

Abstract

The term epigenetics refers to heritable changes in gene expression that do not involve changes in the DNA sequence. A large number of enzymes, which act mainly on histone tails and DNA, carries out epigenetic modifications, influencing several biological mechanisms.

The interplay between epigenetic enzymes and chromatin is highly complex, and despite great progress has been made in understanding the role of these proteins in biological contexts, much remains still unknown. On the other hand, it is widely reported that specific epigenetic modifications are associated with disease states, therefore epigenetic enzymes represent potential therapeutic targets. However, the lack of specific and robust screening methods to evaluate epigenetic enzyme activity limits the identification and development of epigenetic modulators.

In this scenery, this thesis is focused on the development of a robust and widely usable combined screening platform to identify small-molecule modulators of epigenetic proteins. Different biochemical and biophysical techniques were used in order to evaluate potency, selectivity, binding and mechanism of action of the modulators synthesized in the Epigenetic Medicinal Chemistry Laboratory (EMCL).

As model systems, among all the epigenetic enzymes, the attention was focused on the acetyltransferase p300, the methyltransferase SETD8 and the readers Tudor domains of PHF20. By the use of a combined approach, a set of small-molecule modulators was identified. These compounds could be used as chemical probes to further investigate the biological role of these enzymes and their implications in physiological and/or pathological processes.