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MicroRNA expression profiles in prostate cancer bone metastases

Functional effects of microRNA-23c, -375, and -4328

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Hörsal B, byggnad 1D, 9 tr, Tandläkarhögskolan, Norrlands Universitetssjukhus, fredagen den 17 november, kl. 13:00. Avhandlingen kommer att försvaras på engelska.

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Title
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Abstract
Non-coding microRNAs (miRNAs) function as post-transcriptional regulators of gene expression by interacting with messenger RNA. Dysregulation of miRNAs has many possible consequences, including tumor-suppressive or -promoting ones, and restoring or preventing the effects of miRNA alteration has therapeutic potential.

Metastatic prostate cancer (PC) spreads to the bone and is treated with castration therapy. Eventually, metastases relapse into castration-resistant PC (CRPC) growth. Recently, our laboratory described metastatic PC subtypes, termed MetA-C, defined based on transcriptomic differences and linked to different morphology and prognosis. Patients with MetB metastases have particularly poor prognosis.

The overall aim of the thesis was to identify novel biomarkers and therapeutic targets for metastatic PC, with a focus on miRNAs. The specific aims were to: (1) identify miRNAs associated with PC progression into bone metastasis, and their functional roles; (2) verify the MetA-C subtypes, their prognostic importance, and their relation to genetic profiles in independent validation cohorts; (3) explore miRNA expression profiles of PC bone metastases, specifically in relation to the MetA-C subtypes, and whether specific miRNAs show potential to inhibit the aggressive MetB subtype.

Study 1: Differentially expressed miRNAs (n=79) were identified by microarray by comparing miRNA levels in bone metastatic (n=14) or localized PC (n=7) samples to benign samples (n=7). Downregulation of miRNA-23c and -4328 was verified by qRT-PCR analysis, including a larger cohort of bone metastases (n=67). Overexpression of miRNA-23c or -4328 in PC cells resulted in attenuated cell growth in vitro. High levels of miRNA-23c were detected in extracellular vesicles shed from overexpressing cells. Overexpression of miRNA-23c did not obviously affect tumor growth or angiogenesis in vivo.

Study 2: The existence and prognostic value of the MetA-C subtypes was verified by transcriptomic analysis of bone metastasis samples (n=103), and by subtyping publicly available data from metastatic samples (n=573) from external patient cohorts. The MetB subtype was associated with high tumor-cell proliferation, low androgen receptor activity, and poor prognosis in all cohorts, and provided independent prognostic information in addition to genetic aberrations.

Study 3: The miRNA profiles of 96 bone metastasis samples from Study 2 were examined using microarray analysis. Four sample clusters not obviously related to the MetA-C subtypes were observed. Expression levels of miRNA-375, however, were inversely related to MetB. MiRNA-375 overexpression in C4-2B resulted in a cellular switch of subtype, from being dominant MetB to dominant MetA. In parallel, reduced cell growth and signs of increased cell adhesion were observed.

In conclusion, altered miRNA profiles may contribute to progression of PC into bone metastasis, and to the development of different metastasis subtypes. The MetB subtype is associated with poor prognosis and low expression of miRNA-375. Therapy stratification based on the MetA-C subtypes should be considered in the future. Restoration of miRNA-375 in MetB tumors may offer a novel treatment option.

Keywords
Prostate cancer bone metastases, microRNA, metastatic subtypes, extracellular vesicles

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