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Institutionen för Onkologi-Patologi

microRNA expression and function in virus-associated human cancers

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ABSTRACT

microRNAs (miRNAs) are small non-coding RNAs that play important roles in gene regulation. It is now clear that miRNAs participate in tumor development and progression. Despite many studies have reported specific miRNA expression signatures in various tumor types, the functional roles of these deregulated miRNAs in specific tumor types remain to be determined. The general aim of this thesis work was to investigate the expression and functional roles of miRNAs in cervical carcinoma and Merkel cell carcinoma (MCC).

In **Paper I**, we describe the functional roles and targets of *miR-205* in human cervical cancer cells. Using *miR-205* over-expression and suppression experiments, we show that *miR-205* regulates cell proliferation and migration in cervical cancer cells. Using a CLIP-Chip approach, we identified a set of candidate *miR-205* targets functionally associated with cell proliferation and migration. Among them, *CTGF* and *CYR61* were further validated by Western blot and Ago2 CLIP-qRT-PCR analyses. Both genes are also downregulated in human cervical cancer tissues. Our findings suggest that *miR-205* and its targets may play important roles in the pathogenesis of cervical carcinoma.

In **Paper II**, we show that *miR-944* functions as an oncogene in human cervical cancer by promoting cell proliferation, migration and invasion. We identified a set of novel *miR-944* targets using the PAR-CLIP sequencing approach. Among them, *HECW2* and *S100PBP* were further validated as direct targets of *miR-944* by luciferase reporter assays. Our findings reveal novel functions and targets of *miR-944* in human cervical cancer cells, which may provide new insights of its role in cervical carcinogenesis.

In **Paper III**, we report miRNA expression patterns associated with Merkel cell polyomavirus (MCV) status and clinical outcomes in MCC. In addition, we show that *miR-203* overexpression inhibits cell growth and induces cell cycle arrest in MCV-negative MCC cells. We also demonstrate that *survivin* expression is regulated by *miR-203* in MCV-negative MCC cells or by MCV T-antigen(s) in MCV-positive MCC cells.

In **Paper IV**, we demonstrate that *miR-375* functions as a tumor suppressor by inhibiting cell growth and cell migration, as well as promoting cell cycle arrest and apoptosis in MCV-negative MCC cells. In addition, we show that *miR-375* is epigenetically regulated in MCC, and different epigenetic mechanisms may contribute to *miR-375* transcription regulation in MCV-positive and -negative MCC cells.

Overall, this thesis work illustrate the high value of Ago2 CLIP approach for miRNA target identification, and provides evidence for the role of miRNAs in human cervical cancer and Merkel cell carcinoma.

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