Small Molecule Inhibitor of Forkhead Box Protein C2 (FOXC2): Therapeutic Candidate and Diagnostic Tool for Metastatic Cancers

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Technology description

The transcription factor Forkhead Box Protein C2 (FOXC2) is known to be necessary to initiate and maintain the epithelial-mesenchymal transition (EMT), which has been a hot target for therapeutic intervention against cancers. The overexpression of FOXC2 bestows cancer cells with metastatic and cancer stem cell (CSC)-like phenotypes, i.e., higher motility, invasiveness, self-renewal, and therapeutic resistance. Inventors at The University of Texas at Dallas are pioneering the development of small molecule inhibitors against FOXC2 – herein, we reveal one such novel chemical entity, MC-1-F2. MC-1-F2 reverses EMT by inducing cadherin switching through degradation of FOXC2, thereby inhibiting its nuclear localization. In cell lines expressing FOXC2, MC-1-F2 demonstrates its ability to inhibit cell proliferation, tumorigenicity, and metastasis. It serves as a lead compound for future development of potent therapeutic drugs targeting various metastatic cancers. For scientists, it is a key reagent to study the network of EMT signaling pathways.

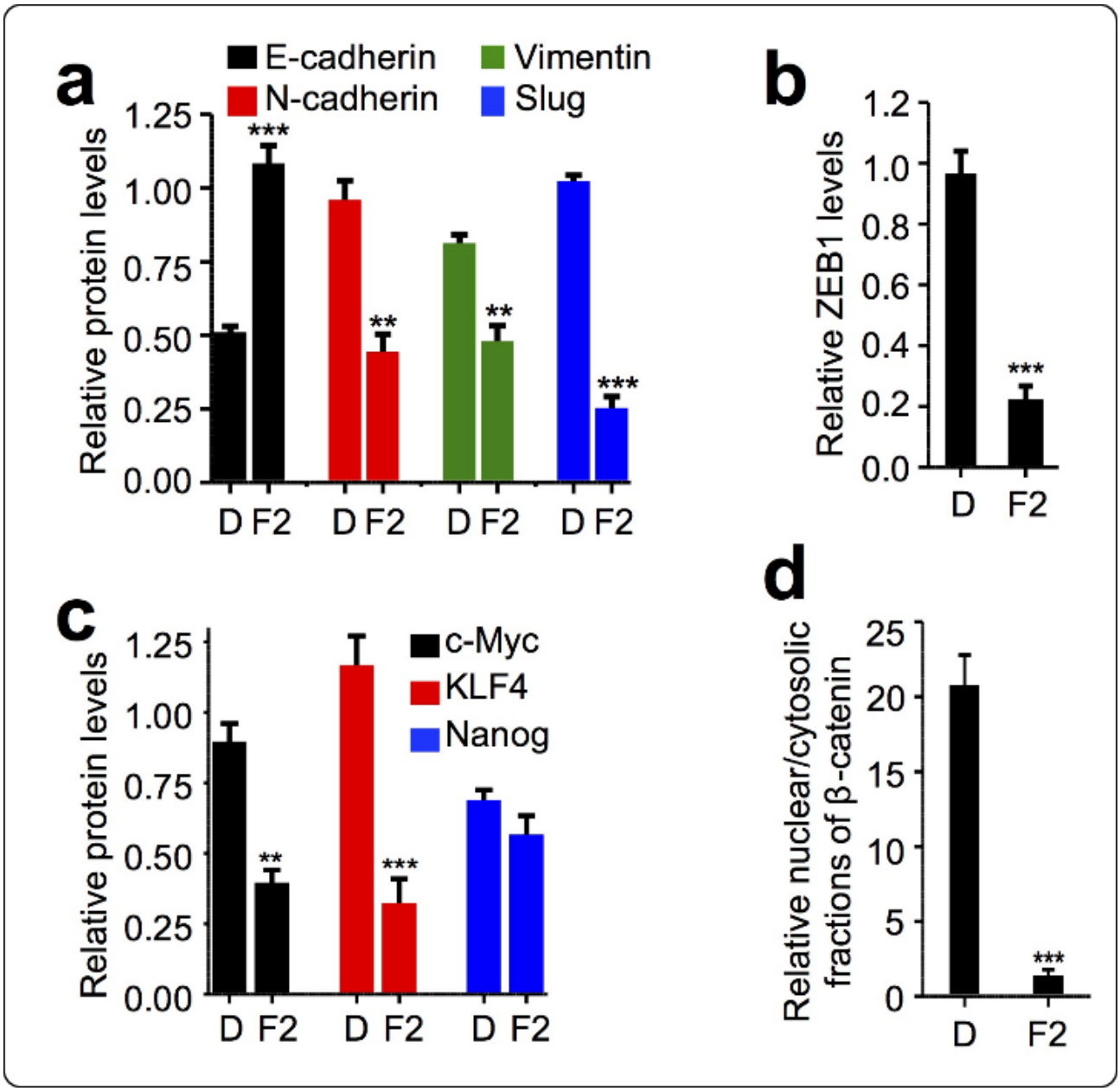

Figure 1: Inhibition of EMT and CSC activity by MC-1-F2.a-d) Western blot analysis of EMT markers (a), ZEB1 (b), CSC markers (c) and the cytosolic and nuclear fractions of b-catenin (d) of MDA-MB-231 cells treated with DMSO (D) or MC-1-F2 (F2, 20 μM) for 48 hours. Error bars represent s.d. from triplicate experiments. Statistical comparisons performed by Student’ s t-test. ***p<0.0005; **p<0.005

Technical Summary:

MC-1-F2 has a high binding specificity for full-length FOXC2; it binds very weakly to DNA-binding domain (DBD) of FOXC2. This is a very significant characteristic of this compound since these transcription factors share very similar DBDs, while MC-1-F2 can distinguish FOXC2 from other forkhead family members. A drug affinity responsive target stability (DARTS) assay further confirmed its binding to endogenously expressed FOXC2.

This small molecule decreases the expression level of mesenchymal markers (i.e., Vimentin, Slug, ZEB1) and CSC markers. It also reverses EMT progression through the induction of FOXC2 degradation, and the inhibition of FOXC2’ s nuclear localization and transcription. There is also a strong possibility for MC-1-F2 to inhibit CSC properties of cancer cells, as results showed decreased nuclear localization of

