中文題目：MDFIC蛋白藉由Wnt/β-catenin訊息傳遞路徑調控上皮型態非小細胞肺癌幹細胞之抗藥性

英文題目：MDFIC protein promotes drug resistance in epithelial type non-small cell lung cancer stem cell through Wnt/β-catenin signaling

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**Background:** The epithelial-to-mesenchymal transition (EMT) has been described to promote drug resistance and cancer stem cell (CSC) properties. Many studies demonstrated that a major proportion of circulating tumor cell (CTC) exhibits EMT and CSC characteristics. A recent finding revealed the presence of epithelial type (EpCAM+) CTC was associated with poor outcome, whereas the mesenchymal type (EpCAM-) CTC were not. We therefore hypothesize that the epithelial-type CSC may have more drug resistant ability.

**Methods:** We isolated epithelial type (E+) and mesenchymal type (E-) CSC (CD133+) cells and non-CSC(CD133-) cells from PC14 lung cancer cell line by fluorescence assisted cell sorting. We used western blot, QPCR, immunofluorescence, sphere formation assay and tumor xenograft assay to characterize the 4 subpopulations. The drug resistant ability was determined by cell viability assay and in vivo drug response assays. The drug resistant signature was identified by comparing the gene expression profile from four subpopulations and Gene Expression Omnibus (GEO) database. Knockdown and overexpression of MDFIC in PC14 subpopulations were established by using lentivirus vectors. Immunoprecipitation and subcellular fractionation were performed for drug resistant mechanism investigation.

**Results:** The epithelial type PC14 cancer stem cell (E+/CD133+ subpopulation) exhibited higher sphere formation ability and was more resistant to the treatment of chemotherapy agents compared to the mesenchymal type (E-CD133+ subpopulation) subpopulation in vitro and in vivo. Gene expression profiling showed 86 genes were bioinformatically predicted as drug resistant signature and were correlated with the disease free survival of the patients with lung cancer. Among these genes, the mRNA level of 20 genes were significantly related to the patient's prognosis in the GSE31210 dataset. Human I-mfa domain-containing protein (MDFIC) was highly expressed in E+/CD133+ subpopulation. Knockdown and overexpression of MDFIC modulates drug resistance ability in cancer cells. MDFIC increased the level of free β-catenin through binding and stabilizing the axin-GSK3-β-β-catenin destruction complex and increased the transcriptional activity of Wnt/β-catenin signaling.

**Conclusion:** The epithelial type lung cancer stem cells are more resistant to the chemotherapy through MDFIC mediated Wnt/β-catenin signaling activation.