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Structure guided design of a therapeutic inhibitor of SALL4-NuRD in liver cancer

Bee Hui Liu

Cancer Science Institute of Singapore, Singapore

Nuclear factors are often considered undruggable and conventional high throughput screening of small molecules has resulted in limited success. SALL4 is a nuclear factor that is specifically expressed in fetal cell, where it is vital to developmental events and the maintenance of stem cell pluripotency. SALL4 has recently emerged as a key player in hepatocellular carcinoma. In cancer cells, SALL4 recruits NURD to PTEN promoter, resulting in histone deacetylation and transcriptional repression. However, the binding mechanism of SALL4 to NuRD remained elusive. Understanding the mechanism will enable the development of specific inhibitors against the SALL4-NURD interaction in liver cancer, a malignancy with fast increasing incidence and mortality rate, with no suitable treatment regime. Here, we report the development of a potent anti-tumor therapeutic SALL4 peptide (named FFW), based on our elucidation of the crystal structure of SALL4-RBBp4 complex at 2.7Å. We show that FFW has 56- fold increase in target affinity compared to wild-type peptide, and exhibits potent anti-tumor activity in xenograft mouse models (tumor growth inhibition=85%), supporting FFW as a highly viable drug candidate. With further refinement, this FFW peptide could potentially fulfill the unmet need in liver cancer and other malignancies characterized by SALL4 expression. This mode of structural analysis to target “undruggable” nuclear factors could also prove a highly viable approach in other areas of cancer research.

Biography

Bee Hui Liu, PhD, is a Molecular Biologist working in the stream of Translational Medicine. She received her PhD from National University of Singapore and is currently a Post-doctoral fellow at Prof. Daniel Tenen's Laboratory in Cancer Science Institute of Singapore. She is interested in developing therapeutic agents against epigenetic complexes in cancer. She solved the first SALL4-RBBp4 structure and invented therapeutic peptides targeting this particular complex that specifically elevated in a subset of liver cancer. She also heads a multi-disciplinary collaborative team of local and international scientists, spearheading small molecule- and fragment based- drug screening projects on liver cancer.

csilbh@nus.edu.sg

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