Secondary DNA structures contribute to promoter activity as nucleosome exclusion modules

Abstract: Promoters were defined more than 60 years ago but the nature of DNA able to promote transcription remains essentially mysterious since the sequences underlying their function are not universally conserved. Overall, sequence contexts rather than motifs hallmark areas located immediately upstream of transcription start sites (TSSs), for example CpG islands in mammals. In our recent work, we have shed light on G-quadruplex (G4) secondary structures of DNA as essential promoter elements (1). First, their predictive sequences are found in more than half of the mammalian promoters, while their experimental signal in the cellular context appears in >40% of all active TSSs. Strikingly, the optimal G4 detection signals overlap the lowest point of nucleosome density in vivo and in vitro, suggesting a causal link between nucleosome exclusion and G4 formation. Second, by combining several approaches to detect G4s experimentally, including a novel methodology called G4access (2), and applying single-cell measurements, we demonstrated that G4 mutations severely impair transcription in integrated constructs coupled to MS2 reporters. Furthermore, by using live imaging data and signal deconvolution, we modelled an additional step in transcription when G4 is mutated that most likely involves chromatin opening. Third, by applying functional genomics experiments and analyses, we showed that G4s are essential components of active CpG islands and a subset of enhancers whose structures can be antagonized by DNA methylation. Overall, our data suggest a novel paradigm in promoter biology by proposing the existence of a nucleosome exclusion module (NEM). This NEM can consist of a DNA secondary structure competing with stable nucleosome positioning, required but not necessarily sufficient for transcription. We propose that this feature is a characteristic of promoters most ubiquitously active in various tissues.

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