

0065 - REDOX PATHWAY DYSREGULATION DEFINES TUMOUR AGGRESSIVENESS AND MITOTANE RESPONSE IN ADRENOCORTICAL TUMOURS

Mode: Research paper

Thematic Unit: Adrenals

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Background/Objectives: The glutathione system is a major cellular antioxidant pathway that preserves redox homeostasis in the adrenal gland. Mitotane, the therapy for advanced adrenocortical cancer (ACC) patients, interferes with the redox balance. The role of glutathione-related pathways in tumor aggressiveness and clinical outcomes associated with mitotane treatment remains poorly understood in pediatric (pACT) and adult adrenocortical tumors (aACT). The objective of this study is to evaluate the association of glutathione-related antioxidant pathways with ACT aggressiveness and mitotane response in pediatric and adult ACT (pACT and aACT).

Methods: Global tumor DNA methylation (EPIC array) and global mRNA expression (RNA-seq) of antioxidant-related genes were evaluated in 43 pACT samples and 76 aACC. Associations with metastatic status, disease-free survival (DFS), and overall survival (OS) were analyzed using Kaplan–Meier curves and false discovery rate correction. Functional studies in human H295R adrenal ACC cells assessed oxidative stress, mitochondrial activity, GPX1 expression, and cell proliferation upon mitotane exposure, the antioxidant N-acetylcysteine exposure, and GPX1 knockdown.

Results: Metastatic pACT exhibited lower expression of REDOX-associated genes: TXNRD2 ($p=0.01$), PRDX3 ($p=0.01$), and GPX1 ($p=0.05$). Reduced PRDX3 expression associated with shorter DFS ($p=0.04$). Increased GPX1 methylation associated with progression to death ($p=2.8 \times 10^{-6}$). In aACC, increased glutathione pathway activity was associated with reduced DFS ($p=0.013$) and, among mitotane-treated patients, with worse OS ($p=0.034$) and DFS ($p=0.021$). Elevated GPX1 expression was also associated with reduced OS in the overall cohort ($p=0.024$) and with worse OS ($p=0.0034$) and DFS ($p=0.021$) in mitotane-treated patients. In vitro, mitotane increased oxidative stress (p

Conclusion: In pACT, reduced antioxidant pathway expression was associated with aggressive disease, whereas in adult ACC, increased glutathione activity and GPX1 expression were associated with poorer outcomes in mitotane-treated patients, supporting a role in resistance to mitotane-induced oxidative stress. Thus, redox homeostasis is a potential biomarker and predicts therapeutic response in ACC.

