Istitutionen för Molekylär Medicin och Kirurgi
Karolinska Institutet, Stockholm

Clinical and functional aspects of microRNA regulation in human cancers

AKADEMISK AVHANDLING

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ABSTRACT

miRNAs are short single-stranded non-coding RNAs which regulate gene expression at the post-transcriptional level in many biological processes, including proliferation, apoptosis and differentiation. A number of studies have shown the importance of miRNAs in carcinogenesis and accumulating evidence supports their role as diagnostic and prognostic biomarkers in human cancers. Moreover, dysregulation of miRNA processing factors, which are needed for miRNA maturation, have been recently shown to play an important role in tumor initiation and progression and to have a prognostic potential in different types of cancer. Despite all the achievements, our knowledge of the biological role of miRNAs and miRNA processing pathway in tumor development and progression is still in its infancy.

The general purpose of this thesis was to improve our understanding of the clinical and functional implications of miRNA deregulation in human cancer.

In **paper I**, we reported frequent deregulation of miRNA expression in lymph node metastases of malignant melanoma and melanoma cell lines as compared to normal melanocytes and showed its association to *BRAF* and *NRAS* mutational status. Moreover, we identified a two-miRNA signature that could predict survival in metastatic melanoma patients.

In **paper II**, we performed genome-wide miRNA expression profiling of adrenocortical tumors and identified distinct miRNA expression patterns in adrenocortical carcinomas (ACC) compared to adenomas and normal adrenal cortex. Over-expression of miR-*483-3p/-5p* and down-regulation of *miR-195* and *miR-497* were the most common features of ACC. We also elucidated the functional consequences of deregulation of these 4 miRNAs on cell proliferation and apoptosis in ACC cells and, in addition, we demonstrated the potential involvement of the pro-apoptotic factor PUMA (a target of *miR-483-3p*) in adrenocortical tumors. Moreover, we found novel miRNAs associated with short survival in ACC.

In **paper III**, we evaluated the expression and the potential role of the main components of the miRNA machinery in adrenocortical tumors. We observed frequent over-expression of TRBP2 in ACC and found that *TRBP2* mRNA expression level is a reliable predictor of carcinoma among adrenocortical tumors. These data suggest that TRBP2 may be a novel and sensitive biomarker for adrenocortical tumors. Functionally, we unraveled the potential oncogenic role of TRBP2 in ACC and identified some of the molecular mechanisms involved in the regulation of TRBP2 expression in this tumor type.

In **paper IV**, we analyzed the expression of miRNAs and miRNA machinery factors in diffuse large B-cell lymphoma (DLBCL). We identified miRNA signatures that could discriminate DLBCL tumors from non-neoplastic tissue and found subsets of miRNAs able to classify DLBCL sub-types. Moreover, we showed dysregulation of miRNA machinery factors in DLBCL and demonstrated that it could influence miRNA processing. We also showed, similarly to our observations in ACC, that deregulation of TRBP2 expression could affect cell proliferation and cell death in lymphoma cell lines, suggesting its potential oncogenic role in DLBCL development.

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