Copenhagen, 4 November 2026

Dear Editors,

We are pleased to submit our manuscript entitled “Annexin A4 mechanically stabilizes the nuclear envelope following membrane rupture” for consideration as an Article in *Nature Communications*.

Maintaining nuclear envelope (NE) integrity is essential for preserving nuclear compartmentalization and genome stability. Although considerable progress has been made in identifying the molecular machinery responsible for repairing NE ruptures, how cells mechanically protect damaged nuclear membranes remains poorly understood. In particular, whether direct reinforcement of membrane mechanics represents a distinct protective response to NE injury has remained largely unexplored.

Here, we identify annexin A4 (ANXA4) as a Ca^{2+}-dependent membrane-stabilizing factor that protects nuclear integrity following membrane rupture. Combining targeted membrane injury with live-cell imaging and molecular perturbations, we demonstrate that ANXA4 accumulates at damaged regions of the NE, where Ca^{2+} binding enables its recruitment and trimerization promotes sustained membrane association. Importantly, ANXA4 limits the loss of nuclear compartmentalization following injury, including in cells with compromised nuclear lamina integrity.

We further establish a mechanistic connection between ANXA4 and membrane stabilization. Using atomic force microscopy of isolated nuclei and reconstituted lipid membranes, we demonstrate that ANXA4 alters membrane mechanical properties and increases resistance to mechanical failure. These findings provide a physical basis for the protective activity of ANXA4 and indicate that its function extends beyond recruitment to damaged membranes.

Our findings identify a previously unrecognized mechanism of nuclear envelope protection based on the direct mechanical reinforcement of damaged membranes. By demonstrating that ANXA4 preserves nuclear compartmentalization and increases membrane resistance to mechanical failure, our study establishes a functional connection between annexin-mediated membrane organization, membrane mechanics and nuclear integrity. Moreover, our findings reveal an unexpected connection between plasma membrane injury and nuclear protection, whereby Ca^{2+} influx associated with cell surface damage promotes ANXA4 recruitment to the nuclear envelope.

We believe that this work will be of broad interest to the readership of *Nature Communications*, particularly researchers studying membrane biology, nuclear envelope integrity, mechanobiology and cellular responses to mechanical stress. By integrating cell biology with quantitative imaging and membrane biophysics, our study provides new insight into how cells preserve the integrity of a vital intracellular compartment following membrane damage.

Thank you for considering our manuscript. We look forward to hearing from you.

Best wishes,

Jesper Nylandsted (On behalf of all authors)