Nuclear target search at the single molecule level: protein interactions define the exploration landscape

Gene regulation relies on transcription factors (TFs) exploring the nucleus in search of their targets. So far, most studies have focused on how fast TFs diffuse and underestimated the role of nuclear architecture. We implemented a single-molecule tracking assay to determine the TFs dynamics using photoactivatable tags in human cells. We found that c-Myc is a global explorer diffusing in the nucleus without spatial constraints. In contrast, the positive transcription elongation factor P-TEFb is a local explorer that oversamples its environment, constrained by a fractal nuclear architecture. Consequently, each c-Myc molecule is equally available for all nuclear sites while P-TEFb reaches its targets in a position-dependent manner. Our observations are consistent with a model in which the exploration geometry of TFs is constrained by their interactions with nuclear structures and not by exclusion properties. The geometry-controlled kinetics of TFs target search link nuclear architecture and gene regulation, which might have a major role in the transcription process.