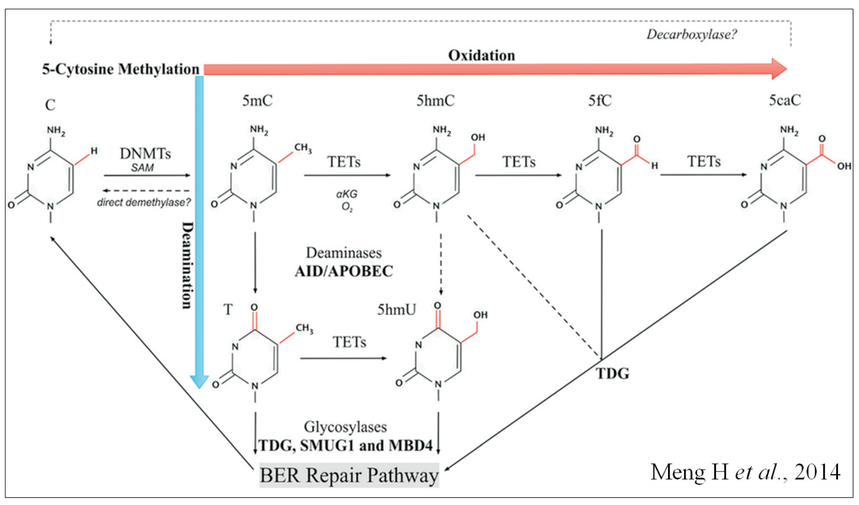
CHARACTERIZATION OF THE EXPRESSION PROFILE OF APOBEC AND TET FAMILIES IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Nicolau, MC[1]; Neto, PN[1]; Santos, PTS; Simão, TA[2]; Pinto, LFR[1,2]; Lima, SCS[1]

[1] Programa de Carcinogênese Molecular– CPQ – Instituto Nacional de Câncer, Brazil;
[2] Departamento de Bioquímica – IBRAG – Universidade do Estado do Rio de Janeiro, Brazil.

INTRODUCTION

- Esophageal squamous cell carcinoma (ESCC) is one of the main histological types of esophageal cancer worldwide and in Brazil[1,2]. Although its high incidence and mortality rates, the mechanisms that lead to ESCC development are still poorly understood[3].
- Alterations of DNA methylation are a common event in ESCC and may preceed the first genetic alterations, however what leads to this deregulation is still unkown4. The specific pattern of DNA methylation depends on the balance between methylation and demethylation processes[5].
- More recently, APOBEC proteins (cytidine deaminases), related to the generation of genetic variability, have also been implicated in active DNA demethylation[6] as well as TET proteins, which are involved in the hydroxylation of 5-methylcytosine[7]. Besides, an APOBEC-mediated mutational signature in ESCC suggests that APOBEC-catalyzed deamination provides a source of mutations in ESCC[8].



OBJECTIVE

- To evaluate the expression profile of APOBECs and TETs in ESCC and the functional consequences of their possible deregulation

