Adrenocortical carcinoma (ACC) is among the deadliest endocrine malignancies. Radical surgical resection of a localized tumor is the only curative option for ACC, but in many patients cancer is diagnosed already at an advanced stage, needing pharmacological treatment. The mainstay of the medical therapy for metastatic ACC is mitotane (o,p′-DDD), a derivative of the insecticide dichlorodiphenyl-trichloroethane, which is also used as an adjuvant treatment in patients resected for localized ACC but at a high risk of relapse. Mitotane is an old drug. More than 60 years ago, Nelson and Woodard showed that technical-grade dichlorodiphenylchloroethane caused selective atrophy of the adrenal cortex in the dog (1). Subsequent studies demonstrated that the active substance was o,p′-DDD, an impurity in the technical-grade product, which was then introduced in the treatment of ACC (2). Today mitotane is the only approved drug for ACC treatment, even if controversies remain concerning its long-term efficacy (reviewed in reference 3). Mitotane has both an adrenolytic action on ACC cells and inhibits steroid hormone synthesis, with beneficial effects in patients with Cushing’s syndrome. However, mitotane therapy often has important side effects that limit its use in the clinic. Furthermore, for many patients it is difficult to attain and maintain the therapeutic levels of plasma mitotane (between 14 and 20 mg/L) (4). A better knowledge of the mechanism of action of mitotane is then required to develop new drugs that are more efficient and better tolerated by ACC patients. Recent studies showed that mitotane treatment negatively affects mitochondrial respiratory chain activity (5) and induces mitochondrial morphofunctional changes in ACC cells (6), but the mechanisms of those effects remained elusive.

A breakthrough in our understanding of how mitotane works as a selective toxic agent for adrenal cells is represented by the study of Sbiera et al (7) published in this issue of Endocrinology. Here the authors show compelling evidence that mitotane treatment rapidly induces endoplasmic reticulum (ER) stress in ACC cells but not in cancer cell lines from tissues other than the adrenal. ER stress generates protein misfolding in the ER, which is sensed by several signaling cascades and triggers a response targeted to limit the effects of ER stress. Collectively this phenomenon is termed the unfolded protein response (UPR) (8).

Mitotane-induced ER stress is correlated with the accumulation of toxic lipids inside ACC cells. In particular, increase in free cholesterol and decrease of cholesteryl esters pinpointed the inhibition of sterol-O-acyl-transferase (SOAT) (also known as acyl-coenzyme A cholesterol acyltransferase) activity as a potential mechanism of action of mitotane. In the adrenal, this enzyme has the role to produce stores of esterified cholesterol protecting cells from the damaging effects of free cholesterol. Cholesterol esters can be rapidly made available as substrates for steroidogenesis after ACTH stimulation by the action of hormone-sensitive lipase (9). Consistently with its important role in steroidogenesis, SOAT1 has been shown to be a target for steroidogenic factor-1, an essential transcriptional regulator of steroidogenic genes (10). Based on those results, Sbiera et al (7) show that mitotane indeed inhibits SOAT1 activity in vitro and that its effect correlates with
SOAT1, but not with the related SOAT2, expression in cancer cell lines. Consistently with those data, the bona fide SOAT inhibitor Sandoz 58–035 compound also decreased cholesterol esters, increased free cholesterol, triggered ER stress, and reduced the viability of ACC cells (7).

It has long been known that SOAT inhibition is toxic to adrenal cells. Adrenal toxicity in various species has limited the development of SOAT inhibitors as hypolipidemic and antiatherosclerotic agents (11). Conversely, this property is exploited by a new orally available SOAT inhibitor (ATR-101) that is currently being tested in a clinical trial for advanced ACC (12). Based on the results by Sbiera et al (7), it is tempting to speculate that the lipid accumulation subsequent to inhibition of SOAT1 by mitotane in ACC cells leads to changes in the composition of intracellular membranes, which triggers the UPR (13, 14). In turn, activation of the UPR may also influence mitochondrial proteostasis (15) and induce mitochondrial dysfunction at late stages after mitotane treatment, consistently with previous studies (5, 6). In addition, the study by Sbiera et al (7) puts into relief a few questions concerning the mechanism of action of mitotane that need to be clarified by future investigations including the following:

- The activation of markers of ER stress and reduction of cellular viability by o,p'-DDD in ACC cells far exceeds in magnitude the effects of equimolar amounts of the Sandoz 58–035 compound. This may indicate that other molecular targets in addition to SOAT1 exist for mitotane in those cells that can account for the massive induction of the UPR.
- It will be interesting to determine whether SOAT1 inhibition by mitotane requires previous metabolic transformation and activation of the drug, which has been hypothesized to be required for its action and may explain its variable activity in different animal species (16).
- Patients treated with mitotane may develop central hypothyroidism, which correlates with the reduction of TSH secretory activity and cell viability in pituitary thymotrope mouse cells (17). Is SOAT1 inhibition also relevant for the effect of mitotane in the pituitary?
- Is SOAT1 inhibition related to the toxic effects (gastrointestinal, neurological) of mitotane or do other targets for the drug exist in those tissues?

Last but not least, another important result presented in the study by Sbiera et al (7), which has direct translational relevance, is the demonstration that SOAT1 expression levels are variable in ACC, being low or absent in about one-third of those cancers. Remarkably, the analysis of a small series of ACC patients who had their tumors surgically removed a short time before the initiation of mitotane treatment showed that time to progression for tumors with low SOAT1 expression was significantly shorter compared with those with high SOAT1 expression, providing further clinical evidence for SOAT1 being a relevant target for mitotane action. If those results will be confirmed on larger cohorts of patients with ACC, the measurement of SOAT1 expression in the tumor is likely to become a useful marker to stratify patients for treatment with mitotane or with new-generation SOAT1 inhibitors.

Acknowledgments

This commentary is dedicated to the memory of Bruno Allolio, a wonderful person and a visionary scientific leader.

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Disclosure Summary: The author has nothing to disclose.

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