The FAK Inhibitors VS-4718 and VS-5095 Attenuate Breast Cancer Stem Cell Function in vitro and Tumor Growth in vivo


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ABSTRACT

As a key mediator of integrin signaling, focal adhesion kinase (FAK) regulates cellular responses to extracellular matrix interactions. Amplification and overexpression of FAK have been observed in aggressive human cancers including breast cancer. FAK has been implicated in multiple steps in carcinogenesis including tumor growth, metastasis and angiogenesis. We now demonstrate the importance of FAK in breast cancer stem cell function, and the reduction of cancer stem cell function by the selective FAK inhibitors VS-4718 and VS-5095.

INTRODUCTION

FAK has been implicated in the self-renewal of cancer stem cells (CSC) and breast cancer development:

- Inactivation of FAK or its integrin-compromised mammary CSC self-renewal (Taddei, Nature Cell Biol 2008)
- In the MMTV-PyMT model, targeted deletion of FAK in mouse mammary epithelium reduced the number and self-renewal capability of cancer/progenitor cells & impaired tumor growth (Luo, Cancer Res 2009)
- FAK amplification correlates with poor survival of breast cancer patients (Pilyavskaya, ICI 2009)
- Integrin β1 – FAK signaling is critical for proliferation of micro-metastatic breast cancer cells in the lung (Shiube & Weinberg, PNAS 2009)

RESULTS

Fig 1: VS-4718 and VS-5095 are selective FAK inhibitors with potent cell-based activities

Fig 2: FAK inhibitor VS-4718 show preferential effects on mesenchymal HMLEs (CSCs)

Fig 3: FAK inhibitor VS-4718 reduce the % of Aldefluor positive cells in contrast to paclitaxel

Fig 4: VS-4718 and VS-5095 inhibit the proliferation/survival of breast cancer cells in 3D matrigel but not in 2D cell culture plates

Fig 5: FAK is important for the self renewal of cancer stem cells in vitro

Fig 6: Potent in vivo antitumor activity and inhibition of FAK in tumors

SUMMARY

Here we provide in vitro evidence that FAK inhibitors VS-4718 and VS-5095 target breast cancer stem cells. These results demonstrate the importance of FAK in the self-renewal of breast cancer stem cells and support the clinical development of the selective FAK inhibitors VS-4718 and VS-5095 to target breast cancer stem cells for the treatment of triple negative breast cancer.