154b Cracking the Histone Code: a Mass Spectrometry Based Approach for the Determination of Histone Modifications

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The post-translational modifications of core histones play a critical role in gene activities such as chromatin remodeling, the regulation of gene transcription, DNA recombination and DNA repair. The ability to localize these modifications is an important first step in the characterization their molecular function. There is mounting evidence that multiple modifications work in a synergistic fashion and give rise to a "histone code" that regulates many of these activities. Furthermore, there is a growing need to characterize the modulation of histone modification in conjunction with the application of new chemoprevention strategies that employ drugs that target enzymes that modify histones (Histone DeACtylase Inhibitors). Mass spectrometry holds great promise as a tool to crack this code. Recently, our group identified 20 novel modification sites by high mass accuracy Fourier transform ion cyclotron resonance mass spectrometry on the four core histone purified from bovine thymus. Two such novel sites of modification (H4 K59 and K91) have been examined in recombinant yeast systems and have been shown to play important roles in gene silencing and DNA damage repair. In addition to mapping novel modifications, quantitative proteomic strategies have been developed to screen for modification changes in transformed cell lines and human patients with acute myeloid or chronic lymphocytic leukemia in conjunction with the testing of histone deacetylase inhibitors in aclinical trials at Ohio State University Medical Center. These studies focus on the development of methods and technologies to 1) investigate global modification patterns and 2) ascertain the changes in concomitant modifications. The results will be used to determining the in vivo specificities of different HDAC inhibitors and to evaluate suspected modification changes as biomarkers for apoptosis in vivo.