Uncovering Cancer-Associated Epigenetic Events Using Novel Chemical Tools

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Cellular proteins continuously undergo non-enzymatic covalent modifications (NECMs), which alter protein structure, function, stability and binding-partner affinity. These chemical modifications accumulate under normal physiological conditions but can also be stimulated by various changes in the cellular environment, such as redox state and metabolite concentration. The half-life of histones is among the longest in the cellular proteome, making them prime targets for NECMs. In addition, histones have emerged as key regulators of transcription, acting primarily through post-translational modification to their disordered N-terminal regions, which are rich in lysines and arginines. Indeed, we have recently shown that non-enzymatic glycation is a pathophysiological modification that specifically accumulates on histones in metabolically abrogated cells such as cancer tumors. We further showed that histone glycation disrupts regulatory post-translational modifications (PTMs, acetylation, methylation, etc.) as well as chromatin architecture. Additionally, we identified several potent regulators of histone glycation *in vitro* and in cells and define it as new therapeutic targets. In my talk I will describe the chemical tools we have developed in order to characterize this new class of histone modifications, their effect on the epigenetic landscape as well as the enzymes we revealed to regulate them, presenting a direct link between metabolism and cell fate through epigenetic mechanisms.