Metal-induced liquid-liquid phase separation of heterochromatin protein 1a

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During liquid-liquid phase separation (LLPS) proteins or nucleic acids form a dense, droplet-like phase which is surrounded by a diluted phase. This phenomenon, occurring in living cells, is responsible for the formation of many membraneless compartments and structures. One of the most important processes associated with LLPS is the formation of heterochromatin. One of the proteins involved in this process is heterochromatin protein 1a (HP1a), itself able to undergo LLPS after the phosphorylation of four serine residues in its N-terminal disordered region. Since LLPS is particularly sensitive to environmental conditions including temperature, ionic strength and pH, we decided to study the effects of divalent metal ions, such as magnesium and calcium, on the ability of HP1a to form droplets in vitro at different temperatures. By means of the solution Nuclear Magnetic Resonance (NMR) spectroscopy, using recombinant human HP1a phosphorylated in vitro by casein kinase II we demonstrate that biometals are specifically coordinated by phosphoserine residues. Moreover, as measured by a spin-down centrifuge assay metal binding promotes LLPS. We determined saturation concentrations as a function of metal concentration and show that calcium and manganese strongly promote droplets formation even at the elevated temperatures. Our research shows that indeed divalent metals interact with phosphorylated residues on human HP1a, and induce LLPS of HP1a, although the phase diagrams obtained differ for each metal. Our results shed light on the possible regulation of the chromatin condensation by biometals.