GATA2-regulated miR-194 targets Suppressor of Cytokine Signaling 2 to promote prostate cancer metastasis

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Background: Dysregulated expression of microRNAs (miRNAs, miRs) is a hallmark of cancer. MiR-194 is elevated in prostate tumors compared to non-malignant tissues and its levels in serum are predictive of post-surgery disease recurrence, but its role in this disease is poorly understood. Here, we demonstrated that miR-194 promotes metastasis of prostate cancer.

Methods: Levels of miR-194 in clinical samples were measured by qRT-PCR and in situ hybridization and by evaluating published transcriptomic datasets. Prostate cancer cell invasion, migration and growth in vitro were measured by specific assays following modulation of miR-194 levels. The effects of over-expressing and inhibiting miR-194 on invasion and metastasis in vivo were assessed by chick chorioallantoic membrane (CAM) assays and murine intravenous and intraprostatic metastasis assays. Levels of miR-194 in clinical samples were measured by qRT-PCR and in situ hybridization. Molecular targets of miR-194 were assessed by qRT-PCR and Western blotting.

Results: Serum levels of miR-194 are higher in men with metastatic versus localized disease, and tissue levels of miR-194 are associated with disease recurrence post-surgery and tumor aggressiveness. Over-expression of miR-194 in prostate cancer cell lines promoted migration, invasion and epithelial-mesenchymal transition *in vitro* and metastasis of xenografts *in vivo*. The ubiquitin ligase Suppressor of Cytokine Signaling 2 (SOCS2) was found to be a direct target of miR-194 in prostate cancer and a mediator of its pro-metastatic functions. Low levels of SOCS2 were strongly associated with disease recurrence and metastasis in patients, and its down-regulation augmented metastatic phenotypes. By targeting SOCS2, miR-194 de-repressed key oncogenic kinases including FLT3 and JAK2, leading to enhanced ERK and STAT3 signalling. GATA2 was found to be an upstream transcriptional regulator of miR-194 *in vitro*, a finding validated by the strong concordance between GATA2 activity and miR-194 levels in patient cohorts.

Conclusions: Collectively, our study has elucidated a novel pro-metastatic pathway in prostate cancer with miR-194 at the nexus, providing further impetus for exploring the potential of this miRNA as a biomarker and therapeutic target.

Conflict of Interest
The authors declare no conflict of interest.

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