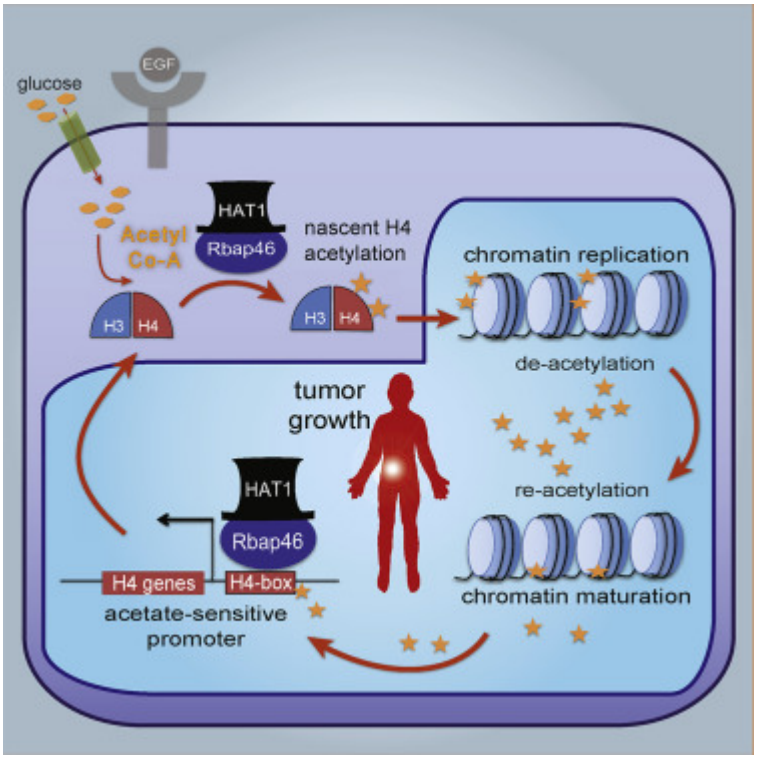
Docket #: S19-163

High-Throughput Screening for Chemical Inhibitors of Histone Acetyltransferase

Histone acetyltransferase 1 (HAT1) is an enzyme which acetylates lysine on histone proteins and is intricately involved with regulating gene transcription. Thus, HAT1 is a promising therapeutic target for cancer and a high-throughput method to discover potent inhibitors would be valuable. A fluorescence-based, enzymatic assay can be constructed using a biotinylated HAT1 substrate, recombinant HAT1, and an acetyl co-A substrate mimetic with an alkyne click handle. The HAT1 substrate can be captured by wells coated with streptavidin. Biotin-azide can be conjugated to alkyne-containing lysine through click chemistry. Addition of streptavidin-HRP facilitates the measurement of activity via plate reader.



Credit: Permission from authors

Applications

- Fluorescence-based screening of novel HAT1 inhibitors on 96-well plates
- High-throughput screen design can be readily adapted to other acetyltransferases

Advantages

- No chemical HAT1 inhibitors currently exist, and this approach enables the discovery of potent HAT1 inhibitors
- High-throughput approach enables rapid measurement of enzymatic activity in vitro
    - Plate reader approach makes it an affordable method
    - No biological material necessary
    - High dynamic range and sensitivity

Publications

- Gruber JJ, Geller B, Lipchik AM, Chen J, Salahudeen AA, Ram AN, Ford JM, Kuo CJ, Snyder MP. HAT1 Coordinates Histone Production and Acetylation via H4 Promoter Binding *Mol Cell* 2019 Aug 22;75(4):711-724.e5. . Epub 2019 Jul 2.

Patents

- Published Application: WO2020219598
- Published Application: 20220196660
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