Insight Medical Publishing

JOURNAL OF INFECTIOUS DISEASES AND TREATMENT

# Molecular drivers of potential immunotherapy failure in adrenocortical carcinoma: Focus on β catenin

**Sandra Sigala**

University of Brescia, Italy

**Abstract**

Adrenocortical Carcinoma (ACC) is a rare, highly aggressive cancer, often insensitive to conventional chemotherapeutics agents. Early diagnosis, followed by radical surgical resection plus/minus adjuvant mitotane therapy, is nowadays the only valuable option, although most of ACC patients are destined to recur. Multiple genes and pathways have been identified as potentially targetable in ACC patients; however, despite the strong preclinical rationale, translational findings to clinical trials led to date to disappointing results. The immunotherapeutic intervention targeting T-cell checkpoint molecules has been proposed as well, but results obtained indicate that ACC patients would be unlikely to benefit from immunotherapy. Genetic alterations of different pathways involved in ACC carcinogenesis are known substrates of resistance to immunotherapy. Among them, β-catenin gene CTNNB1 and TP53 gene are frequently mutated in ACC samples. Overactivation of the β-catenin pathway and loss of p53 protein function are potential tumor-intrinsic factors that, impacting on the ability of ACC cells to recruit dendritic cells, leading to T-cell exclusion. Moreover, the steroid phenotype, which implies glucocorticoids hypersecretion in a subset of ACC, contributes to generating an immunosuppressive microenvironment. While waiting for the development of targeted drugs, an approach could come from drugs already marketed for other therapeutic indications and that are endowed, as ancillary mechanism, with the ability to target this pathway. Preclinical experimental models could be strategic to shed light on this field. We demonstrated that in the ACC cell line NCI-H295R, characterized by an abnormal β-catenin nuclear accumulation, both the CYP17A1 inhibitor abiraterone acetate that induces an increase of progesterone levels and progesterone itself induce cytotoxicity and partially reduce the nuclear accumulation of β-catenin. Although this finding needs a molecular characterization, it could stimulate further research in this direction, demonstrating as well the possible contribution of the Wnt/β catenin in the resistance to immunotherapy of ACC.  cardiac function. These results indicate, in this/these models of obesity, UA is not causative of metabolic dysfunction whereas elevated XOR activity does alter cardiovascular function.

**Biography:**

Sandra Sigala is a M.D., with a Ph.D. title in in Experimental Pharmacotherapy. She has a permanent position as Associate Professor of Pharmacology at the University of Brescia. Her expertise in the cancer field took origin from studies on the role of Nerve Growth Factor as a cell differentiation factor and its possible involvement in the progression of neoplastic degeneration, in particular pituitary tumors and prostate adenocarcinoma. In the last years, her research was focused on the preclinical and translational oncological pharmacology, in particular, of tumors of the male genital system and adenocarcinoma of the adrenal cortex. Besides the preclinical research, she participates to the design and conduction of clinical trials, as clinical pharmacologist.n driving the inflammatory phenotype.

**Publication**

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**Citation:** Sandra Sigala, *Molecular drivers of potential immunotherapy failure in adrenocortical carcinoma: Focus on β cateni*, Euro Immunology 2020, European Congress on Immunology, Edinburgh, Scotland, March 4 -5 , 2020, 12