Oncolipid Sphingosine Kinase is involved in neuroendocrine transdifferentiation of prostate cancer (NEPC)

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Introduction

Androgen deprivation therapy (ADT) is considered the most effective regimen to treat metastatic prostate cancer (PCa). Eventually, almost all patients develop castration resistant PCa (CRPC) that is often associated with neuroendocrine phenotypes. Until now, there is very limited agents available for NEPC therapy. Obviously, identifying underlying mechanism of NEPC could provide new targeting strategies to eradicate this disease. From cBioPortal of PCa database, it appears that 22% NEPC patients exhibit sphingosine kinase-1 (SphK1) gene amplification as well as positive correlation of expression between SphK1 and NE genes; this enzyme produces sphingosine 1-phosphate (S1P) that is known for tumor cell growth, survival, and therapeutic resistance. Thus, in this study, we have dissected the underlying mechanism of Sphk1-elicited NEPC and further explored Sphk1 as a potential druggable target.

Methods

CRISPR technology was used to knockout (KO) Sphk1 gene in PC3, 22RV1, ARCaP-IIB5 and ARCaP-IIG5 cells and SphK1 cDNA vector was used for overexpression (OE) in LNCaP. The gene expression is measured via qRT-PCR and Western blot. ChIP assay is used to map the interactive site of REST. The REST–transcriptional activity is determined using the luciferase assay from BRN2 and SOX2 gene promoter. The SCID male mice carrying 22RV1 or IIG5 tumor are subjected to experimental therapy.

Results

Elevation of Sphk1 can be detected in several PCa cell lines treated with anti-androgens. Data from SphK1-KO or -OE cells demonstrated the Sphk1-S1P-S1P receptors (S1PRs) is a key pathway to up-regulate the master neural transcription factors (NETFs: BRN2, EZH2, FOXA2 and SOX2) and NE biomarkers leading to the onset of NEPC that is resistant to ADT. Mechanistically, Erk activation by S1P appears to be the key downstream effector of S1PRs, which further phosphorylates REST (a master neural transcriptional repressor) at the S861 and S864 sites resulted in protein degradation. Indeed, elevated REST expression was detected in SphK1 KO cells. ChIP and reporter gene data confirmed the activity of REST in NETF expression and REST OE in PC3, 22RV1 and IIG5 cells significantly reduced NE phenotypes. Noticeably, FTY720 or

SKI-II (Sphk1 inhibitors) exhibited high potency to suppress the growth of 22RV1 and IIG5 using xenograft mouse models.

Conclusions

SphK1-S1P-S1PRs is a critical upstream pathway involved in NEPC progression. SphK1 targeted small molecule inhibitors have potential impact on clinical application on NEPC therapy.