HYPOTHESIS

Deregulation of the APOBECs and TETs in ESCC

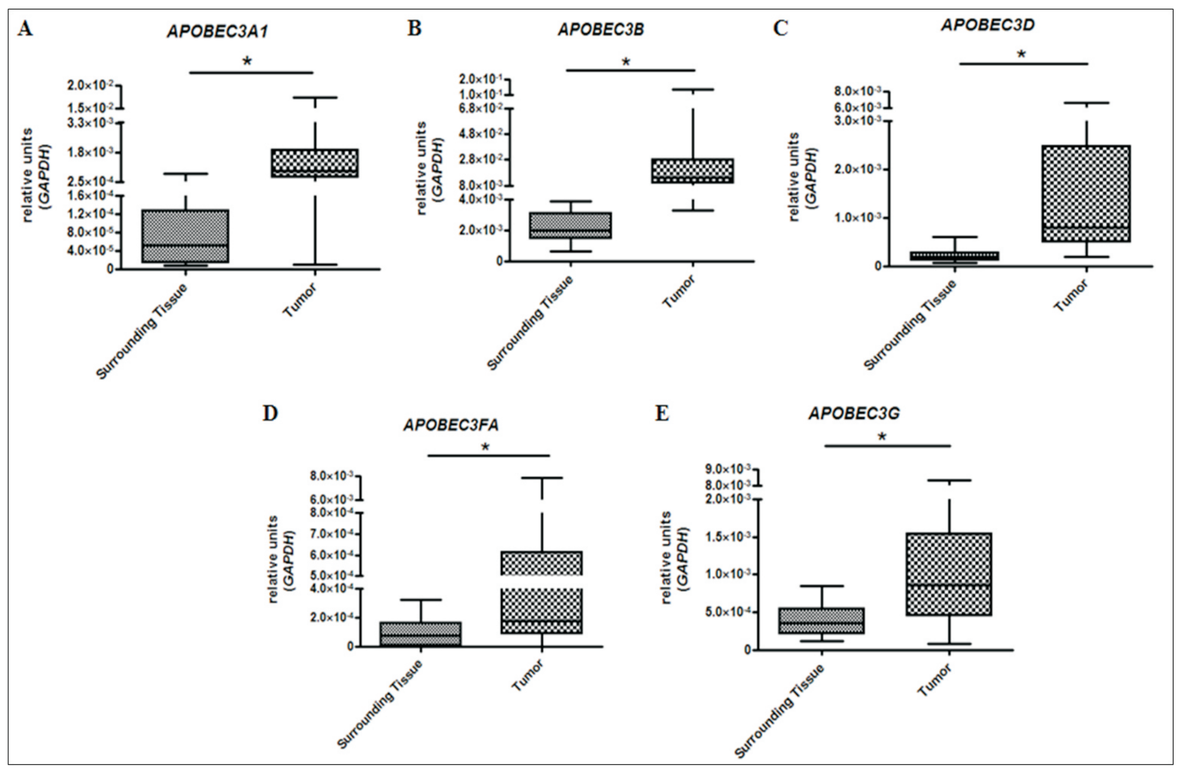
→ Mutational signature C>T; C>G

→ Global demethylation

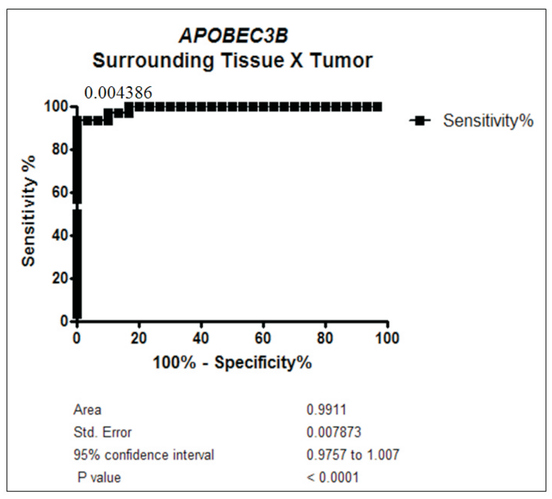
METHODOLOGY

- The mRNA expression of APOBECs and TETs was determined by RT-qPCR in tumor and matched surrounding non-tumor tissue from 30 patients with a confirmed diagnosis of ESCC;
- A receiver operating characteristic (ROC) curve was plotted for the use of gene expression as a marker to distinguish normal-appearing surrounding mucosa and tumor tissue;
- *TP53* mutations were evaluated by NGS in ESCC and correlated with APOBECs expression.

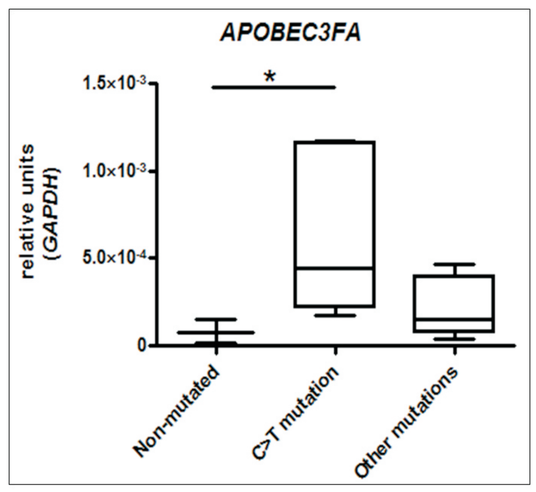
RESULTS



Evaluation of *APOBECs gene* expression in ESCC patients. Evaluation by RT-qPCR of the mRNA expression of *APOBEC3A1* (A), *APOBEC3B* (B), *APOBEC3D* (C), *APOBEC3FA* (D) and *APOBEC3G* (E) in non-tumor surrounding mucosa and tumor tissue from ESCC patients. * p<0.0001, Wilcoxon signed rank test.

