18-2967

Cancer-associated fibroblasts secreted exosomal miR-146a promotes bladder cancer stem-like features

Junlong Zhuang[1], Lan Shen[2], Jun Yan[2], Hongqian Guo[1]

[1] Department of Urology, Drum Tower Hospital, Medical School of Nanjing University, Institute of Urology, Nanjing University, Nanjing, China;
[2] MOE Key Laboratory of Model Animals for Disease Study, Model Animal Research Center, Nanjing University, Nanjing, China

Introduction

Urinary bladder cancer (UBC) patients at muscle invasive stage have poor clinical outcome, due to high propensity for progression. Chemoresistance and subsequent recurrence of cancers are driven by a subpopulation of cancer stem-like cells (CSCs). Cancer-associated fibroblasts (CAFs), one of the principal constituents of the tumor stroma, play an important role in tumor development. Exosomal microRNAs (miRNAs) are emerging mediators of cancer-host crosstalk with other cells around. However, it is unclear whether CAFs from UBC promote cancer progression through exosomal miRNAs.

Methods

CAFs and normal fibroblasts (NFs) were isolated from human bladder cancer specimens and adjacent normal tissues. CAFs and NFs were subcutaneously co-injected with bladder cancer cell lines (T24 and 5637) into male athymic nude mice. Exosomes isolated from conditional media of NFs and CAFs were used for *in vitro* study and miRNA microarray analysis. Sphere formation assay and ALDH enzyme activity were used for representation of CSCs features. Human UBC samples were enrolled to analyze their potential clinical relevance.

Results

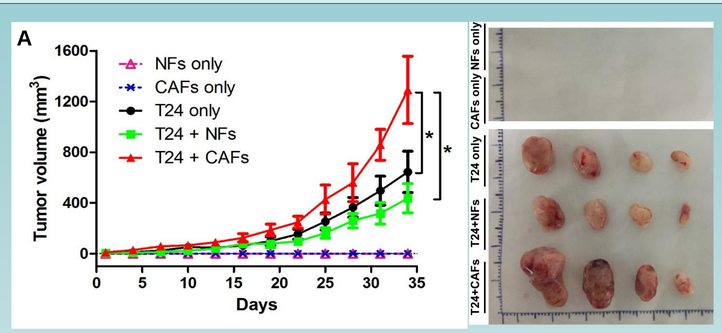
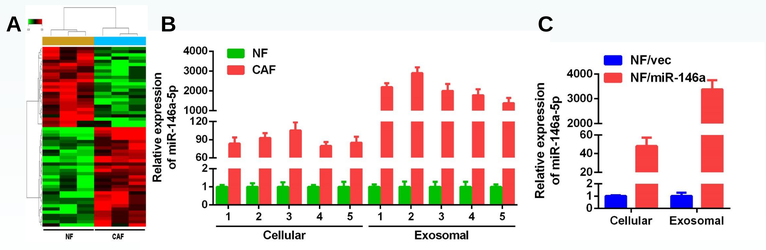


Fig.1 A) Tumor volume was determined in different subcutaneous xenograft groups. B) Primary and secondary sphere number was counted in different xenograft groups. C-E) ALDH$^+$, CSC markers and sphere formation were determined in T24 and 5637 cells fed with exosomes of NFs or CAFs.



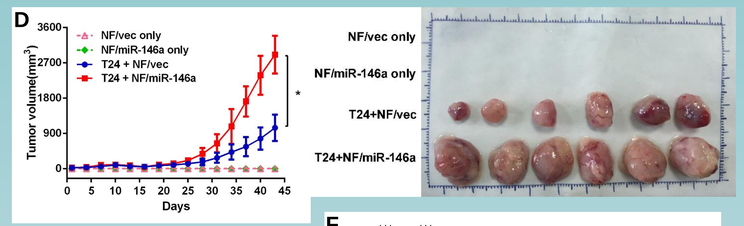


Fig.2 A) Cluster map of miRNA microarray in NF and CAF exosomes. B) Expression of miR-146a in five pairs of NF and CAF. C) Stable overexpression of miR-146a in NFs (NF/miR-146a). D-F) Tumor volume, CSC markers and sphere formation were determined in NF/vec and NF/miR-146a xenografts.

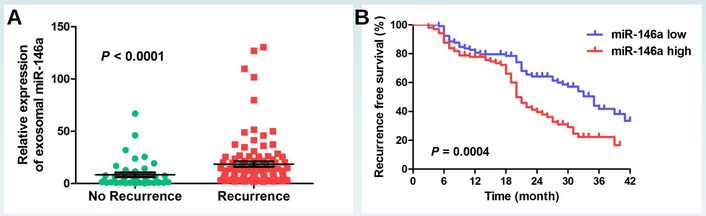


Fig.3 A) Expression of serum exosomal miR-146a in patients with bladder cancer recurrence or not after primary TURBT within two years. B) Recurrence free survival rate in bladder cancer patients with exosomal miR-146a high or low (median value as cut-off point).

Conclusions

Cancer-associated fibroblasts secreted exosomal miR-146a promotes bladder cancer stem-like features *in vitro* and *in vivo*. Exosomal miR-146a is associated with clinical bladder cancer recurrence.