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Understanding nucleosome dynamics and interactions through integrative approaches

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Nucleosome are elementary building blocks of chromatin that wrap DNA around an octamer of histone proteins. They not only compact the genomic DNA in eukaryotes but also intricately participate in all genomic processes including gene expression regulation, epigenetic memory, and development [1]. Nucleosomes bridge the "digital" nature of the genetic information stored in the DNA sequence with the "analog" world of physical interactions between the nucleic acids and proteins used to interpret this genetic information. Nucleosome dynamics, its conformational flexibility, and its dependence on nucleosome composition and environmental factors is an important pathway used to regulate genome functions. Understanding nucleosome structure and dynamics, as well as its functional implication, requires a complex integrative approach which combines molecular modeling, experimental, and bioinformatics analysis.

Methods and Algorithms: To understand nucleosome dynamics and interactions we have employed a combination of experimental, molecular modeling, and bioinformatics approaches. These include all-atom molecular dynamics simulations, DNA footprinting techniques, small angle X-ray scattering, solution NMR, fluorescence-based assays, en masse analysis of the available X-ray and cryo-EM structures, analysis of genomics data to identify histone protein variants and mutations [2–8].

Results: Our recent reanalysis of the human genome and the available gene expression data allowed us to update the current nomenclature of the histone genes for the human genome, suggesting that there are collectively 90 protein-coding core histone genes (histone H3, H4, H2A, H2B) that may be incorporated into nucleosomes conferring different properties through sequence variations [2]. Some of these genes are often mutated in cancer, with mutations affecting nucleosome stability or the functioning of important histone post-translational modification sites [3]. We have shown that all-atom molecular dynamics simulations at a multi-microsecond timescale may reveal new functional dynamics modes within nucleosomes that are responsible for DNA unwrapping and sliding [4]. The analysis of nucleosomes incorporating different histone variants and mutations with MD simulations confirmed that the intrinsic dynamics of nucleosomes are affected by such variations [5]. We have also shown that nucleosome dynamics is affected by their interaction with nucleosome-binding peptides and proteins [6]. A comprehensive analysis of all available PDB structures of nucleosomes conducted by us suggests that certain modes of nucleosome dynamics can be characterized by such high-throughput comparison [7, 8]. Still, such processes as DNA unwrapping and histone tail dynamics remain poorly characterized. Our efforts in analyzing nucleosomes with small-angle X-ray scattering suggest that these methods can be used to understand the effects of DNA sequence on nucleosome compactness. The characterization of the

flexible histone tails is possible through the application of solution NMR techniques. The measurement of the NMR relaxation parameters (R1 and R2) may be used to assess the histone tail dynamics and validate different molecular dynamics force fields.

Conclusion: We have shown that the characterization of nucleosome structure and dynamics, especially, its dependence on its composition and interactions requires a complex integrative approach uniting different experimental methods, molecular modeling methods, and bioinformatics methods. However, further progress is needed, especially focused on our ability to characterize and predict the dynamics of nucleosomes with varying composition, including variations in DNA sequence, histone sequence, histone PTMs, and DNA modifications.

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