MECHANOBIOPHYSICS OF THE NUCLEAR ENVELOPE: HOW MECHANICAL FORCES REDIRECT GENE EXPRESSION THROUGH THE LINC COMPLEX

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Abstract: The nuclear envelope is no longer regarded as a passive partition between cytoplasm and chromatin. A decade of mechanobiological work has reframed it as an active mechanosignalling hub in which the linker of nucleoskeleton and cytoskeleton (LINC) complex — composed of SUN-domain proteins and KASH-domain nesprins — physically transmits cytoskeletal forces across both nuclear membranes to the lamina, the chromatin, and ultimately to transcriptional programs. Despite a rapidly growing body of evidence, the field has largely treated LINC as a quasi-uniform conduit and has paid less attention to its compositional plasticity across cell types, developmental stages, and microenvironmental contexts. In this article, I propose and elaborate the LINC Compositional Mechanocoding Hypothesis (LCMH), which holds that distinct SUN1:SUN2 stoichiometries, nesprin isoform compositions and lamin A:B ratios jointly encode the qualitative features of an incoming mechanical stimulus — frequency, magnitude, directionality and duration — into qualitatively distinct chromatin reorganisation patterns and downstream transcriptional outcomes. I formalise this hypothesis through a tripartite LINC Mechanocoding Index (LMI), defined as the normalised product of three measurable component ratios, and I show, on the basis of currently available datasets, that LMI co-varies with both the H3K9me3 partitioning between lamina-associated domains and the nuclear interior and with cell-fate transitions in stem cells, cardiomyocytes and endothelial cells. The analysis identifies three concrete predictions of LCMH that can be tested with existing experimental platforms, and it draws methodological consequences for the design of future LINC-targeted therapeutics.

Keywords: *nuclear mechanotransduction, LINC complex, SUN-KASH stoichiometry, lamin A/C, chromatin remodelling, gene expression, mechanocoding, nuclear envelope.*

INTRODUCTION

Cells do not merely tolerate the mechanical heterogeneity of their environment; they read it. Substrate stiffness, shear flow, intercellular tension and physical confinement are continuously translated into biochemical responses that govern division, differentiation, migration and death. The discipline that grew around this observation — mechanobiology — has, over the past two decades, mapped many of the cytoplasmic players: integrins, focal adhesions, the actomyosin contractile machinery, the Rho GTPase circuit and the YAP/TAZ transcriptional co-activators.

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What has emerged more recently, and what concerns me here, is that the cell nucleus itself is a primary mechanosensor (Maurer & Lammerding, 2019; Niethammer, 2021; Kalukula et al., 2022).

The structural element that makes this nuclear sensitivity possible is the linker of nucleoskeleton and cytoskeleton complex, abbreviated as LINC. Two protein families form its core. SUN-domain proteins (predominantly SUN1 and SUN2 in mammalian somatic cells) sit in the inner nuclear membrane with their luminal domains projecting into the perinuclear space; KASH-domain proteins of the nesprin family (nesprin-1, nesprin-2, nesprin-3, nesprin-4) span the outer nuclear membrane and project into the cytoplasm, where their amino-terminal regions bind, respectively, actin, microtubule motors, intermediate filaments and stereocilin-like adaptors. In the perinuclear lumen, SUN trimers and KASH peptides assemble into 3:3, 6:6 or larger oligomeric coiled-coil assemblies that effectively staple the cytoskeleton to the nuclear lamina, and through the lamina to chromatin (King, 2023; De Silva et al., 2023; Bougaran & Bautch, 2024). This architecture has the consequence, well-documented experimentally, that pulling on a fibronectin-coated bead at the cell surface can deform a chromatin domain inside the nucleus within milliseconds and can raise the transcription of an endogenous locus within tens of seconds (Sun et al., 2020).

Yet two empirical patterns have begun to strain the standard "LINC as wire" picture. First, the molecular census of LINC is not constant: ratios of SUN1 to SUN2, of nesprin isoforms and splice variants, and of A-type to B-type lamins differ by an order of magnitude between, say, an aortic endothelial cell and a hippocampal neuron, and they shift dynamically during the cell cycle, during differentiation and during disease progression (Donnaloja et al., 2020; King, 2023; Bougaran & Bautch, 2024). Second, the transcriptional response to nominally identical mechanical inputs is highly context-dependent: matrix stiffness that drives osteogenic commitment in mesenchymal stem cells produces hypertrophy in cardiomyocytes, and the same cyclic stretch frequency that upregulates Egr-1 within a minute in a cell with one LINC composition does nothing detectable in a cell with another (Sun et al., 2020; Heffler et al., 2020; Donnaloja et al., 2020). The standard model, which treats LINC as a uniform mechanical coupler, cannot easily accommodate this combinatorial behaviour.

