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MiRNAs in Cancer

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av

Masako Harada

Huvudhandledare:
Professor Dan Grandér
Institutionen för onkologi-patologi
Karolinska Institutet

Bihandledare:
Doktor Martin Corcoran
Institutionen för onkologi-patologi
Karolinska Institutet

Docent Andor Pivarcsi
Institutinen för molekylär medicin
Karolinska Institutet

Docent Olle Sangfelt
Institutionen för cell- och molekylärbiologi
Karolinska Institutet

Fakultetsopponent:
Professor Urban Gullberg
Hematologi och transfusionsmedicin
Lunds universitet

Betygsnämnd:
Professor Ann-Kristin Östlund Farrants
Wenner-Gren institut för experimentall biologi
Stockholms universitet

Professor Lars Holmgren
Institutionen för onkologi-patologi
Karolinska Institutet

Professor Neus Visa
Institutionen för molekylärbiologi och funktionsgenomik
Stockholms universitet

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ABSTRACT

There are many layers of complexity involving the processes through which somatic cells transform into malignant cancers. Historically, cancer was considered to be a disease primarily caused by gene mutations, however it is now well established that the dysregulated expression of the genes leading to the tumorigenic phenotype involves not only mutations but also epigenetic changes. To understand the process of malignant transformation, it is thus important to determine the specific genes targeted by both types of changes.

The studies in this thesis have focused on miRNA expression and its dysregulation in various malignancies and the subsequent role of such dysregulation in tumor pathogenesis. The work includes an analysis of the functional consequences of miRNA alterations in three distinct malignancies, (1) chronic lymphocytic leukemia (CLL), (2) Squamous cell carcinoma (SCC) and (3) Basal cell carcinoma (BCC). Furthermore, acute lymphoblastic leukemia (ALL) was used as a model to describe the role of miRNAs in anticancer treatment. Moreover, we analyzed the effect of the anticancer drug dexamethasone on miRNA expressions and the impact of manipulation of miRNA levels on drug efficacy.

In the CLL study, we demonstrated that the frequently deleted *DLEU2* gene functions as a regulatory host gene for two miRNAs, miR-15a and miR16-1, which negatively regulate the cell cycle by direct targeting G1 cyclins D1 and E1 at the post-transcriptional level, and which, when expressed at high levels in cell line models, lead to the inhibition of colony formation ability. In addition, we demonstrated that the oncoprotein Myc negatively regulates *DLEU2* transcription by targeting the *DLEU2* promoter. These results suggest that the loss of *DLEU2* may be an important pathogenic factor in CLL development.

Our studies on two non-melanoma-skin cancers, SCC and BCC, identified the preferential loss of expression of a skin-specific miRNA, miR-203, in these tumors. Our results further indicate a function of miR-203 in cell cycle regulation, migration and invasion, through the post-transcriptional targeting of the oncogenes *c-JUN* and *c-MYC,* and ultimately leading to an inappropriate inactivation of Hedgehog pathway.

Finally, in the ALL study we demonstrated dexamethasone mediated global down-regulation of miRNAs, in particular the rapid downregulation of *MIR17HG* which occurred following direct binding of the glucocorticoid receptor protein to the *MIR17HG* promoter. The subsequent repression of miR-17 expression aids in dexamethasone cytotoxicity of ALL cells, possibly through de-repression of miR-17 mediated targeting of the anti-apoptotic protein Bim. Analysis of primary B-ALL tumor samples also demonstrated that the cytotoxic efficacy of dexamethasone is associated with its ability to regulate miR-17 levels.

Collectively, these results provide new evidence, not only on the function and importance of microRNAs in tumor pathogenesis, but also suggest the possibility of miRNA targeting to improve the efficacy of existing therapies.

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