Helicase-like Transcription Factor (HLTF) expression in Non Small Cell Lung Cancer (NSCLC) is associated with a poor prognosis.

Dhont L.1,2, Pintilie M.3, Kaufman E.3,4, Navab R.5, Tom S.6, Shepherd F.1, Burny A.3, Belayew A.3, Yao MS.2,4, Mascaux C.2,4-6
1 Laboratory of Molecular Biology, Université de Mons, Mons, Belgium; 2 Laboratory of Medicine and Pathobiology and 4 Biostatistics department, University of Toronto, Toronto, Canada; 3 Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada; 4 Université Libre de Bruxelles (ULB), Brussels, Belgium.

Introduction

HLTF is a Tumor Suppressor Gene

→ HLTF promoter hypermethylation in gastric and colon cancers

HLTF and lung cancer (NSCLC)

Methylation of the HLTF promoter

21/53 (39.6%) patients:
• 7/12 (58.3%) adenocarcinoma
• 9/20 (45.0%) squamous cell carcinoma

→ Shorter survival when HLTF is hypermethylated vs. Hypomethylated (p=0.035)

Only ONE study was carried out

No data on HLTF form expression in NSCLC

HLTF is located in 3q25.1-26.1, an area in which genes are frequently amplified in lung squamous cell carcinoma

Objectives

Alterations in HLTF expression have shown a clinical relevance in various types of cancer. Our aim is to assess the expression of wild-type (WT) and spliced forms (I21R) of HLTF mRNA in a cohort of 171 patients with resected stage I-II NSCLC.

In silico analyses

Genomic profiling data (mutation, copy number, DNA methylation, and mRNA expression)

The Cancer Genome Atlas

For HLTF in NSCLC

(Lung adenocarcinoma and Lung squamous cell carcinoma) were downloaded and analysed from:

http://cancer.sanger.ac.uk/cosmic

In silico analyses: HLTF alterations in Lung cancer

Lung adenocarcinoma

Lung squamous cell carcinoma

Mutations

Methylation

Copy Number Alterations

Results

HLTF expression by RT-ddPCR

Association of HLTF expression with clinical factors

HLTF WT and HLTF I21R expressions and their relative expression (ratio WT/I21R and groups of co-expression) were tested for their association with patient clinical factors (age, sex, histology and stage). No significant association was shown.

Conclusion

By in silico database analysis, HLTF alterations were found more frequently in lung squamous cell carcinoma than in lung adenocarcinoma. Those alterations include mutations, copy number alterations, methylation and mRNA expression modifications. Using cell lines and patient samples, expression of both HLTF WT and variant (I21R) forms were detected in NSCLC. The combination of a low HLTF WT expression with a high HLTF variant I21R expression is associated with a poor DFS both in univariate and multivariate analyses. These findings endorse our hypothesis that HLTF variant I21R expression could be a predictor of poor outcome for patients.

Acknowledgements

L. D. is a F.R.S.-FNRS Research fellow. C.M. is a Télévie (F.R.S.-FNRS) Research Associate. We acknowledge funding from the « Fonds National de la Recherche Scientifique » (FNRS), from « Télévie » and from the « Fonds pour la Recherche Médicale dans le Hainaut » (FRMH). We thank C. Lachance, Ph.D., (Biorad Canada) for his help in ddPCR.