Changes in cellular RNA metabolism can affect a variety of processes, like gene expression, and thus dysregulated RNA metabolism frequently leads to disease. The RNA-binding protein TDP-43, for example, is associated with a range of neurodegenerative disorders including amyotrophic lateral sclerosis (ALS). Yet, the RNA targets and protein binding partners of TDP-43 remain largely uncharacterized, an issue that was addressed in this Paper of the Week by Chantelle Sephton and colleagues. Using RNA immunoprecipitation followed by deep sequencing, they identified a set of TDP-43 RNA targets in cortical neurons. The targets could be divided into three major groups: those primarily found in introns, those in exons, and targets spanning both introns and exons. TDP-43 RNA targets were especially abundant in and around genes related to synaptic function, RNA metabolism, neuronal development, and proteins implicated in neurodegeneration such as Tau. Sephton and colleagues also identified 25 potential TDP-43 binding partners using co-purification, which included many nuclear proteins involved in pre-mRNA splicing and RNA stability and transport. This comprehensive work reveals insight into the nature of TDP-43-containing ribonucleoprotein complexes and should provide a framework for understanding how TDP-32 dysregulation contributes to altered RNA metabolism and subsequent neurodegeneration.

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