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5 - IMPLICATION OF MIR200A, MIR103 AND MIR383 IN THE SILENCING OF CORTICOTROPH TUMORS

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Resumen

Introduction: Silencing mechanisms of corticotroph tumors (CT) remain unclear. Epigenetic mechanisms can occur during tumorigenesis. MiRNAs capable of inhibiting the expression of *POMC* have been described at the level of neurons of the hypothalamus, which gives us a basis to advance in the knowledge of CT.

Objectives: To determine if post-transcriptional regulation by miRNAs is involved in the silencing of CT.

Methods: We quantified the relative gene expression of 8 factors (*PKA, MAP3K8, MEK, MAPK3, NGFIB, NURR1, PITX1, STAT3*) and 5 miRNAs (miR375, miR383, miR488, miR200a, miR103) by qRT-PCR with TaqMan probes in 24 functioning CT (fCT) and 23 silent CT (sCT).

Results: miR200a and miR103 expression was higher in silent CT than in macro functioning CT (p = 0.049 and p = 0.05, respectively). Both miRNA biomarkers could be a good tool to distinguish between both variants (AUC = 0.739, 95%CI = 0.592-0.887, p = 0.007; AUC = 0.727, 95%CI = 0.574-0.880, p = 0.011, respectively). These two miRNAs correlated negatively with *MAP3K8* (rho = -0.686, p = 0.001 and rho = -0.782, p < 0.001, respectively). MiR383 was up-regulated in functioning (3.607 ± 5.016) and silent (8.918 ± 12.009) CT compared with normal pituitary gland. Using different computational algorithms, we found that *NEUROD1* was a potential target for miR383. Interestingly we observed a negative correlation between *TBX19* and miR383 in both subtypes, stronger in silent CT (rho = -0.583, p = 0.007) than in functioning ones (rho = -0.431, p = 0.051). We also found other interesting potential targets for miR383, as *SSTR2, SSTR3* and *SSTR5.* Finally, we observed a negative correlation between miR383 and the expression of *STAT3* (rho = -0.544, p = 0.016) in silent CT.

Conclusions: MiR200a and miR103 may be involved in the silencing of this subtype and could be used as diagnostic tool. The negative correlation between miR383 and *TBX19* expression could indicate a potential silencing mechanism of these tumors. Moreover, miR383 may be a possible therapeutic target in CT.