

Finding Order in Disorder: the Laws of Gene Expression

For diseases like cancer, which arise when certain genes are over- or underexpressed, this could open a “new world” of treatment options.

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The process of transcription, in which DNA is copied into RNA, is carried out by a complex cellular machinery that controls which genes are expressed as proteins. Researchers have observed certain organizational features of this machinery, such as the clumping of certain proteins into “condensates,” which function as a unit though unbound by a membrane. Proteins with “intrinsically disordered regions” (IDRs), sections that lack a stable three-dimensional structure, seem to be involved in the formation of these condensates, but the role of IDRs—and how they control gene expression—has long remained a mystery.

Now, findings from former Damon Runyon Fellow Benjamin R. Sabari, PhD, at his lab at The University of Texas Southwestern Medical Center, have shed some light. The team focused their investigation on a major component of transcriptional machinery: a protein complex known as Mediator, which communicates signals between DNA-binding proteins and RNA polymerase. Specifically, they zoomed in on a subunit of Mediator, called MED1, which contains a large IDR and has been found in condensates.

The team found that, like the host of an invite-only party, MED1 gathers transcription activators and RNA polymerase together while excluding transcription repressors. As a result of this partitioning, transcription occurs where the MED1 condensate is positioned along the genome. In other words, the gene is the venue, and the condensate “party” makes it active.

But the team didn’t just locate the party—they identified the invitation. The transcription activators that join the condensate have IDRs of their own, while the transcription repressors do not. The researchers demonstrated the importance of this difference by swapping the IDRs of the proteins; they saw that the transcription repressors then joined the condensate while the activators lost their access. As you might expect when invitations swap hands from partiers to killjoys, genes at the location of that condensate were not expressed.

While this study focused on MED1, the team observed that proteins with similar IDRs exhibited similar behavior, allowing them to extrapolate general principles about how condensates form and how IDRs contribute to gene expression.

“We think this is likely just the tip of the iceberg. Interactions among these disordered regions of proteins have largely been ignored because it was unclear how they worked,” Dr. Sabari told his institution. “Now, they’re opening a new world of regulatory interactions that we previously didn’t know existed.”

Knowing they exist, researchers can now begin to figure out how to disrupt or alter the interactions that regulate gene expression. For diseases like cancer, which arise when certain genes are over- or underexpressed, this could open a “new world” of treatment options.

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