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Abstract

Lung cancer is the leading cause of cancer deaths accounting for about 22% of all cancer related cases in both males and females. Lung cancers are broadly grouped into two types mainly small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) with SCLC accounting for about 15% of all lung cancer cases. SCLC is different from NSCLC because in most cases it originates centrally in the bronchi and is frequently seen in smokers. SCLC is aggressive and one of the most malignant forms of tumor characterized by uncontrolled rapid growth of certain cells in the lungs. SCLC displays poor prognosis because of early-stage metastasis, acquisition of chemoresistance, and has a high rate of recurrence. One of major drivers of chemoresistance is the transcription factor Forkhead box protein M1 (FOXM1) that is responsible for modulating cell cycle proliferation, maintenance of genomic stability, DNA damage response, and cell differentiation in numerous tumor entities. In order to explore properties of SCLC cancer cell lines, human non-bone metastatic SBC3, bone metastatic SBC5, H1688, and murine (RPM) cells were treated with a FOXM1 inhibitor known as FDI-6. As a transcription factor FOXMI binds sequence-specific motifs on DNA through its DNA-binding domain activating proliferation and differentiation-associated genes. Anomalous overexpression of FOXMI is a crucial characteristic in oncogenesis and the development of SCLC. FDI-6 is a novel small molecule inhibitor of FOXM1, and it works by binding directly to FOXM1 protein, to displace FOXM1 from genomic targets in SCLC cells prompting concomitant translational downregulation. Functional assays performed confirm that FDI-6 is a viable FOXMI inhibitor showing therapeutic efficacies in SCLC.

Hypothesis

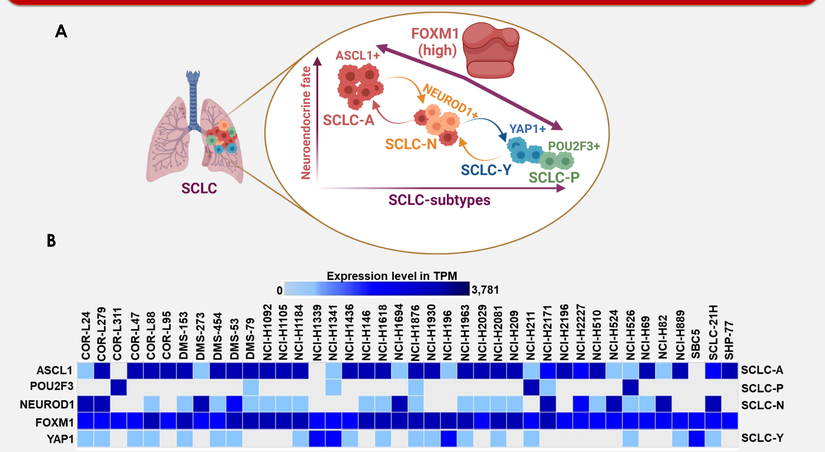
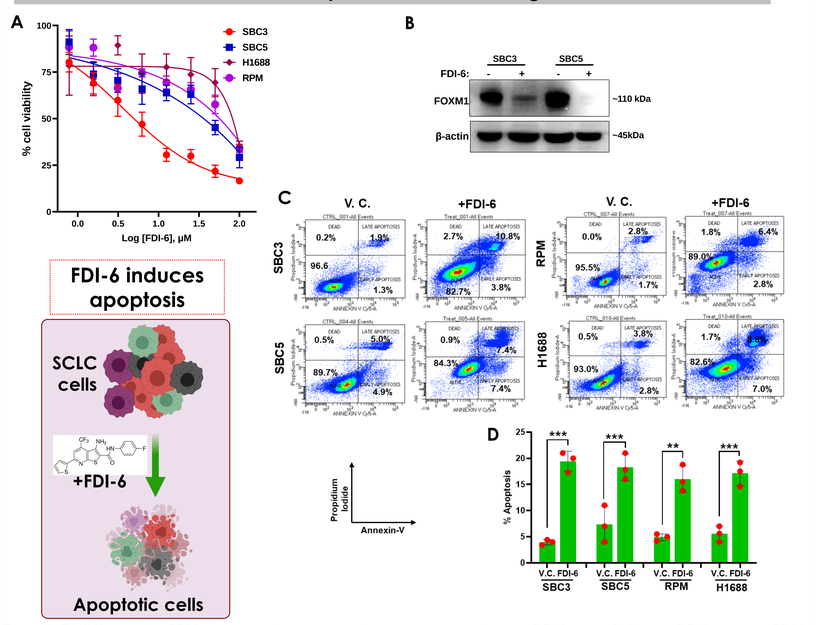


Figure 1: Expression of FOXM1 in association with lineage specific markers such as neuroendocrine (NE) or non-neuroendocrine (Non-NE) in SCLC cell lines. (A) Hypothetical representative image showing the involvement of FOXM1 in different SCLC subtypes. **(B)** Heat map of lineage specific markers (ASCL1, POU2F3, NEURORD1, and YAP1), and FOXM1 as analyzed in NCI-panel of SCLC cell lines. (NCI: National Cancer Institute, NIH).

