Cancer TNT

Ashwin Ram
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Background: Chromatin Writers, Readers, Erasers

- **Writer**
  - eg. HAT, HMT

- **Reader**
  - eg. bromodomain

- **Eraser**
  - eg. HDAC, KDM
The writer HAT1:
A known H4 lysine 5,12 di-acetyltransferase

Western blot for histone H4 modifications after control and HAT1 siRNA transfections.
HAT1: EGF-stimulated

Immunoprecipitation / WB to measure HAT1 levels +/- EGF

Heatmap of gene expression changes of all human histone acetyltransferases +/- EGF and siRNA treatments shows HAT1 expression is EGF-dependent
Working model of HAT1: The oldest “new” histone acetyltransferase

- EGF
- EGFR
- HAT1
- Rbap46/48
- H3
- H4
- H2A
- H2B
- S phase

plasma membrane

nuclear membrane

HAT1
Surprise: HAT1 also binds (a few sites) on chromatin
HAT1 ChipSeq signal sits on Hist1 locus on Chromosome 6

HAT1 bound sites (zoom)

HAT1 ChIP-seq peaks cluster at histone H4 promoters.
Is HAT1 a transcription factor for its substrate (H4)?

EGF → EGFR → plasma membrane

HAT1 → Rbap46/48 → nuclear membrane

H4 → H3 → S phase

H2B
HAT1 is required for S-phase burst of histone H4 mRNA
HAT1 loss: Life with less histones

EGF

EGFR

plasma membrane

HAT1

Rbap46/48

nuclear membrane

H4

H3

H2B

S phase
HAT1 loss: Life with less histones

• Implications: A new cancer target?
  • Multimodal
    • Depletion of H4
    • Epigenomic “scrambling” leading to sensitization to genotoxic stressors
    • EIO – new gene expression signatures leading to neoantigen expression
Population doubling defect
Next Steps...

-Xenograft failed (cells wouldn’t persist long enough for engraftment)
-Dox-inducible shHAT1 KD
  -Syngeneic, immune competent BALB/c xenograft using CT26 cells (Ras driven CRC)

-Compound library screen
  -All HATs bind cofactor AcCoA, transfer acetyl group leaving CoA with free thiol group
  -HTS result in assay artifacts w/ small molecules having thiol reactivity/difficult to find adequate competitors of AcCoA binding

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Histone acetyltransferase inhibitors: where art thou?

“...is catalytic activity of histone acetyltransferase an undruggable mechanism?”

Exosomes?
Nature’s means of intercellular communication and transmission of diverse macromolecules including proteins, lipids, RNA, and DNA

Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer
Sushrut Kamisetty¹, Yasser S. LeBlanc¹, HiKaru Sagimoto¹, Sujuan Yang¹, Carolina P. Raiser², Sonia A. Moh³,⁴, J.Jack Lee⁵ & Raghu Kalluri⁶

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Why interesting?

Optimal vehicles for therapeutic delivery
Challenge: Harvesting

Very low production yield with poor consistency!
End