Redox-dependent phase separation and cytoplasmic granulation by human single-stranded DNA binding protein 1 (hSSB1) delineate new mechanisms of cellular stress response

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Single-stranded DNA binding (SSB) proteins are present in all domains of life, and are essential in protecting single-stranded (ss) DNA segments and organizing protein complexes during DNA replication, recombination, and repair. Our recent discovery on the liquid-liquid phase separation (LLPS) propensity of E. coli SSB highlighted a novel role for macromolecular condensation in genome maintenance (Harami et al. 2020 PNAS 117:26206). Two recently discovered human SSB homologs (hSSB1, hSSB2), structurally resembling bacterial SSBs, have been found central to preserving genome stability. In our current work (bioRxiv 2023.07.25.550517) we define an unprecedented cytoplasmic stress response role for hSSB1, demonstrated in human cell culture and in vivo rodent models for ischemia-reperfusion. This function scales in proportion to stress exposure, is linked to stress granules, and is brought about via redox-dependent phase separation of hSSB1 mediated by cysteine/methionine switches. As these mechanisms are probably central to tissue development and regeneration, immune cell function, and cancer cell survival under chronic stress, pharmacological targeting of SSB condensation appears as a promising route for both suppressing drug resistance and enhancing regenerative therapy. Accordingly, we have established a screening and functional evaluation pipeline for substances affecting condensation by SSB and other nucleoprotein complexes.