RESULTS

FDI-6 decreases the viability of SCLC cells through FOXM1 inhibition



FDI-6 induces apoptosis

Figure 2: FOXM1 inhibitor (FDI-6) decreases the cell viability and induces apoptosis in SCLC cells. (A) Multiple SCLC cell lines (SBC3, SBC5, H1688, and RPM) were treated with FDI-6 for 48h and subjected to MTT assay/cell viability assay. **(B)** Protein expression studies of FOXM1 in SBC3 and SBC5 cells treated with IC_{50} dose of FDI-6. **(C)** SCLC cells (SBC3, SBC5, H1688, and RPM) were treated with FDI-6 and subjected to FACS analysis for apoptosis using the Annexin V-Cy5/PI staining. **(D)** Quantification of percent apoptosis, statistical analysis showed that FDI-6 significantly increases the percentage of apoptotic cells compared to vehicle control. ***p<0.0001, **p<0.001.

FDI-6 inhibits the cell migration and colonogenic potential of SCLC cells

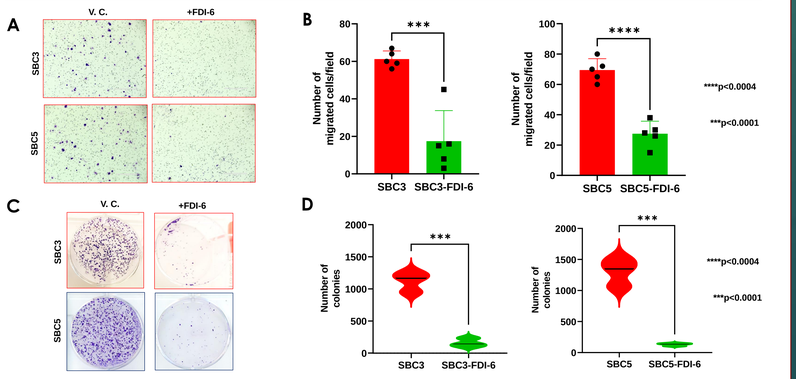
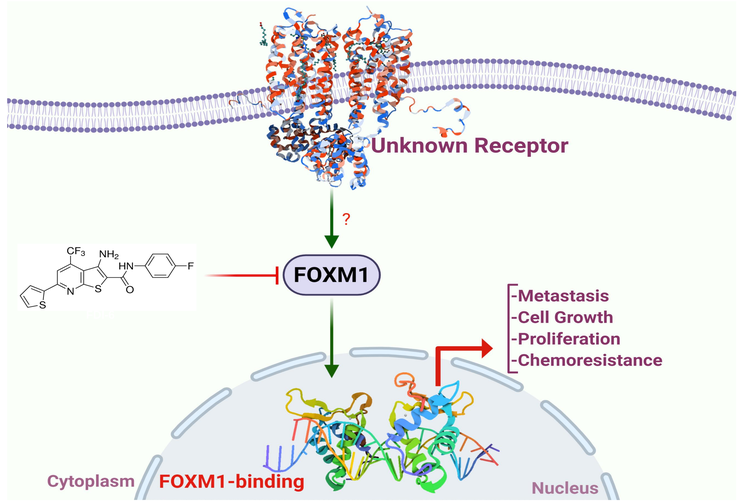


Figure 3: FOXM1(i) decreases the migration and colonization of SCLC cells. (A) SBC3 and SBC5 cells are treated with FDI-6 and analyzed for cell migration using transwell chamber assay. **(B)** Quantification of migrated cells through transwell chamber in SBC3 and SBC5 cells treated with vehicle control or FDI-6. **(C)** SBC3 and SBC5 cells were subjected for colony formation under different treatments (vehicle control and FDI-6) showing decreased colony formation in FDI-6 treated cells. **(D)** Quantification of colonies obtained in vehicle control or FDI-6 treated groups.

Mechanism?



Conclusions

- FOXM1 is a transcription factor found overexpressed in multiple cancers, including SCLC.
- High FOXM1 in all SCLC subtypes contributing towards;
  - cell growth
  - metastasis
- FOXM1 constitutes as an important therapeutic target.
- FOXM1 binds to the promoter region of oncogenic regulators in SCLC and contributes to tumorigenesis.
- Novel small molecules inhibitor of FOXM1 named FDI-6 shows therapeutic efficacies in SCLC cell lines.
- FDI-6 (FOXM1i) decreases the cell viability of human and mouse SCLC cell lines.
- FDI-6 induces apoptosis in SCLC cells.
- FDI-6 decreases the colonization and cell migration potential of SCLC cell lines.
- Targeting of FOXM1 and associated oncogenic axis is a novel therapeutic approach for SCLC.

References

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