β-catenin, a hallmark of a major CSC pathway. Furthermore, it demonstrates specific anti-tumor activity, such as higher cytotoxicity, metastasis inhibition, and stronger anti-proliferative effects against cancer cell lines in a FOXC2 expression level-dependent manner. Previously, downregulation of ZEB1 has been shown to restore tumor cell' s lost sensitivity to anticancer therapy. Our data opens the possibility for MC-1-F2 to re-sensitize cancer cells to chemotherapy and radiation therapy.

Value Proposition:

As a novel small molecule inhibitor of FOXC2 and EMT-associated transcription factor, MC-1-F2 serves as a lead compound for future anti-cancer therapeutics. Behind this great invention is our discovery and validation platform which can also support any third party' s drug development program of FOXC2 modulators. MC-1-F2 will also contribute significantly as an essential research reagent to elucidate mechanisms by which FOXC2 orchestrates the EMT signaling network.

Publication:

Castaneda, Maria, et al. "A Forkhead Box Protein C2 Inhibitor: Targeting Epithelial-Mesenchymal Transition and Cancer Metastasis." ChemBioChem, 25 Mar. 2018, doi:10.1002/cbic.201800022.

Application area

Lead compound for developing anti-cancer agents
Highly-useful research reagent to study EMT-signaling pathway
Drug screening platform for developing FOXC2 modulators

Advantages

Novel Inhibitor –New chemical entity to inhibit EMT-associated transcription factor, FOXC2
High Specificity– The MC-1-F2 may have very weak interaction with forkhead transcription family members except FOXC2, most of all share a common DBD. This data leads to an assumption that the high specificity of MC-1-F2 to FOXC2 is most likely to be mediated by domains other than the DBD
Expression-Dependence– MC-1-F2 exerts its cellular activity proportionally against cell lines with elevated FOXC2 expression levels
Anti-cancer activity– Inhibits cancer cell metastasis, mediates proteosomal degradation, and blocks nuclear localization of FOXC2
Reverses EMT Progression– Induces cadherin switching which decreases the nuclear fraction of β-catenin and inhibits EMT/CSC properties of cancer cells

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