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p53 Transactivation Domain Mediates Binding and Phase Separation with Poly-PR/GR

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Background/Aims: The most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is the presence of poly-PR/GR dipeptide repeats (DPRs) which are encoded by the chromosome 9 open reading frame 72 (C9orf72) gene. Recently, it was shown that poly-PR/GR alters chromatin accessibility which results in stabilization and enhancement of transcriptional activity of the tumor suppressor p53 in several neurodegenerative disease models. Reduction of p53 protein levels in cell and model organisms protects against neurotoxicity of poly-PR, and partially protects against neurotoxicity of poly-GR. The mechanistic details leading to poly-PR mediated stabilization and activation of p53 remain enigmatic. Here, we aimed to study the detailed molecular mechanisms how p53 contributes to poly-PR/GR mediated neurodegeneration. Our findings might help to understand the mechanistic role of p53 in poly-PR/GR - associated neurodegeneration. Method/Results: Using a combination of biophysical techniques such as nuclear magnetic resonance (NMR) spectroscopy, fluorescence polarization, turbidity assays and differential interference contrast (DIC) microscopy, we found that p53 physically interacts with poly-PR/GR and triggers liquid-liquid phase separation of p53. We identified p53 transactivation domain 2 (TAD2) as the main binding site for PR25/GR25 and show that binding of poly-PR/GR to p53 is mediated by a network of electrostatic and/or hydrophobic interactions. We demonstrated that binding of PR25/GR25 to p531-94 enhances rigidity and formation of ?-helical propensity. Conclusion: Poly-PR/GR mediated LLPS of p53 observed here might be of general importance in the regulation of transcriptional condensates. In the future it will be interesting to reveal if poly-PR/GR modulates formation of p53 transcriptional condensates and through this regulates expression of p53 target genes.