Level of FACT complex subunit, SSRP1, in cancer as a prognostic marker of aggressive disease

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Summary

Background: SSRP1 is a subunit of the FACT (Facilitates Chromatin Transcription) complex involved in chromatin remodeling. We have found that SSRP1:FACT, expression which in normal tissues is limited to stem cells, is expressed in different types of cancer.

Material and methods: We assessed expression of FACT in normal and cancerous tissues of different organs (>2,000 samples) and protein (>800 samples) levels to evaluate the correlation between FACT expression and clinical features of different cancers. We also ran in vitro and in vivo experiments to evaluate how modulation of FACT levels affects tumorigenic transformation and tumor cell properties. Finally we obtained genome wide distribution of FACT using ChIP-seq to identify genes which transcription requires FACT assistance.

Results: FACT expression is significantly higher in tumors of patients with poor overall survival (all cancers, breast cancer (BC), NSCLC), higher incidence of metastasis (BC, NSCLC, RCC) and the presence of other markers associated with poor prognosis (BC, NSCLC, colon cancer). Ectopic expression of FACT in normal cells does not drive transformation, but increases efficiency of oncogene-driven transformation. Conversely a reduction of FACT level, using a RNAi approach, reduces transformation efficiency and interines with tumor, but not normal cell growth.

Conclusion: FACT is an attractive target and marker of poorly differentiated aggressive cancers based on its role as an accelerator of oncogenic transformation through selective chromatin remodeling of genes involved in cancer stress response and maintenance of pluripotent cell state.

Background

FACT (Facilitates Chromatin Transcription)

- FACT is heterodimer of two subunits SPT16 (Suppressor of Ty 16) and SSRP1 (Structure Specific Recognition protein 1)
- Chromatin remodeling complex: exchanges histones dimers and tetramers within nucleosome
- Involved in transcription, replication, DNA repair

Curaxins and CBL0137

- We have found that FACT is a target of small molecule with anti-cancer activity, Curaxins (Ref.1).
- Toxicity of Curaxins to tumor cells depends on the level of FACT

Lead Curaxin compound, CBL0137, is being tested in Phase I clinical trials against advanced treatment resistant solid cancers and refractory lymphomas

SSRP1/FACT expression in normal tissues