The Cancer Stem Cell-Targeting Wnt Inhibitor VS-507 Reduces Breast Cancer Growth and Metastasis


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ABSTRACT

Cancer stem cells (CSCs) support tumor viability and growth through their ability to self-renew and differentiate into heterogeneous tumor tissue. CSCs are typically resistant to standard cytotoxic agents, leading to their enrichment and the consequent regrowth of refractory tumors. While this population has been challenging to directly target therapeutically, we are focused on novel agents, such as VS-507, that selectively target the cancer stem cell subpopulation in vivo.

Previously, we and others have shown that VS-507, a cancer stem-cell specific agent, inhibits Wnt signaling with corresponding reduction of the β-catenin protein, a Frizzled co-receptor upregulated in breast cancer cell lines. In the current study, we have continued to examine the effect of VS-507 on the Wnt/β-catenin signaling pathway to further elucidate its mechanism of action. We determined that VS-507 also decreases expression of the second Frizzled co-receptor LRP5 in MDA-MB-231 breast cancer cells stimulated by Wnt3A. The combined inhibition of the co-receptors LRP5 and LRP6 may contribute to the observed inhibition of β-catenin-mediated transcription by VS-507 in a TOP-Flash assay. Accordingly, VS-507 reduced expression of Axin2, a transcriptional target of β-catenin.

Because human breast cancer cell lines represent a mixed population of CSC and non-CSC cells, we evaluated VS-507 across a panel of cell lines by monitoring changes in viability and in the percentage of CSCs. In SUM159 triple negative breast cancer cells, VS-507 had micromolar potency against the bulk population with preferential nanomolar potency against the ALDEFLUOR+ CSC population with similar effects observed in the MCF7 side population (SP) CSC assay. In contrast, cytotoxic anticancer drugs such as paclitaxel and cisplatin increased the percentage of ALDEFLUOR+ CSCs under similar conditions.

In vivo, oral administration of VS-507 (3 mg/kg, BID) as a single agent partially inhibited MDA-MB-231 tumor growth, consistent with its observed inhibition of the CSC subpopulation. Furthermore, VS-507 inhibited lung metastasis in a 4T1.2 murine breast cancer model. In summary, these results further elucidate the mechanism by which VS-507 inhibits Wnt/β-catenin signaling. VS-507 reduces tumor cell proliferation in vitro with preferential effects on CSCs which translate to inhibition of tumor growth and inhibition of metastasis in mouse models. These data further elucidate the mechanism and promise of VS-507 as a novel CSC agent.

INTRODUCTION

Structure of VS-507 and the Wnt/β-catenin pathway.

VS-507 is a natural product that was identified from a chemical screen for agents that selectively target breast cancer cells.

(Grupa PK, et al., Cell, 2009)

RESULTS

Fig 1: VS-507 causes dose-dependent inhibition of Wnt3A-stimulated β-catenin-mediated transcription in MDA-MB-231 breast cancer cells

Fig 2: VS-507 reduces CSCs in a secondary tumoursphere assay in contrast to paclitaxel as evidenced by a decrease in tumoursphere formation

Fig 3: VS-507 reduces CSC side population (SP) cells

Fig 4: VS-507 exhibits selective potency against ALDEFLUOR+ CSCs as compared to ALDEFLUOR- non-CSCs.

Fig 5: VS-507 partially inhibits MDA-MB-231 xenograft tumor growth and reduces 4T1.2 triple negative breast cancer metastasis to the lung

SUMMARY

VS-507 inhibits Wnt/β-catenin signaling in breast cancer cells
- Reduction of LRP5 & LRP6 expression
- Dose-dependent inhibition of β-catenin-mediated transcription
VS-507 selectively targets cancer stem cells in triple negative breast cancer lines
- Dose-dependent reduction in the percentage of side population CSC cells
- Blockade of secondary tumoursphere formation in contrast to paclitaxel
- Selective reduction of ALDEFLUOR-positive CSCs in contrast to standard of care agents

VS-507 inhibits tumor growth and metastasis
- Partial inhibition of MDA-MB-231 tumor growth
- Reduction of 4T1.2 lung experimental metastasis