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A MULTIOMIC ANALYSIS OF
TRANSCRIPTIONAL REPRESSOR MBP-1 FUNCTIONS
IN GYNECOLOGICAL TUMORS

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Abstract

Background: Myc promoter-binding protein-1 (MBP-1, 37 kDa), product of alternative translation of ENO1 mRNA, acts as a transcriptional repressor of c-MYC, ERBB2 and COX2 genes (1-3). Exogenous MBP-1 expression suppresses proliferation and induces apoptosis in several cancer cell lines (4, 5). In infiltrating ductal carcinoma (IDC), loss of MBP-1 nuclear expression significantly correlates with adverse outcome, suggesting MBP-1 as a novel valuable histochemical marker with potential prognostic value in breast cancer (6). In prostate cancer cells, MBP-1 upregulates hsa-miR-29b expression, which inhibits the translation of anti-apoptotic and pro-metastatic proteins (7). MicroRNAs (miRNAs) are a large class of small non-coding RNAs that post-transcriptionally negatively regulate gene expression (8). Numerous studies have shown that miRNAs are involved in the regulation of different biological processes, such as cell proliferation and apoptosis (9). To date, observations of relationship between MBP-1 protein expression and miRNAs in breast cancer have not been undertaken.
Finally, no data are available about α-enolase and MBP-1 relative expression and subcellular localization in other gyneacological tumors, including ovarian cancer.

Methods: A preliminary *in silico* study was performed to hypothesize the existence of a relationship between the expression of MBP-1 protein and hsa-miR-29b in breast cancer. Subsequently, expression levels of hsa-miR-29b were assessed by q-RT-PCR, *in vivo*, in MBP-1^{+ve} and MBP-1^{-ve} non metastatic infiltrating ductal carcinomas (IDCs) and, *in vitro*, in SKBR-3 cells, overexpressing MBP-1. To further investigate the existence of a relationship between MBP-1 and other miRNAs, a microarray analysis was conducted *in vitro* on SKBR-3 cells relative to MBP-1 protein expression and microarray results were validated by q-RT-PCR. miRNAs expression data were also integrated with mRNAs expression profiles.
To evaluate the expression and subcellular localization of α-enolase and MBP-1 protein in ovarian normal and both primary and metastatic tumor tissues, a preliminary immunohistochemical study was performed using ovarian Tissues Microarrays (TMAs).

Results: Bioinformatic analysis has shown that infiltrating ductal carcinomas are characterized by a considerable variability in the expression of hsa-miR-29b and to date no significant association of hsa-miR-29b with the clinicopathological characteristics of breast tumors has been observed. Hsa-miR-29b target genes are differentially expressed in MBP-1^{+ve} and MBP-1^{-ve} IDC and these genes act in regulatory networks, which include adhesion and cell migration. However, q-RT-PCR of hsa-miR-29b *in vivo* and *in vitro* has not allowed to assign a significant relationship between hsa-miR-29b and MBP-1 in breast cancer. Microarray analysis, in SKBR-3 cells, have shown that MBP-1 regulates both miRNAs and mRNAs expression involved in regulation of cell proliferation, cell migration and apoptosis.
Tissue Microarrays have revealed that both α-enolase and MBP-1 are expressed in normal ovarian tissues while their expression in tumor tissues is variable. Further analysis are necessary to correlate α-enolase and/or MBP-1 expression with clinicopathological characteristics of the ovarian cancers analyzed.

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