American Thyroid Association

View Abstract

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TITLE: A role for the small GTPases RAC1 and RAC1b in the modulation of NIS expression: potentiation of therapy with radioactive iodine in differentiated thyroid carcinoma.

PRESENTATION TYPE: Basic : 1. Poster Preferred

PRESENTATION PREFERENCE: 1. Poster Preferred

CURRENT CATEGORY: Thyroid Cancer

AUTHORS (LAST NAME, FIRST NAME): Faria, Marcia[1, 3]; Félix, Daniela[1, 2]; Domingues, Rita[1, 2]; Bugalho, Maria J.[1, 5]; Matos, Paulo[4, 3]; Silva, Ana L.[1, 2]

INSTITUTIONS (ALL): 1. Serviço de Endocrinologia, Hospital de Sta Maria-CHULN. EPE, Lisboa, Portugal.
2. ISAMB- Instituto de Saúde Ambiental, Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal.
3. BioISI- Biosystems and Integrative Sciences Institute, Faculdade de Ciências da Universidade de Lisboa, Lisboa, Portugal.
4. Departamento de Genética Humana, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa, Portugal.
5. Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal.

KEYWORDS: RAC1, NIS, radioactive iodine, RAC1b.

ABSTRACT BODY:

Introduction or Background: The Sodium Iodide Symporter (NIS) is responsible for active transport of iodide into thyroid follicular cells. The retention of its functional expression in most of the well-differentiated thyroid carcinomas (DTCs) enables the use of radioactive iodine (RAI) for treatment of metastatic disease. Still, about 30% of patients with advanced forms of DTC became refractory to RAI which makes their management very challenging. The main reason for impaired iodide uptake in refractory-DTC is the defective functional expression of NIS. Several molecular players have been described as critical for TSH-induced NIS expression, an example being the p38 mitogenic kinase. In breast cancer cells, the small GTPase RAC1 was shown to mediate the positive impact of p38 kinase activity on NIS expression. We, on the other hand, have previously shown that overexpression of RAC1b, a tumor-related splicing variant of RAC1, is associated with worse outcomes in DTC and correlates with the MAPK-activating BRAFV600E mutation, which has been related to the loss of NIS. Since RAC1 and RAC1b may act in an antagonistic fashion to regulate specific cellular responses, we asked if RAC1b would be implicated in NIS downregulation observed in DTCs.

Methods Section (for Abstracts) or Case Presentation Section (Case Reports): NIS expression levels were analyzed by RT-qPCR in a RAC1/RAC1b expression model system developed in non-transformed thyroid cell lines. A non-radioactive iodide influx assay was used to confirm the impact of RAC1-signaling on the efficacy of iodide uptake.

Results Section (Abstracts) or Discussion Section (Case Reports): We demonstrate that ectopic overexpression of RAC1b is sufficient to decrease TSH-induced NIS expression, antagonizing the positive effect of RAC1 GTPase. Moreover, we clearly document, for the first time in thyroid cells, that both NIS expression and iodide uptake are downregulated upon RAC1 inhibition, supporting the role of canonical RAC1 signaling in promoting TSH-induced NIS expression.

Conclusion (Abstracts): Our findings provide evidence that RAC1 and RAC1b signaling are implicated in the regulation of NIS expression in thyroid cells and suggest that RAC1b overexpression may be one of the mechanisms contributing to the low levels of NIS observed in some subgroups of DTCs, antagonizing RAC1 stimulatory effect on the TSH/cAMP-mediated induction of NIS expression.

Disclosure of Relevant Financial Relationships (AS): No - no financial relationships or commercial interests

Faculty Disclosure Terms and Conditions (AS): I agree to the Terms and Conditions

Extra Info: Ana Luísa Silva:12/06/2019

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Clinical Thyroidology Trainee Case Reports and Visual Abstracts Program : (none)

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