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Deciphering structural and functional effects of protein citrullination

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Background: Arginine-glycine(-glycine) (RG/RGG) regions are highly abundant in RNA-binding proteins (RBPs) and play roles in numerous physiological processes. Aberrant liquid-liquid phase separation (LLPS) and recruitment into membraneless organelles of RG/RGG regions have been implicated in the onset of several neurodegenerative disorders. Both, LLPS and the association with biomolecular condensates of RG/RGG proteins, can be regulated by the interaction with nuclear import receptors, such as transportin-1, and by post-translational modifications, such as phosphorylation or arginine methylation. Furthermore, arginine residues within RG/RGG regions harbour potential sites for the conversion to a citrulline that is catalyzed by calcium-dependent protein arginine deiminases (PADs). The increased levels of protein citrullination have been observed in patients suffering from autoimmune, inflammatory, and neurodegenerative diseases. Here, we hypothesize that RG/RGG-rich RBPs constitute substrates for PADs-mediated citrullination, and this modification regulate their function, structure, and subcellular localization. **Aims:** The aim of this project is to uncover whether and how citrullination regulates structural and functional properties of RNA-binding proteins enriched with RG/RGG regions. **Method/Results:** Here, by applying solution NMR spectroscopy we show that arginines within RG/RGG regions of different RBPs constitute sites for citrullination in vitro. With the use of biophysical techniques, we demonstrate that citrullination suppresses in vitro phase separation and RNA binding of RG/RGG-rich RBPs. Our data furthermore reveal that citrullination of RG/RGG-rich RBPs impairs binding to the nuclear import receptor transportin-1. **Conclusion:** In conclusion, our findings indicate that citrullination regulates the function and structural properties of RNA-binding proteins.