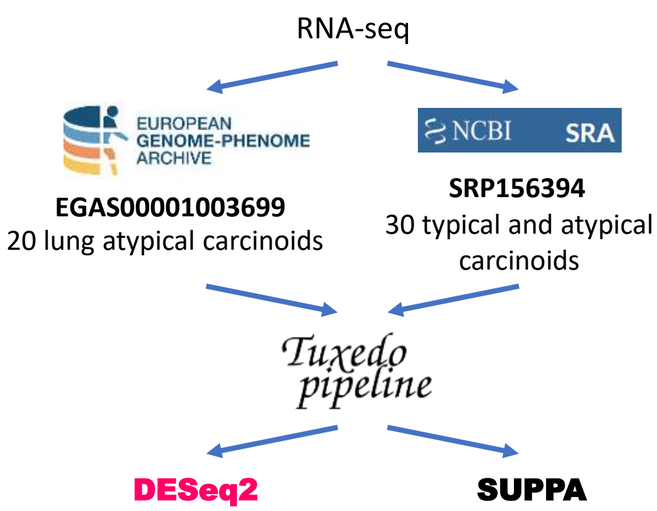
BACKGROUND

Pulmonary carcinoids (PC) comprise a heterogeneous group of rare tumors that entail complex management and treatment. Interestingly, known components of the chromatin-remodeling (CR) pathway, such as *MEN1*, *PSIP1* and *ARID1A*, comprise the most frequently mutated genes in PC. CR 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 CR is sufficient to drive transformation; however, the precise mechanisms that link mutations in those genes with the development of PC are not known.

MAIN OBJECTIVE

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.

MATERIALS AND METHODS



RESULTS

A clear dysregulation was observed in the pattern/level of expression of genes related with chromatin-remodeling pathways in tumor samples from patients harboring mutations in genes that belong to those complexes (**Fig. 1**).

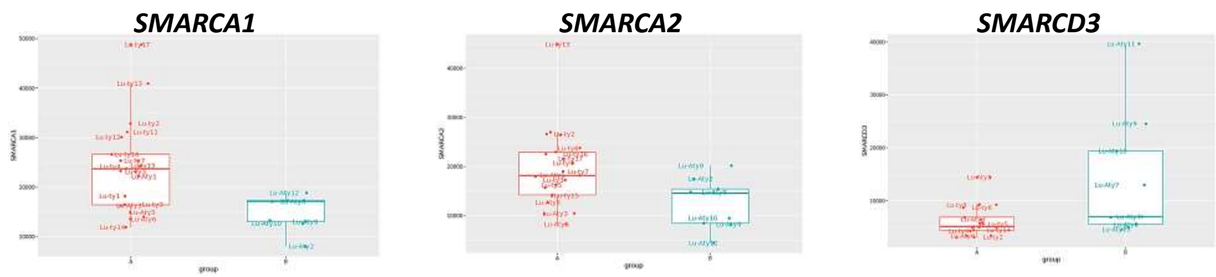


Figure 1. Chromatin-remodeling expression in tumor samples harboring mutations in genes that belong to those complexes. *SMARCA1* and *SMARCA2* are downregulated in patients without mutations in the CR complex (p = 0.0004 and p = 0.0085). *SMARCD3* is upregulated in patients with mutations in the CR complex (p = 0.08).

Analysis of genes involved in RNA regulation revealed differences in expression levels between samples with alterations in genes related with chromatin-remodeling complexes and without these alterations. Specifically, we observed marked differences in the profile/levels of expression of key genes related with splicing. (**Fig. 2**).

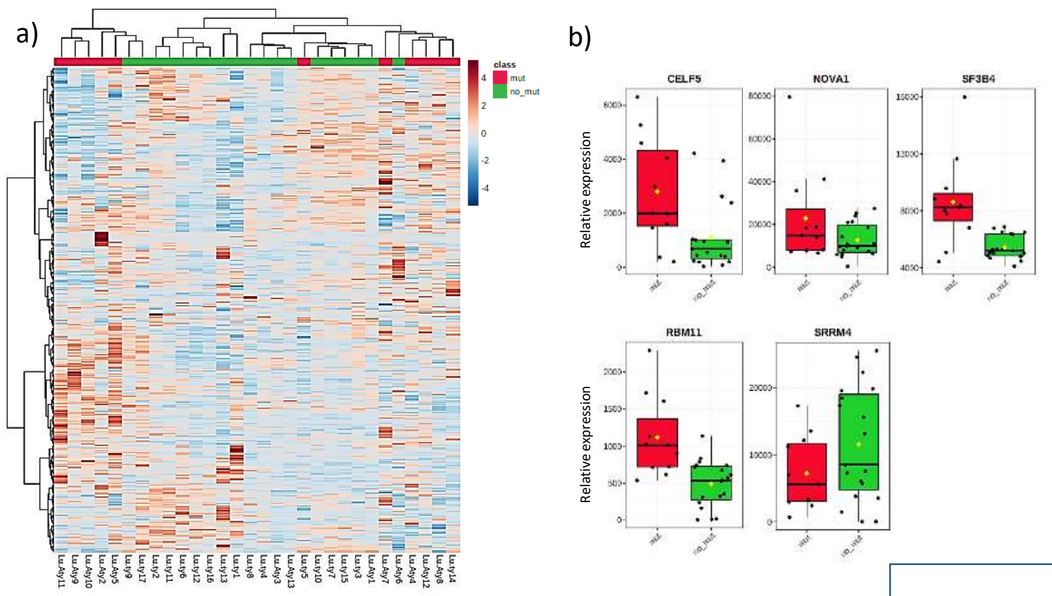


Figure 2. Transcriptional signature of splicing-related genes depending on mutational status in genes of Chromatin-remodeling complexes. Red class are mutated and green class non-mutated samples. a) Heatmap that revealed a dysfunctional RNA processing machinery in samples harboring mutations in chromatin-remodeling complexes. b) Altered expression in splicing factors as *CELF5*, *NOVA1*, *SF3B4*, *RBM11* and *SRRM4* associated to alterations in genes related with chromatin-remodeling complexes.

CONCLUSIONS AND NEXT STEPS

- 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.

ACKNOWLEDGEMENTS

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