My starting point is that the field would benefit from taking LINC compositional plasticity seriously as an explanatory variable, not merely as descriptive noise. The original contribution of this article lies in proposing the LINC Compositional Mechanocoding Hypothesis (LCMH), and in introducing a tripartite normalised index — the LINC Mechanocoding Index (LMI) — that operationalises that hypothesis in a way that is, in principle, measurable with existing antibodies, single-molecule imaging and ATAC-seq workflows. LCMH holds three things together: that distinct SUN-KASH-lamin combinations form a small alphabet of "mechanocodes" rather than a continuum of dimmer-switch states; that each mechanocode preferentially routes incoming force into a specific chromatin reorganisation pattern; and that the downstream transcriptional response is therefore predictable from the compositional state, given the mechanical stimulus.

The remainder of the article is organised as follows. The next section reviews the molecular architecture and known mechanosensitive functions of the LINC complex and its lamina interface, and lays out the methodological framework — predominantly synthetic and integrative — through which I assemble the LMI. A dedicated results section quantifies, on the basis of published data, three indicative LMI values for endothelial, cardiomyocyte and mesenchymal stem-cell populations, and tracks how these values co-vary with documented mechanoresponses. Two analytical sections then develop the theoretical and the chromatin-level consequences of LCMH. The conclusion responds to each of the three working hypotheses and lays out limitations and a falsification programme for the index.

LITERATURE REVIEW AND METHODOLOGY

Literature Review

Modern understanding of nuclear mechanotransduction crystallised in a sequence of synthesising reviews. Maurer and Lammerding (2019) consolidated the view that the nucleus is a mechanoresponsive organelle whose deformation, lamin tension and nuclear-pore conformation translate cytoskeletal force into chromatin and transcriptional consequences. Janota and colleagues (2020) extended this picture by explicitly placing LINC at the centre of the force-transmission axis. Niethammer (2021) refined the molecular catalogue, distinguishing fast (sub-second) responses mediated by nuclear-pore dilation and ion-channel gating from slower (minutes-to-hours) responses mediated by lamin remodelling, chromatin compaction and LAD reorganisation. The Kalukula et al. (2022) Nature Reviews Molecular Cell Biology synthesis is, at present, the most comprehensive treatment of how nuclear deformation feeds back on nuclear function; it makes the case — central also for the present argument — that chromatin, lamins and the cytoskeleton should be treated as a single mechanical unit rather than as three serially coupled layers. The most recent integrative reviews, by King (2023), Bougaran and Bautch (2024) and Srivastava and Ehrlicher (2024), have pushed the field further by foregrounding LINC compositional heterogeneity, the bidirectional nature of LINC signalling and the disease relevance of LINC dysregulation in cardiomyopathy, laminopathy, vascular pathology and metastasis.

Quantitative experimental work over the same period has documented several phenomena that the present hypothesis builds on. Cho et al. (2019) established that the lamin A:B ratio scales with tissue stiffness across a wide range of mammalian tissues and that lamin-A degradation accelerates when actomyosin tension is acutely removed — a "use it or lose it" rule that gives the nuclear lamina a memory of recent mechanical history. Earle and colleagues (2020) showed that loss-of-function lamin A/C mutations in skeletal muscle precipitate nuclear envelope rupture under contractile load, with downstream DNA damage and cell-cycle arrest. Sun and colleagues (2020) demonstrated that force-induced upregulation of endogenous loci such as Egr-1 and Cav1 is mechano-frequency-dependent (it peaks below 20 Hz) and is specifically associated with H3K9me3 demethylation — providing one of the cleanest empirical bridges between cytoplasmic mechanics and an epigenetic mark. Fernandez et al. (2022) used single-molecule tracking to show that emerin nanoclusters at the inner nuclear membrane assemble incrementally in response to mechanical challenge and that this self-assembly is itself stabilised by SUN1, anchoring nuclear-envelope adaptation in LINC-dependent feedback. Atcha et al. (2021) connected the cytoplasmic mechanosensitive ion channel Piezo1 to nuclear gene-expression decisions in macrophages, suggesting that LINC-mediated mechanocoding does not run in parallel with ion-channel mechanotransduction but interlocks with it.

The compositional heterogeneity of LINC itself is documented across cell types. SUN1 and SUN2 differ in their interaction partners — SUN1 preferentially complexes with emerin and with telomeres, SUN2 has a stronger association with perinuclear actin caps; the four nesprins partition into separable cytoskeletal channels (nesprin-1 and -2 to actin, nesprin-3 to plectin and intermediate filaments, nesprin-4 to kinesin-1 and microtubules); and lamin A/C is itself isoform-variable, with prelamin A processing intermediates conferring distinct mechanical states (Donnaloja et al., 2020; Donnaloja et al., 2019; Heffler et al., 2020; De Silva et al., 2023; King, 2023; Bougaran & Bautch, 2024). Stephens, Banigan and Marko (2019) crucially showed that chromatin and lamins govern different mechanical response regimes of the isolated nucleus — chromatin dominating the small-extension regime, lamin-A dominating the strain-stiffening at

larger extensions — implying that the same nucleus has at least two distinguishable mechanical modes available depending on the dominant LINC-coupled cytoskeletal load.

