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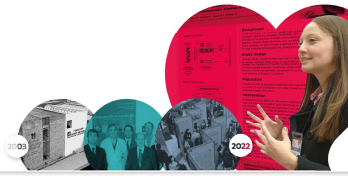

Determination of metabolomic profiles related to pathogenesis, prognosis ,and recurrence in differentiated thyroid tumors: A non-targeted metabolomic analysis of tumor tissues.

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INTRODUCTION

Well differentiated thyroid tumors

The differentiated thyroid cancer (DTC) is characterized by its biological heterogeneity and variability in clinical outcomes. Is the most common malignant endocrine neoplasm and constitutes 1-2% of all cancers. The diagnostic classification tools are still invasive and late (1,2).

Worldwide thyroid cancer incidence:
6.6 Colombian thyroid cancer incidence: 9.1 Mortality rate: 0.74.

In 2018, 114 new cases of thyroid cancer in male population were presented and 512 in female population (5).

It has a high variability of recurrence risk according to pathological and clinical characteristics

ATA Classification for recurrence risk (Stratification system)

Low risk: PTC, which is M0, was completely removed, does not have aggressive histology, clinical N0 or <5 N1 micro metastasis --> Inetrathyroidal (3).

Intermediate risk: PTC with vascular invasion, microscopic invasion in perithyroidal tissue, aggressive histology, clinical N1 or >5 N1 with all lymph nodes involved, *ETE and BRAF known mutations (3).*

High risk: FTC with extensive vascular invasion macroscopic invasion of perithyroidal soft tissues, incomplete tumor resection, distant metastasis and postoperative serum thyroglobulin, pathologic N1 (3).

OBJETIVE

Establish metabolomic profiles related to the development, prognosis and recurrence of DTC by using non- targeted metabolomics analysis in tumor tissues.

METHODOLOGY

- Samples were collected from patients treated in "Hospital Universitario Mayor – Mederi" diagnosed with thyroid cancer
- 29 samples were classified according to the ATA recurrence risk stratification system
- Samples were cryopreserved and subsequently sent for analysis
- The samples were analyzed by gas chromatography couple to a mass spectrometer (GC-MS) in Metcore center.
- *Quality of metabolites* was assured using the coefficient of variation in the metabolites in the QC samples, being less than 20%.
- Once the metabolites were obtained a multivariated and univariated analysis was carried out, in order to determine the differences between the metabolic profiles between the groups of low, moderate and high risk.
- Metabolites were obtained from univariate analysis and corrected with the Benjamini- Hochberg
- Therefore, we analyze through ROC curves the metabolites from the univariated analysis
- The metabolic pathways of the metabolites with significant difference in the univariated analysis were identified through MetaboAnalyst 5.0.

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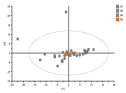
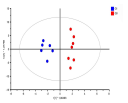




MetaboAnalyst 5.0

RESULTS

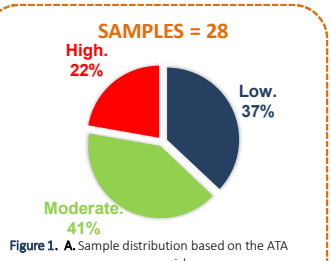
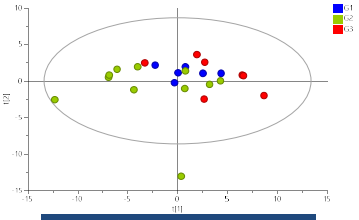


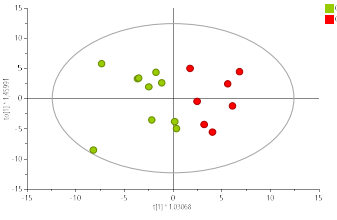
Figure 1. A. Sample distribution based on the ATA recurrence risk.

Figure 2A PCA SAMPLE



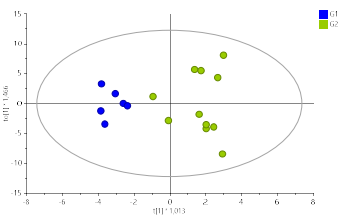
R²=0.726, Q²=0.456

Figure 2C OPLS-DA R2X=0.596



R2X=0.694 Y Q2=0.462
CV-ANOVA=0.093

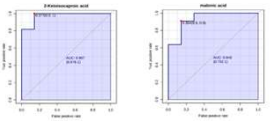
Figure 2B OPLS-DA R2X=0.596



R2X=0.593, Q2=0.149c
CV-ANOVA=0.720

Metabolite	Fold Change	p-value*
Amino acids, peptides, and analogues		
Mimosine	2,54	2.93E-02*
Carboxylic acids and derivatives		
malonic acid	2,68	2.50E-02*
Fatty Acids		
Stearoylglycerol	1,52	2.22E-02*
Suberic acid	1,63	2.75E-02*
Lauric acid	1,61	2.75E-02*
Octanoic acid	1,91	2.22E-02*
pimelic acid	1,73	2.98E-02*
Myristic acid	1,86	2.22E-02*
Hydroxy acids and derivatives		
Gulonic acid	3,43	3.66E-02*
Lactic acid	2,03	2.22E-02*
Hydroxybutyric acid	4,12	3.66E-02*
Keto acids and derivatives		
3-methyl-2-oxobutanoic acid	1,47	2.98E-02*
Ketoisocaproic acid	3,72	1.33E-02*
Alpha Ketoglutaric acid	4,74	3.66E-02*
Organic phosphoric acids and derivatives		
Phosphorylethanolamine	3	3.13E-02*
Organooxygen compounds		
Ribose	2,49	2.93E-02*
1,5-anhydro-D-sorbitol	4,87	2.50E-02*
Maltose	1,49	2.75E-02*
Myo-Inositol	2,14	2.75E-02*
Hydroxybenzaldehyde	1,3	2.98E-02*
Phosphoglyceric acid	4,21	3.66E-02*
Purines and purine derivatives		
Hypoxanthine	3,99	4.47E-02*
Ribothymidine	2,7	2.50E-02*

Figure 3 ROC CURVE (AUC>0.9)



The metabolites with AUC > 0.9 in the ROC curve were:

- 2-ketoisocaproic acid
- Malonic acid
- Ribothymidine
- Octanoic acid
- 2-stearoylglycerol
- 1,5-anhydro-D-sorbitol
- Lactic acid
- Myristic acid

Pathway Name
Ascorbate and aldarate metabolism
Valine, leucine and isoleucine biosynthesis
Valine, leucine and isoleucine degradation
Fatty acid biosynthesis
D-Glutamine and D-glutamate metabolism

- 28 of the 29 samples were analyzed.
- Results with multivariated analysis did not have a significant p value with ANOVA test
- A greater difference between the metabolites present in the high and moderate risk group was evidenced.
- 8 metabolites were found to have a AUC>0.9 in the ROC curves.
- Pathway analysis using MetaboAnalyst 5.0 showed five significant pathways.

CONCLUSION

1. The group in which the greatest number of significant differences in metabolites were observed was between high and moderate recurrence risk.
2. The metabolites that showed the greater variation between the moderate and high-risk groups were Ascorbate and aldarate metabolism, Valine, leucine and isoleucine biosynthesis, Valine, leucine and isoleucine degradation, Fatty acid biosynthesis.
3. Our findings are consistent with previously reported upregulated pathways α-Ketoglutaric acid and Hydroxybutyric acid[4].
4. Metabolomics represents a promising tool for the identification of patients at high risk of recurrence in patients with DTC who are deficient in post-surgical adjuvant therapy.

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