Novel role of XPO1 in regulating MicroRNAs related to pancreatic ductal adenocarcinoma invasion and metastasis

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ABSTRACT

There are no known reports on the role of exportin 1 (XPO1) in microRNA biology. In this study, we for the first time demonstrate that interfering with XPO1 machinery can influence miRNA signaling leading to suppression of pancreatic ductal adenocarcinoma (PDAC) proliferation, invasion and metastasis. Our molecular experiments showed that the inhibition of cell proliferation and migration by the XPO1 inhibitor, selinexor, is mediated through the up-regulation of miR-145 and down-regulation of its target genes including EGFR, MMP1, MT-MMP, c-Myc, Pak4 and Sox-2. Selinexor also regulates the expression of miR-34c, let-7d, and miR-205.

RESULTS

Selinexor treatment or miR-145 mimic transfection inhibited the expression of miR-145 target or downstream genes at protein or RNA level. MiaPaCa-2, Aspc-1, Panc-1, Colo357 and HPAC cells were treated with 500nM selinexor or transfected with miR-145 mimic or control mimic or L3.6pl for 48 hours. The total protein was extracted from each sample and subjected to Western Blot analysis for detection of EGFR, MMP1, MT-MMP, c-Myc, Pak4 and p21 expression at protein level. Total RNA was extracted and subjected to real-time PCR for detection of Sox-2 and Pak4.

METHODS

miRNA arrays and RT-PCR were performed on total RNA samples from PDAC cell lines (HPAC, MiaPaCa-2, Asp-1 and L3.6pl) and normal human pancreatic ductal epithelial (HPDE) cells. PDAC cells were treated with selinexor or transfected with XPO1 siRNA or miR-145 mimic. The total RNA and protein from treated or transfected cells were subjected to real-time PCR or immunoblot analysis. The impact of selinexor on PDAC proliferation, invasion and migrations was also evaluated using MTT and scratch assay.

CONCLUSIONS

These results are the first to show that targeted inhibition of the nuclear exporter protein XPO1 by RNAi or chemically by selinexor could restore tumor suppressive miRNAs in PDAC. Selinexor, a Phase II drug, could be used in combination with conventional chemotherapeutics for better treatment outcome in aggressive PDAC that warrants further clinical investigations.