ADRENOCORTICAL CARCINOMA: IN THE SEARCH FOR A PRE-OPERATIVE BIOMARKERR. Pezzani^{1,2,*}

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Abstract

Adrenocortical tumors (ACT) are common malignancies of the cortex adrenal gland frequently non-functioning and benign. Differently, adrenocortical carcinoma (ACC) is a very rare neoplasia with an incidence of 0.7–2.0 cases per million people and an aggressive behaviour. Moreover ACC shows a poor prognosis with an estimated survival of 16–38%. Only surgery and the use of mitotane (sometime associated to standard chemotherapy) can represent a useful tool to fight against this malignancy, nonetheless ACC often metastasizes and recurs, decreasing considerably patient survival prospect. In the search of new potential tools to combat cancer, in the latest years omics works extended our knowledge on the ACC pathogenesis and made possible the investigation of novel ACC biomarkers. In this field of research, epigenetic studies identified a common signature in ACC, where the most altered miRNA found in ACC (miR-483-5p) seems now to represent a concrete biomarker to be used in the pre-operative diagnosis of ACC. A larger patient cohort is necessary to confirm this pivotal data: collaboration between scientific communities will be the key to determine the success of this fundamental discovery.

Key words: adrenocortical carcinoma, miRNA, biomarker.

Adrenocortical tumors (ACT) represent a common entity in human, often discovered during normal diagnostic procedures for other medical investigations (incidentalomas), while adrenocortical carcinomas (ACC) are an aggressive cancer of the cortex adrenal gland (1). They are a rare neoplasia with an incidence of 0.7–2.0 cases per million people and a survival rate of approximately 16–38% at 5 years after diagnosis affecting both adults and children (2). ACC can be steroidogenic, i.e. many biochemical studies demonstrated the overexpression of hormones in more than 60% of patients (3). However, ACC is not always hormonally bioactive, indeed it can be hormonally

silent and characterized by altered production with increased precursors of steroidogenic factors (4). Many pharmacological approaches have been tested in preclinical and clinical studies, but at present mitotane is the only approved drug for advanced ACC and as adjuvant (5). Mitotane is an adrenotoxic compound with the ability to block steroidogenesis and to induce cell death: it is frequently used in combination with etoposide, doxorubicin and cisplatin and/or radiation therapy (2). Nonetheless the use of mitotane or chemotherapy alone is not recommended as the main recognized therapeutic approach to ACC remains radical surgery (adrenalectomy). Despite complete resection, some ACC can recur or metastasize providing a very poor prognosis (6).

Given these premises, numerous works have attempted to explore the pathophysiology of ACC. In the latest few years, the use of omics techniques has provided new hope in the search for novel therapeutic targets or diagnostic/prognostic biomarkers to understand this challenging malignancy. Remarkably comprehensive omics works in 2014 (7) and in 2016 (8) elucidated the main signaling pathways and key factors involved in ACC tumorigenesis, presenting new light into a neglected disease such as ACC.

Numerous cellular alterations can be found in ACC. The most common ones are subdivided into genetic/genomic and epigenetic alterations:

Genetic/genomic alterations include: TP53, CTNNB1 (β -catenin gene), CDKN2A, RB1, MEN1, ZNR3F3, DAXX, TERT, ATRX, MED12, PRKAR1A, RPL22, TERF2, CCNE1 and NF1 mutations, chromosomal gains at 5, 7, 12, 16, 19, and 20 and chromosomal losses at 13 and 22, loss of heterozygosity of the 11p15 region, which leads to IGF2 overexpression in more than 90% of ACC (7-9);

Epigenetic alterations include: hypermethylation of the promoters of genes such as H19, G0S2, PLAGL1 and NDRG2, aberrant global

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methylation status, dysregulation of miR-483-5p and many others altered miRNAs (10, 11).

All these data are considered extremely useful to study potential applications for new pharmacological targets or new biomarkers. Of recent interest, as no blood biomarker for the pre-operative diagnosis of ACC is available, miRNAs in plasma samples seem to be a valid diagnostic tool to identify a patient affected by ACC. Indeed a current work demonstrated how miR-483-5p could be a usable and minimally invasive biomarker to distinguish ACC patients (12). The study showed the powerful potential of extracellular vesicle-associated miRNAs (from blood sample) in adrenocortical tumors, even if a larger cohort validation is needed. Nonetheless the data suggest a concrete starting point: in future it means a more rapid diagnosis and a leap forward in the clinical management of ACC. Furthermore as underlined by Chabre *et al.* (13), miR-483-5p could represent a prognostic factor (associated with poor prognosis and cancer recurrence). The pioneering study on miR-483-5p will lay the basis - from a simple blood sampling - for the diagnosis of ACC, a result highly necessary in adrenocortical tumors.

In addition, it is to underline that similar results originate from the collaborative effort of many different competences, again emphasizing that the union is strength. In this regard the scientific community is actively participating in joint actions, such as the ENS@T study group (14, 15). It is expected in the next few years an improvement of ACC treatment, as these new information coming from omics and epigenetic works will provide a novel basis for the diagnosis, prognosis and treatment of ACC. Unquestionably the journey is still long, but we are on the way.

Conflict of interest

The author declares no conflict of interest.

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