Novel Small Molecule Compound disrupts the SIX1/EYA2 Complex and Inhibits Breast Cancer Metastasis

Hengbo Zhou¹, Melanie Blevins², Deguang Kong³, Jessica Hsu³, Rui Zhao³, Heide L. Ford³
1 Department of Cancer Biology, University of Colorado Anschutz Medical Campus
2 Department of Biochemistry and Molecular Genetics, University of Colorado Anschutz Medical Campus
3 Department of Pharmacology, University of Colorado Anschutz Medical Campus

Introduction

Homeobox protein SIX1 and its interacting partner E14 family are proved to be highly correlated to several hall marks of cancer. Especially, co-overexpression of SIX1 and EYA2 dramatically reduces survival of breast cancer patients. Based on our previous study, SIX1/EYA2 complex could up-regulate TGF-β signaling, thereby promoting epithelial-mesenchymal transition and metastasis of breast cancer cells. Therefore, disruption of SIX1/EYA interaction may be substantial to inhibit metastasis in breast cancer context.

Method

Our previous work has shown V17 of SIX1 and Y537 of EYA2 at the interface are crucial to SIX1/EYA interaction and suppress SIX1-induced metastasis, indicating potential of developing small molecule inhibitor to disrupt SIX1/EYA2 complex at the interface thereby inhibiting metastasis.

Results

8430 is found to break SIX1-EYA2 interaction demonstrated by A) proximity ligation assay and B) immunoprecipitation.

Figure 1 8430 disrupts SIX1/EYA2 complex

Figure 2 8430 reverse SIX1-induced cellular phenotypes

Figure 3 8430 reverses SIX1-mediated transcription profile

Figure 4 8430 suppresses SIX1-driven metastasis

Summary

Pharmaceutical inhibition of SIX1/EYA2 interaction is able to abolish SIX1-driven cellular phenotypes as well as metastatic burden in breast cancer.

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