WITH CYSTEAMINE, THE PROTEOME OF A PATIENT WITH CYSTINOSIS APPROACHED THE PROFILE OF A HEALTHY CONTROL

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INTRODUCTION:

- Cystinosis is a rare genetic disease causing end-stage renal disease, hypothyroidism, diabetes and myopathy.
- Treatment with cysteamine improves survival and quality of life.
- Additional studies demonstrating the benefits of cysteamine in patients with renal failure already established and few extra-renal symptoms can improve adherence to cysteamine and access to this medication

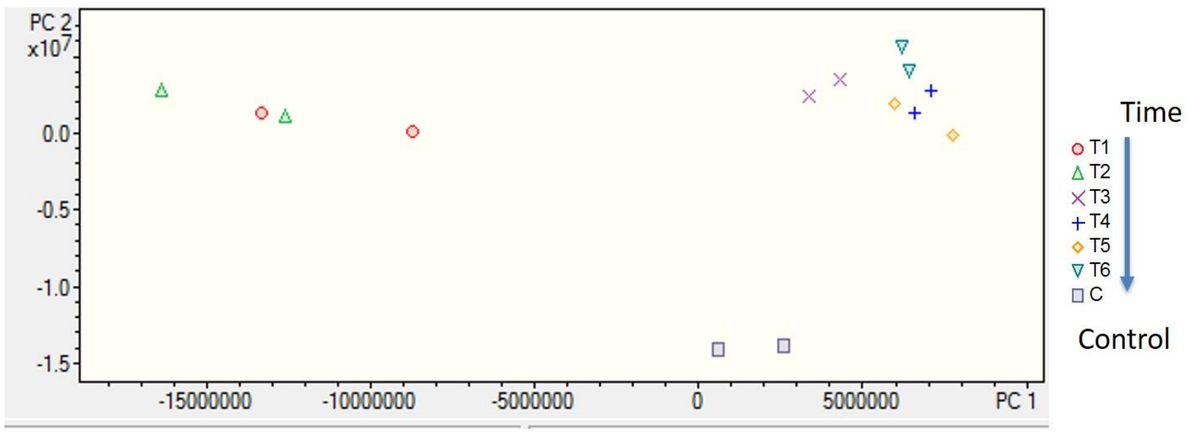
WE AIM TO COMPARE THE PROTEOME OF A PATIENT WITH CYSTINOSIS TAKING CYSTEAMINE WITH:
1) THE PROTEOME OF THE PATIENT BEFORE STARTING MEDICATION; 2) THE PROTEOME OF A HEALTHY CONTROL.

METHODS:

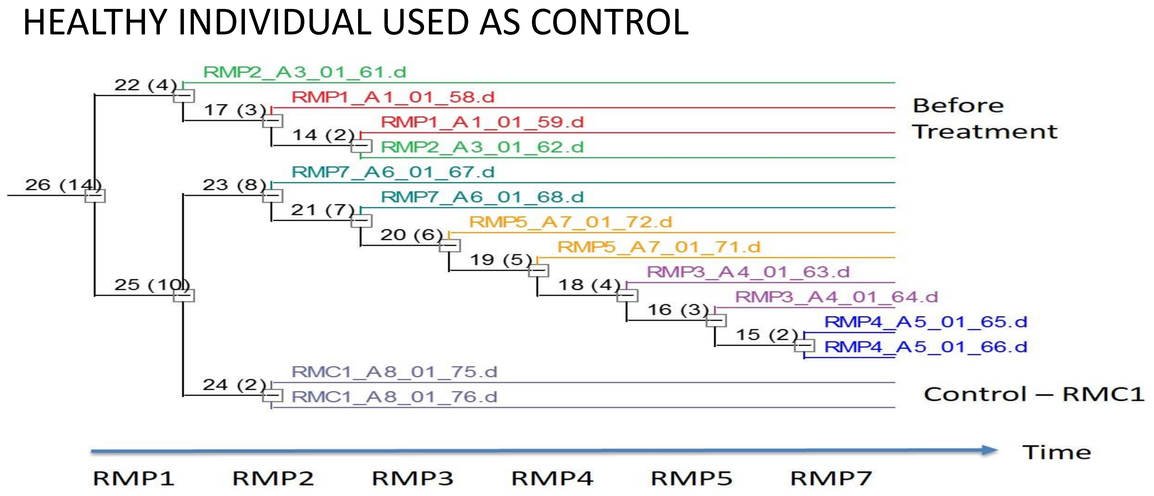
- PATIENT: 40 year-old male patient; late-onset naïve-treated cystinosis; on dialysis since the age of 18, second kidney transplant at the age of 27, normal serum creatinine; hypothyroidism
- CONTROL:
  - 38 year-old male, donor of the kidney graft; HLA-identical non-twin sibling of the patient; healthy
- SERUM SAMPLE COLLECTION:
  - 1 month before and after starting cysteamine (months 1, 4, 7, 10 and 14); Control: month 7
- PROCEDURES:
  - Plasma depletion; centrifugal ultrafiltration of urine
  - Determination of the total amount of protein
  - Reduction, alkylation and digestion of samples
  - Proteomic analysis: liquid chromatography + mass spectrometry
- COMPARISON OF PROTEINS:
  - Global analysis: Principle Component Analysis + Unsupervised Hierarchical Clustering
  - Identification of changing proteins, defined by:
    - p-value < 0.05 when comparing the relative amount of protein present before therapy with the amount present in the healthy control AND
    - p-value ≥ 0.05 on all time points after cysteamine was started when comparing with the relative amount of protein present in the healthy control

