Accepted Manuscript

Epigenetic dysregulation in adrenocortical carcinoma, a systematic review of the literature

P.K.C. Jonker, V.M. Meyer, S. Kruijff

PII: S0303-7207(17)30431-8

DOI: 10.1016/j.mce.2017.08.009

Reference: MCE 10046

To appear in: *Molecular and Cellular Endocrinology*

Received Date: 31 March 2017

Revised Date: 17 August 2017

Accepted Date: 17 August 2017

Please cite this article as: Jonker, P.K.C., Meyer, V.M., Kruijff, S., Epigenetic dysregulation in adrenocortical carcinoma, a systematic review of the literature, *Molecular and Cellular Endocrinology* (2017), doi: 10.1016/j.mce.2017.08.009.

TITLE

Epigenetic Dysregulation in Adrenocortical Carcinoma, a Systematic Review of the Literature

P.K.C. Jonker, V.M. Meyer, S. Kruijff

HIGHLIGHTS

- Methylation levels of promotor regions in adrenocortical carcinoma (ACC) are inversely correlated with overall survival.
- ACCs can be categorized based on CpG-island methylation phenotypes (CIMPs) with a different overall survival.
- DNA methylation levels might be useful to differentiate adrenocortical carcinomas from adrenocortical adenomas and normal adrenocortical tissue.
- 14 hypermethylated genes with low mRNA expression in ACC are reported in two or more independent studies.
- Pyrosequencing and Methylation Specific Multiplex Ligation Dependent Probe Amplification (MS-MLPA) are potential platforms for future application of DNA methylation as diagnostic and prognostic tool.

ABSTRACT

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy with a poor prognosis. Diagnosis and treatment of this tumor remains challenging. The Weiss score, the current gold standard for the histopathological diagnosis of ACC, lacks diagnostic accuracy of borderline tumors (Weiss score 2 or 3) and is subject to inter observer variability. Furthermore, adjuvant and palliative systemic therapy have limited effect and no proven overall survival benefit. A better insight in the molecular background of ACC might identify markers that improve diagnostic accuracy, predict treatment response or even provide novel therapeutic targets. This systematic review of the literature aims to provide an overview of alterations in DNA methylation, histone modifications and their potential clinical relevance in ACC.

BACKGROUND

Adrenocortical carcinoma (ACC) is an endocrine malignancy with a prevalence of 0.7-2 per million inhabitants.(1) The overall prognosis of ACC is poor with reported 5-year overall survival rates ranging between 16% and 44%.(2-8) At initial presentation, 48% of the tumors is localized within the adrenal gland (stadium I-II), 16-27% has locoregional invasion or lymph node metastasis (stadium III) and 11-36% of the patients present with distant metastasis (stage IV a-c).(9-11) Five-year survival of patients with ACC is stage dependent. From stage I to IV it declines from 82%, towards 61%, 50% and less than 13 % respectively.(1) Surgical resection of locoregional disease remains the sole curative treatment option for ACC.(1) Despite novel insights in the carcinogenesis of this rare and aggressive tumor, accurate diagnosis of borderline adrenocortical tumors remains difficult. More importantly, there is no proven effective adjuvant therapy for ACC that improves overall survival.

Accurate diagnosis of a subcategory of “borderline” adrenocortical tumors with a Weiss score of 2 or 3 may be challenging.(12-14) The Weiss score is accepted as the gold standard for histopathological diagnosis of adrenocortical tumors due to its accuracy, simplicity and reliability.(15,16) However, the score has a low accuracy for accurate diagnosis of borderline adrenocortical tumors.(13,14) Some patients initially diagnosed with benign borderline tumors develop local recurrence during follow-up, sometimes with distant metastasis.(12,17,18) Current understanding about carcinogenesis of borderline tumors is hampered because of a low number of reported cases, limited follow-up and heterogeneity of endpoints.(13) The identification of molecular diagnostic markers that differentiate