Characterizing the regulatory role of combinatorial and spatial deposition of epigenetic marks

1:00 p.m., Monday, March 5, 2012

Abstract

Epigenetic mechanisms, such as post-translational modifications of histone proteins, play an important role in regulating gene expression. Individual histone modifications, such as acetylation, methylation, and phosphorylation, have been shown to regulate gene expression by changing chromatin structure and creating binding sites for effector proteins. In addition to co-occurrence of an epigenetic mark with others, it has been shown that the spatial pattern of its deposition sites might have an impact on the functionality. We developed and utilized computational models to reveal the importance of spatial and combinatorial patterns of epigenetic mark deposition sites. Joint analyses of large scale histone modification maps are starting to reveal combinatorial patterns of histone modifications which are associated with functional DNA elements, providing support to the unified ‘histone code’ hypothesis. However, due to the lack of computational methods, only a small number of histone modification patterns have been associated with well-known functional DNA elements, e.g. promoters and enhancers. To identify the complete set of combinatorial and coherent histone modification patterns across the entire human genome, we propose a scalable bi-clustering algorithm, which identified many combinatorial histone modifications that are frequently repeated on the human DNA. Some of these patterns involve known modification combinations associated with functional DNA elements in addition to novel patterns identified with their potential functional roles that warrant further experimental characterization. In addition to combinatorial patterns of epigenetic marks, recent studies show that different spatial patterns at epigenetic mark deposition sites might also have differing functional meaning. For example longer H3K4me3 deposition sites are known to mark key regulators of a given cell. By the computational analysis of existing high-throughput datasets, we characterized the functional role of long H3K4me3 deposition sites in four different organisms including human.