Nature Reviews Endocrinology **11**, 631 (2015); published online 15 September 2015; doi:10.1038/nrendo.2015.156

ADRENAL GLAND

CANCER TARGET OF MITOTANE IDENTIFIED

Treatment of adrenocortical carcinoma (ACC) with mitotane is hampered by low rates of tumour regression, serious adverse effects and an unknown mechanism of action. A new study published in *Endocrinology* has identified sterol *O*-acyltransferase 1 (SOAT1) as the molecular target of mitotane in ACC cells and could facilitate the development of improved therapies for the disease.

The researchers, led by Matthias Kroiß from the University Hospital Würzburg, Germany, used gene expression profiling and mass spectrometry to study the effects of mitotane on the NCI-H295 cell line, a model of ACC. "Although gene expression in these cells in response to mitotane had been studied previously, our data showing that the cells respond quite quickly after starting treatment convinced us to look at earlier time points," explains first author Silviu Sbiera. After just 6 h of treatment, mitotane altered the expression of up to 1,976 genes (1.5-fold cut-off). Gene ontology analyses of the expression data revealed that two key pathways were markedly affected by mitotane treatment: endoplasmic reticulum (ER) stress and lipid metabolism. Mass spectrometry analysis of total lipid content isolated 0.5 h, 2 h and 6 h after mitotane treatment revealed increased levels of free cholesterol, oxysterols and fatty acids as the cause of ER stress, thereby providing a mechanistic link between these two apparently unrelated pathways.

Finally, the team showed that mitotane inhibits SOAT1—an enzyme catalyzing cholesterol esterification—which leads to accumulation of toxic lipids in ACC. Further evidence of SOAT1 as the target of mitotane in ACC cells was obtained by immunohistochemistry of ACC tissue samples. SOAT1 was expressed at higher levels in tumours from patients who responded to mitotane treatment than in those from patients who did not respond.

The findings suggest new therapeutic approaches for ACC: exploiting SOAT1 inhibition and combining mitotane with inducers of ER stress to reduce the dose of mitotane and adverse effects. Kroiß believes that targeting cancer-specific lipid metabolism might have wider utility: "As other tumours are known to heavily rely on lipids for structural components and metabolic substrates, targeting SOAT1 and the downstream lipotoxic ER-stress pathway might be useful for treating other cancers."

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Original article Sbiera, S. *et al*. Mitotane inhibits sterol-*O*-acyl transferase 1 triggering lipid-mediated endoplasmic reticulum stress and apoptosis in adrenocortical carcinoma cells. *Endocrinology* doi:10.1210/en.2015-1367