Concerted dance of protein on DNA, choreography by protein binding affinity and DNA motion

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A fundamental question in biology is how proteins efficiently locate their targets on DNA. Although this process has been widely studied, the combined effects of binding affinity, DNA motion, and protein mobility remain incompletely understood. Here, we use fluorescence microscopy to monitor the movements of the nucleoid-associated architectural protein Hfq and the restriction enzyme EcoRV along double-stranded DNA molecules with varying base methylation levels and/or molecular weights, stretched within nanofluidic channels of 60–120 nm in diameter (approximately one to two times the DNA persistence length). Our results show that base methylation increases binding affinity, reduces protein dissociation, and extends residence time in the bound (sliding) state, thereby reducing overall protein mobility. Furthermore, we reveal a strong correlation between protein mobility and DNA internal dynamics, emphasizing the impact of DNA motion on enzyme activity and highlighting that “it takes two to tango.” These findings suggest that the interplay of binding affinity and DNA dynamics plays a fundamental role in regulating protein mobility via transient binding events, with broad implications for understanding DNA search mechanisms and chromosome organization.