

Development of Inhibitors and Assay Methods for Histone Acetyltransferases

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Facilitator	: Prof. Bian Zhaoxiang

Abstract

Histone acetyltransferases (HATs) are important enzymes in transcriptional control and potential targets for chemotherapeutic intervention in malignant diseases. Among different HAT members, the yeast Esa1 and human Tip60 (the HIV-1 Tat interactive protein, 60KDa) play multiple roles in normal cellular processes including transcription, cell cycle and checkpoint machinery, double strand DNA break repair, apoptosis, and cell cycle progression. Tip60 is also implicated in several human diseases such as prostate cancer, and gastric cancer. These studies suggest that Tip60 is a potential therapeutic target for new cancer treatment. So, we designed experimental work to synthesize and investigate organic inhibitors of Tip60 using different strategies, including substrate analogs, small molecule screening, and modification of the natural product anacardic acid. These studies provide important chemical agents for basic biology research of HAT function, and produce potential lead compounds for future pharmacologic intervention of HAT deregulation in cancer.

Currently, of the methods used for the measurement of acetyltransferase activities, many comprise tedious separation procedures and involve enzyme-coupled steps or radioactive materials. These shortcomings have limited their applications in high-throughput screening (HTS) of HAT inhibitors. To circumvent these problems, a homogenous fluorescent HAT assay based on engineered H4 peptide was designed, synthesized, and evaluated. The data showed that these fluorescent reporters can be used to detect the acetyltransferase activities.

Biography

Dr. Wu was born in Xining, Qinghai. He obtained his BS degree (chemistry) in 2004, Lanzhou University. Then, he did his PhD work (medicinal chemistry) at Georgia State University with Professor George Zheng. In 2012, he started his independent research as a lecturer at Lanzhou University. Since 2013, his group has been supported by NSFC. His main research interests include peptide-based fluorescence sensors, epigenetics, and cross-talk of histone modification. Dr. Wu has published 30 papers on the journal of EMBO.J, JBC, BB, EJMC, JMCB et al.

*** All are welcome ***