Facilitated Dissociation of Transcription Factors from Single DNA Binding Sites

Ramsey Kamara, Edward Banigan, Aykut Erbas, Rebecca Giuntoli, Monica Olvera de la Cruz, Reid Johnson, and John Marko

Department of Molecular Biosciences, Department of Physics and Astronomy, Department of Material Science and Engineering, Department of Chemistry Northwestern University; and Department of Biological Chemistry, UCLA

The binding of transcription factors (TFs) to DNA controls most aspects of cellular function, making the understanding of their binding kinetics imperative. The standard description of bimolecular interactions posits that TF off rates are independent of TF concentration in solution. However, recent observations have revealed that proteins in solution can accelerate the dissociation of DNA-bound proteins. To study the molecular basis of facilitated dissociation (FD), we have used single-molecule imaging to measure dissociation kinetics of Fis, a key Escherichia coli TF and major bacterial nucleoid protein, from single dsDNA binding sites. We observe a strong FD effect characterized by an exchange rate $\sim 1 \times 10^4 \text{M}^{-1}\text{s}^{-1}$, establishing that FD of Fis occurs at the single-binding site level, and we find that the off rate saturates at large Fis concentrations in solution. Although spontaneous (i.e., competitor-free) dissociation shows a strong salt dependence, we find that FD depends only weakly on salt. These results are quantitatively explained by a model in which partially dissociated bound proteins are susceptible to invasion by competitor proteins in solution. We also report FD of NHP6A, a yeast TF with structure that differs significantly from Fis. We further perform molecular dynamics simulations, which indicate that FD can occur for molecules that interact far more weakly than those that we have studied. Taken together, our results indicate that FD is a general mechanism assisting in the local removal of TFs from their binding sites and does not necessarily require cooperativity, clustering, or binding site overlap.

ACKNOWLEDGMENTS. Work at Northwestern University was supported by NIH Grants R01-GM105847 and U54-CA193419 (CR-PS-OC), a subcontract to NIH Grant U54-DK107980, and National Science Foundation Grants MCB-1022117, DMR-1611076, and DMR-1206868. Work at the University of California, Los Angeles, was supported by NIH Grant GM038509

The full report can be found on the Web: http://www.pnas.org/content/early/2017/03/30/1701884114