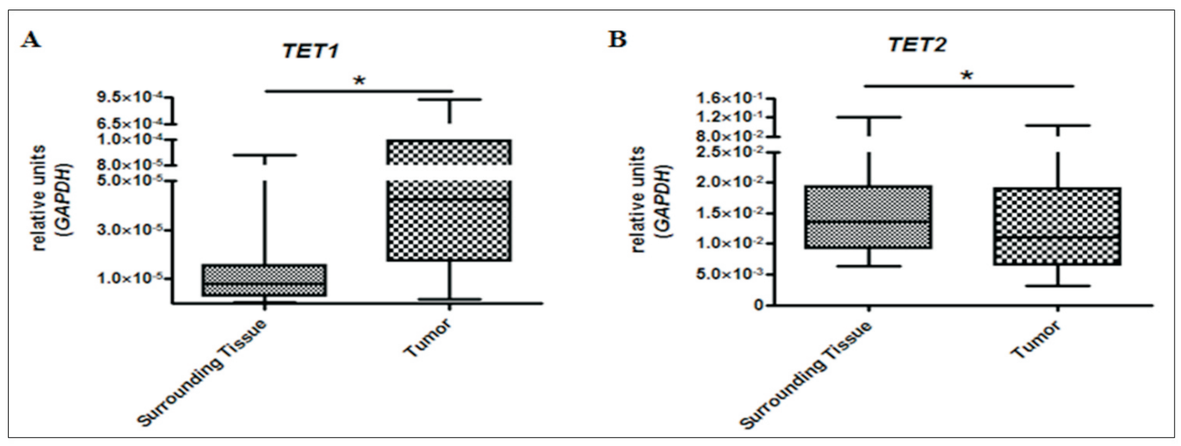


Receiver operating characteristic (ROC) curve for the discrimination of normal-appearing surrounding mucosa and tumor tissue of ESCC patients, according to *APOBEC3B* expression. For an *APOBEC3B* expression cut-off of 0.004386, the area under the curve (AUC) was 0.9911, with a sensitivity of 93.33% and a specificity of 100%, p<0.0001.



Association of *TP53* mutation type with *APOBEC3FA* expression. The overexpression of *APOBEC3FA* was associated with C>T *TP53* mutations.*p=0.0287, Kruskal Wallis test and Dunn's post-test.

The most common *TP53* mutations were AT>GC (41%) followed by CG>TA (28%).



Evaluation of *TETs gene* expression in ESCC patients. Evaluation by RT-qPCR of the mRNA expression of *TET1* (A) and *TET2* (B) in non-tumor surrounding mucosa and tumor tissue from ESCC patients. * p<0.05, Wilcoxon signed rank test.

CONCLUSION

- The deregulation of the APOBEC family of genes is a common feature in ESCC and may be associated with the occurrence of *TP53* mutations.

REFERENCES

1. Parkin DM, et al (2005). CA Cancer J Clin. 55(2):74-108;
2. INCA. Estimativa 2016/2017: Incidência de Câncer no Brasil. Instituto Nacional de Câncer José Alencar Gomes da Silva, Coordenação de Prevenção e Vigilância. Rio de Janeiro: INCA, 2016 [Internet]. Available from: http://www.inca.gov.br/wcm/dncc/2015/index.asp, accessed on 2016 Jan 7.
3. Napier KJ, Scheerer M, Misra S. (2014). World J Gastrointest Oncol. 6(5):112-20;
4. Lima SC, et al (2011). Epigenetics. 6(10):1217-27
5. Ciesielski P, et al (2015). Postepy Hig Med Dosw (Online).69:1371-83.
6. Knisbacher BA, Gerber D, Levanon EY. (2016). Trends Genet. 32(1):16-28.
7. Tahiliani M, et al (2009). Science. 324(5929):930-5.
8. Zhang L, et al (2015). Am J Hum Genet. 96(4):597-611.
9. Meng H et al (2014). Int J Mol Sci. 15(12):22604-25.

Funding source: Ministério da Saúde, FAPERJ.

Projeto Gráfico: Serviço de Edição e Informação Técnico-Científica / INCA

Ministério da Saúde

GOVERNO FEDERAL BRASIL PÁTRIA EDUCADORA