PROTEOMIC AND PATHWAY ANALYSIS OF ADRENOCORTICAL CANCER IN AN IN VIVO XENOGRAFT STUDY

Zoltán Nagy[1], Kornélia Baghy[2], Éva Hunyadi-Gulyás[3], Ilona Kovalszky[2], Katalin F. Medzihradszky[3], Károly Rácz[1,4], Attila Patócs[4,5], Peter Igaz[1]

[1]2nd Department of Medicine, Faculty of Medicine, Semmelweis University, H-1088 Budapest, Szentkirályi str. 46., Hungary, [2]1st Department of Pathology and Experimental Cancer Research, Faculty of Medicine, Semmelweis University, H-1088 Budapest, Üllői Str. 26., Hungary, [3]Biological Research Centre, H-6726 Szeged, Temesvári krt. 62., Hungary, [4]Molecular Medicine Research Group, Hungarian Academy of Sciences and Semmelweis University, Szentkirályi str. 46., H-1088 Budapest, Hungary, [5]"Lendület-2013" Research Group, Hungarian Academy of Sciences and Semmelweis University, Szentkirályi str. 46., H-1088 Budapest, Hungary

INTRODUCTION

Few effective medical treatment options are available for adrenocortical carcinoma (ACC). Intensive efforts are going on for exploring novel pathways and treatment targets. In our previous functional genomics study, retinoid signaling via the retinoid X receptor (RXR) was identified as a major pathogenic pathway in ACC and we have demonstrated the *in vitro* activity of 9-cis retinoic acid (9-cisRA) acting via the RXR on NCI-H295R cells. In this present study we have investigated the antitumoral effects of 9-cisRA and mitotane on ACC *in vivo* in a large-scale xenograft model.

METHODS

- 43 male H295R xenografted SCID mice in four groups (i. control, corn oil; ii. mitotane, 200 mg/kg; iii. 9 cisRA, 5 mg/kg; iv. combined, 200 mg/kg mitotane, 5mg/kg 9-cisRA)
- Protein isolation
- 3 protein sample/groups for LC-MSMS analysis
- Validation of one selected protein with Western-blot
- Pathway-analysis with David 6.7
- Western blot of 2-2-2 sample from physiologic, benign and malignant adrenal tissues

OBJECTIVE

To perform a proteomics and pathway analysis on a 9-cisRA (9-cis retinoic acid) and mitotane-treated ACC xenograft model.

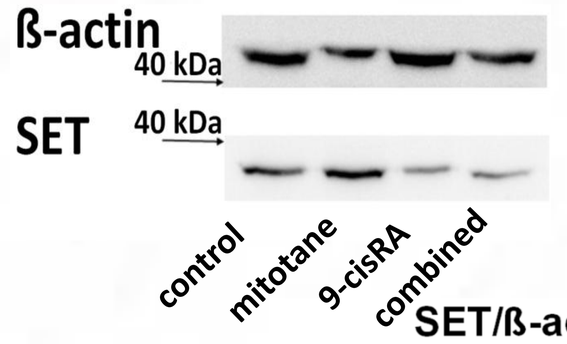
RESULTS

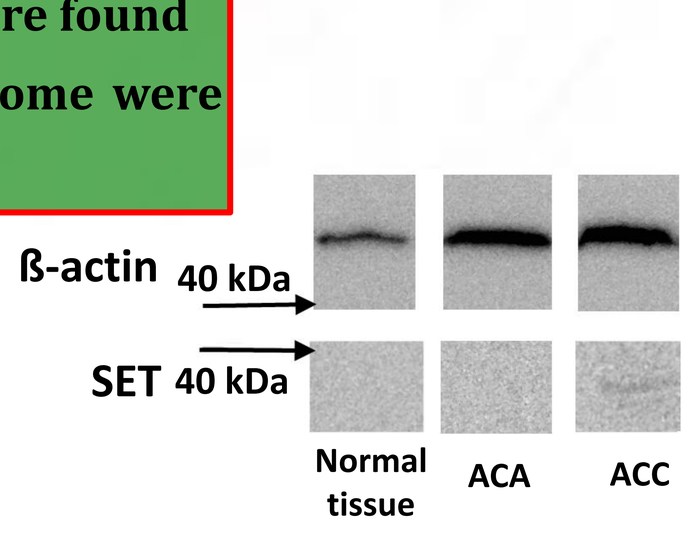
- 47 significant protein changes found with proteomics between the combined and control groups
- Protein SET was validated by Western-blot to be significantly underexpressed in the combined treated group relative to control
- Protein SET was found weekly expressed in human ACC tissue samples
- Proteins affected in p53- and Wnt-pathways were found
- Pathways linked to the ribosome and proteasome were identified

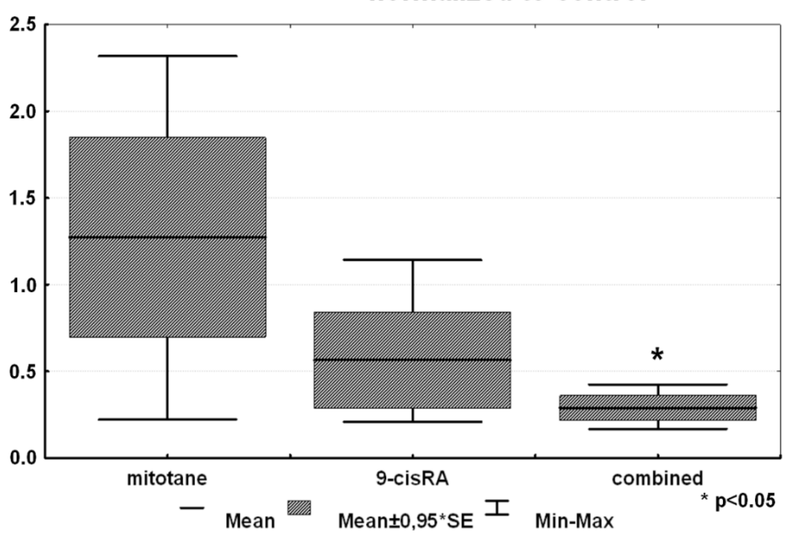
Proteomics analysis

47 significant protein changes → *Literature data* → SET

Western blot







Pathway analysis

P04398:p53 pathway feedback loops 2	
P00021:FGF signaling pathway	
P00018:EGF receptor signaling pathway	
P04397:p53 pathway by glucose deprivation	
REACT_11045:Signaling by Wnt	
REACT_15295:Opioid Signalling	
REACT_71:Gene Expression	
REACT_17015:Metabolism of proteins	
REACT_1505:Integration of energy metabolism	
REACT_1762:3' -UTR-mediated translational regulation	
KEGG_PATHWAY	Ribosome
KEGG_PATHWAY	Wnt signaling pathway

CONCLUSIONS

1. **The SET protein might be a novel player in ACC biology, but its pathogenic relevance need to be confirmed**
2. **We have identified that combination of 9-cisRA and mitotane influences several pathways involved in ACC pathogenesis**

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