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Adrenal cortex and microRNAs
An update

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Among the first tissues to be studied for their micro-RNA expression is the adrenal cortex; in this brief overview, we provide the first update on micro-RNAs for this tissue, which a useful trailblazer for other endocrine and steroidogenic glands. Our laboratory studied both normal adrenal cortex and benign adrenal tumors, such as bilateral adrenal hyperplasias (BAH). Massive macronodular adrenocortical disease (MMAD) [also known as ACTH-independent macronodular adrenal hyperplasia (AIMAH)] causes Cushing syndrome and is characterized by multiple bilateral cortical nodules or adenomas that lead to significant enlargement of the adrenal glands.[1] Primary pigmented nodular adrenocortical disease (PPNAD) is a relatively unique form of BAH that is often associated with Carney complex, a multiple neoplasia syndrome; unlike MMAD, a disease of mostly adults, PPNAD presents with Cushing syndrome in early life.[2]

MicroRNAs (miRNAs) are RNAs of about 21–26 nucleotides in length and comprise a class of non-coding RNAs that are derived by cleavage from much larger precursor RNAs. Until now we can find up to 600 miRNAs in the miRBase Sequence Database but between 1,000 and 10,000 could be predicted.[3] miRNAs have an important role in several biological processes, from regulation of immunity to organ biogenesis and cancer. miRNA genes can function as promoters of tumorigenesis (oncogenes) or suppressors of tumor formation (tumor suppressors), and hitherto have been reported to be altered in many tumors. An aberrant miRNA expression signature that is often shared has now been found in tumors from several tissues.[4,5]

We recently obtained miRNA expression analysis, in MMAD/AIMAH and PPNAD.[4,6] Some downregulated or upregulated miRNAs were found to be implicated in adrenal tissue tumorigenesis and, like in other tissues, we found alterations in some miRNAs that are known to be altered in other tumors. Such an example was the family of miRNA *let-7*, members of which (*let-7*a, *let-7*b, *let-7*c and *let-7*g) were downregulated in PPNAD (but not in the MMAD) and have been significantly downregulated in lung and other cancers.[7] A recent study shows that this miRNA is important as a regulator of the self-renewal of breast cancer stem cells.[8] In addition, we detected other miRNAs to be expressed at high levels in MMAD and in PPNAD (despite their histologic differences) such as miR-210; this miRNA has been found to be upregulated in breast cancer and is regulated by the hypoxia-inducible factor.[9]

MiR-203, whose putative target gene is *ABL1*, a well known oncogene that is activated in chronic myelogenous leukemia,[10] was downregulated in both MMAD and PPNAD[4] and, thus, may act as a tumor suppressor in adrenocortical tumors. MiR-203 also targets the transcription factor p63 involved in proliferation and differentiation of epithelial cells.[11]

Notably, there are some miRNAs whose pattern of expression appears to be unique for adrenal tumors, such as the miR-449; one of the highest downregulated miRNA in PPNAD. Interestingly, when we used a bioinformatics algorithm (that was constructed to predict miRNA gene targets) that integrated expression data on PPNAD that we have previously published,[12] a correlation was found between miR-449 and *WISP2* expression levels, supporting the potential involvement of Wnt signaling in PPNAD that has been suggested by other studies.[12,13] The Wnt signaling pathway, now under study for its wide regulation by miRNAs, is a complex network of proteins and has an important role in embryogenesis and cancer.[14] We have shown that inhibition of PKA activity using PKA inhibitor H89 increased miR-449 expression and decreased *WISP2* mRNA expression.[4]

Although the phenotype of the adrenal tumors may be immunologically or histologically widely different, these tumors can vary greatly in their clinical behavior and prognosis. When a more carefully and broader view is applied to the analysis of miRNA patterns of expression in the adrenal tumors, a very interesting correlation with clinicopathologic variables, which are important diagnostic/prognostic factors, can be observed. It seems that two miRNAs (miR-130a and miR-382) are showing an expression pattern that correlates with the diurnal cortisol levels in patients with MMAD, an index of the severity of their disease.

We can conclude that, if carefully analyzed, miRNAs may show a specific signature in basically all tissues and their diseases; this property makes the analysis of the expression of miRNAs useful in differential diagnosis, prognosis and maybe the treatment of a variety of disorders.

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