RESULTS - GLOBAL ANALYSIS

After beginning cysteamine, the serum proteome of the patient with cystinosis became INCREASINGLY DIFFERENT FROM THE PROTEOME BEFORE STARTING THERAPY



The proteome of the patient became CLOSER TO THE PROTEOME OF A HEALTHY INDIVIDUAL USED AS CONTROL



Protein that increase in serum after treatment	Acession	Before cysteamine (Mean mass ± SD)	Control (Mean mass ± SD)	p-value (before vs control)	p-value* (after vs control)
Ig heavy chain V-III region TIL	HV304_HUMAN	1.17 ± 0.03	2.48 ± 0.08	0.02	0.13-0.99
Ig heavy chain V-III region BRO	HV305_HUMAN	1.82±0.04	2.25±0.08	0.03	0.13-0.99
Ig mu chain C region (isoform1)	IGHM_HUMAN	2.84±0.14	3.70±0.12	0.02	0.05-0.5
Ig mu chain C region (isoform 2)		2.84±0.14	3.7±0.12	0.02	0.05-0.5
Ig kappa chain V-II region Cum	KV201_HUMAN	0.50±0.01	0.62±0.02	0.03	0.13-0.99
Ig kappa chain V-III region VH (Fragment)	KV310_HUMAN	0.50±0.01	0.62±0.02	0.03	0.63
Ig kappa chain V-I region Wes	KV119_HUMAN	0.54 ± 0.01	0.67±0.02	0.03	0.36-0.99
Ig lambda chain V-I region NEWM	LV105_HUMAN	0.57±0.01	0.71±0.02	0.03	0.33-0.99
Ig lambda chain V-IV region Hil	LV403_HUMAN	1.26± 0.03	1.56 ± 0.05	0.03	0.26-0.99
Complement C1q subcomponent subunit C	C1QC_HUMAN	0.24± 0.01	0.30 ±0.01	0.03	0.13-0.99
Apolipoprotein C-I	APOC1_HUMAN	0.69± 0.02	0.85± 0.03	0.03	0.36-0.99
Immunoglobulin J chain	IGJ_HUMAN	0.74 ± 0.02	0.41 ± 0.01	<0.01	0.11-0.63
Ig kappa chain V-IV region Len	KV402_HUMAN	2.95±0.07	2.39±0.08	0.02	0.36-0.99

Table 1:

Proteins of the patient before starting cysteamine were significantly different from the healthy control

(p-value < 0.05 when comparing the relative amount of protein present before therapy with the amount present in the healthy control);

After cysteamine was started significant differences on these protein were no longer present

(p-value ≥ 0.05 on all time points after cysteamine was started when comparing with the relative amount of protein present in the healthy control).

*the interval corresponds to the minimum and maximum p-value throughout the follow-up (from month 1 to 14 after starting therapy with cysteamine).

CONCLUSION:

- With cysteamine the proteome of the patient became increasingly similar to the proteome of a healthy control.
- Identification of the proteins that change with therapy may provide insight into the pathophysiology of cystinosis and unravel new therapeutic targets.

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