TUMOR SUPRESSOR miRNAs IN HPV-RELATED CERVICAL ONCOGENESIS

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MicroRNAs (miRNAs) are small, noncoding RNAs that can contribute to cancer development and progression by acting as oncogenes or tumor suppressor genes. Identification of genes that undergo cancer-specific CpG island hypermethylation and correlation of these data with pre-neoplastic lesions, tumor stage, progression, and long-term prognosis are becoming increasingly common

This study was conducted to investigate the promoter methylation status of the miR-124a, miR-34b, miR-203 genes promoters in pre-neoplastic lesions and cervical cancer and to evaluate their *in silico* identified potential targets.

miRNAs promoter methylation was evaluated using a methylation-specific polymerase chain reaction for bisulphite treated DNA samples (EpiTect Bisulfite Kit – Qiagen) isolated from cervical swabs (High Pure PCR Template – Roche). In order to re-establish miRNAs gene expression, HeLa and CaSky cell lines were treated with demethylating agent 5-azacytidine. The expression levels of the studied miRNAs and of the potential gene targets (SETDB1, CHEK2, MAP3K13, DABLO, MCM2, c-Myc, UBE3A, CCNJ, and CCNA) were evaluated using qRT-PCR.

We found significantly higher methylation frequencies (especially for miR-124a gene promoter) in pre-neoplastic lesions and in cervical cancer lesions. The methylation pattern of *miR34b* gene promoter offers a new explanation for *c-myc* oncogene overexpression.

The involvement of miRNAs *124a* and *203* in cell cycle regulation is more complex, highlighting their dual role. It is possible that the interaction between miRNAs molecules and their targets to be realized not only based on sequence omology, but eventually on an action code, toghether with others miRNAs that target the same mRNA molecule. It seems that miRNAs action is context dependent. This dependence could be linked to the cell differentiation, cell division rate and the cell cycle stage.