**Phase separation directs ubiquitination**

**of gene body nucleosomes**

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**Abstract**

**The conserved yeast E3 ligase Bre1 and its partner E2 Rad6 monoubiquitinate histone H2B across gene bodies during the transcription cycle. While processive ubiquitination might in principle arise from Bre1/Rad6 traveling with RNA polymerase II, we provide a different explanation. Here we implicate liquid-liquid phase separation as the underlying mechanism. Biochemical reconstitution shows that Bre1 binds the scaffold protein Lge1, whose intrinsically disordered region phase separates via multivalent interactions. The resulting condensates comprise a core of Lge1 encapsulated by an outer catalytic shell of Bre1. This layered liquid recruits Rad6 and the nucleosomal substrate, accelerating H2B ubiquitination. *In vivo*, the condensate-forming region of Lge1 is required to ubiquitinate H2B in gene bodies beyond the +1 nucleosome. Our data suggest that layered condensates of histone modifying enzymes generate chromatin-associated reaction chambers with augmented catalytic activity along gene bodies. Equivalent processes may occur in human cells, causing neurological disease when impaired.**