Selective Inhibitor of Nuclear Export (SINE) compounds prevent migration and proliferation of Triple Negative Breast Cancer (TNBC) cells by restoring expression of ARRD3C

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Introduction

TNBC is the most aggressive types with worst clinical outcomes among the four distinct subtypes (Luminal A, Luminal B, HER2-positive and TNBC) classified by gene expression profiles.

Currently, there is no approved targeted therapy for either early or late stage TNBC patients as a majority of TNBC lack therapeutically targetable hormone receptors (estrogen and progesterone) and HER2. Some TNBC-targeted therapies includes cetuximab and anti-EGFR monoclonal antibody, imatinib (c-KIT tyrosine kinase inhibitor), irinap (PARP inhibitor) and cisplatin are currently undergoing preclinical/clinical investigation, but the trials of these agents have failed to demonstrate clinical efficacy. For this reason, discovering effective molecular targets and associated therapies for TNBC is an urgent issue.

ARRD3C (arrestin-related domain-containing protein-3) is a 65 human-arrestin family, is a negative regulator of the β2-adrenergic receptor (β2AR) and integrin β4 (ITGB4), thereby regulating ubiquitination and subsequent degradation of phosphorylated forms of these receptors. A constitutive regulation of β2AR and ITGB4, whose roles in breast cancer progression are established, indicates the role of ARRD3C as a potential metastatic suppressor. Our previous studies demonstrated that epigenetic silencing of ARRD3C is linked to aggressive nature of TNBC cells, suggesting that ARRD3C could be a novel therapeutic target of TNBC.

Selective Inhibitors of Nuclear Export (SINE) compounds are small molecule inhibitors of Exportin-1 (XPO-1, also known as CRM1). Expression of XPO-1 is up-regulated in various types of cancers and its overexpression is linked to poor prognosis. Inhibition of XPO-1 by SINE compounds results in nuclear retention and activation of tumor suppressor proteins such as p53, Ikβ and FOXO. In the following study we used two SINE compounds, KPT-185 and selinexor, a clinical SINE compound which is being evaluated in multiple later stage clinical trials in patients with relapsed and refractory hematological and solid tumor malignancies.

Objective

The main aim of this project is to investigate the hypothesis that small molecule compounds restoring ARRD3C level could potentially be a novel therapeutic option for TNBC.

Questions to be investigated:
1. Can SINE compounds induce anti-cancer effects in TNBC model?
2. If yes, then does ARRD3C mediate the anti-cancer affects of SINE compounds?

Results

SINE compounds restore ARRD3C expression in TNBC cell lines

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Sensitivity of SINE compounds inversely correlates with basal levels of ARRD3C expression in breast cancer cell lines

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SINE compounds synergize with cisplatin to inhibit TNBC cell proliferation

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Conclusions

1. SINE compounds have potent inhibitory effects in TNBC model in vitro and in vivo.
2. SINE compounds restore ARRD3C expression and re-stabilization of this expression shows important therapeutic effects in TNBC.
3. SINE compounds and specifically selinexor could be an effective therapeutic option for TNBC with down-regulated ARRD3C expression.

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