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Different Sequence Domains of Transcription Factors Promote the Formation of Transcriptional Condensates but Regulate Differential Gene Expression

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The eukaryotic nucleus contains phase-separated transcriptional condensates, which are observed to form at specific genomic sites through a multi-step process. These transcriptional condensates are considered to create tunable transcription programs that govern gene expression. Here, we show that the N-terminal domain (NTD) of the progesterone receptor (PR) and the DNA-binding domain (DBD) are essential for the formation of PR transcriptional condensates in response to progestin induction in breast cancer cells. Indeed, using single-particle tracking (SPT) of WT-PR (WT), NTD- (ΔNTD), and DNA-binding domain-deleted (ΔDBD) PR mutants we show that the different sequence domains modulate the lateral mobility and DNA binding of PR. Importantly, by applying machine learning analysis, we assessed that both the DBD and the NTD control the formation of PR-transcriptional condensates. Finally, to investigate the functional impact of PR condensates on gene regulation, we applied RNA sequencing revealing that the NTD and the DBD fine-tune progestin-induced transcription. However and importantly, only the NTD is crucial for the precise expression of approximately 20% of progestin-induced genes essential for oncogenic processes. Our work underscores the different roles of the transcription factor domains in regulating transcriptional condensate formation and gene expression.