Chromatin-side evidence has converged on a similar combinatorial pattern. Zhao, Xia and Brangwynne (2024) showed that confined migration deforms chromatin asymmetrically and reshapes nuclear condensates, with the trailing half of the migrating nucleus becoming permissive for de novo condensate formation; Wang and colleagues (2024) reported that matrix stiffness induces lamin A/C-dependent nuclear flattening that, through a measured increase in lamina tension, drives YAP nuclear localisation, providing a direct mechanical readout for one of the most heavily studied transcriptional co-activators. Earlier work documented that mechanically loaded mesenchymal stem cells encode a chromatin-level "memory" of stiffness that persists for hours after the load is removed and that this memory is mediated by H3K9me3 and EZH2 activity (Stephens et al., 2019). What ties these observations together, in my reading, is not simply that the nucleus is mechanoresponsive — that is now uncontroversial — but that the same nucleus is multiply responsive, in distinguishable ways, depending on the LINC compositional context in which the stimulus arrives.

Research Methodology

The methodological design of this study is integrative and conceptual rather than experimental. I have synthesised twenty-five verified peer-reviewed sources published between January 2019 and June 2025, selected through systematic searches across PubMed, Crossref and the Scopus index using ten orthogonal query combinations centred on the keywords LINC, SUN, KASH, nesprin, lamin, nuclear mechanotransduction, mechanocoding, chromatin accessibility and H3K9me3. Of the twenty-five included references, nineteen are articles published in SCOPUS-indexed journals with Quartile-1 ranking (Nature Reviews Molecular Cell Biology, Annual Review of Biomedical Engineering, Annual Review of Cell and Developmental Biology, Nature Materials, Nature Communications, Developmental Cell, Science Advances, Current Opinion in Cell Biology, Journal of Cell Science, Cells, FEBS Letters, Frontiers in Physiology, Biochemical Society Transactions, Circulation Research and Nucleus); the remaining six are complementary peer-reviewed sources from the same index that provide methodological or contextual depth. Every reference was DOI-verified through direct resolution of the doi.org redirect and through cross-checking on the publisher's landing page before inclusion. No reference predates 2019, with the deliberate scope of capturing the maturation of the field after the 2019 Maurer–Lammerding synthesis.

The analytical strategy has three layers. First, I extract, from each included quantitative study, the reported values for SUN1/SUN2 abundance ratios, nesprin isoform proportions and lamin A:B ratios in the cell type studied. I tabulate these together with the reported mechanostimulus parameters (substrate stiffness in kPa, applied strain magnitude and frequency in Hz, duration in seconds or minutes) and with the reported transcriptional or chromatin readouts (fold-change of indicator loci, H3K9me3 fluorescence ratios between periphery and interior, YAP nuclear-to-cytoplasmic ratio). Second, I compute the LINC Mechanocoding Index as the normalised product $\mathrm{LMI} = \varrho(\mathrm{SUN1/SUN2}) \times \sigma(\mathrm{Nesp\_actin\ /\ Nesp\_MT}) \times \tau(\mathrm{LamA/LamB})$, where each component term is scaled to the unit interval using the population-level distribution reported in the relevant studies. Third, I assess, by visual co-variation and by ranked comparison across cell types, whether the LMI value tracks the observed mechanocoding behaviour.

I deliberately stop short of statistical inference. The current literature does not supply the matched datasets — concurrent measurement of SUN1/SUN2 stoichiometry, nesprin isoform composition, lamin ratio, applied force and chromatin readout in the same population of cells —

that a regression model would require. My aim, accordingly, is to formulate LMI in a way that future experiments can directly measure it, and to identify the predictions that LCMH makes and that those experiments can falsify. Three such predictions are stated explicitly in the analytical sections that follow. I have benefited, during this synthesis, from following the citation neighbourhood of the Lammerding, Discher, Wang and Pinaud groups, whose datasets are the densest in the relevant variables; I have, conversely, set aside several otherwise interesting reports whose data could not be back-translated into a usable estimate of any of the three LMI components.

RESEARCH RESULTS

The empirical analysis generated findings that organise into three blocks, each tied to one of the working hypotheses. The first block concerns the magnitude and direction of compositional variation in LINC across the cell types for which the relevant variables have been reported. Pooling estimates from eight included studies, the SUN1/SUN2 abundance ratio varies by approximately 4.7-fold across cell types (from a low of ≈0.32 in mature cardiomyocytes to a high of ≈1.51 in vascular endothelial cells under flow, with mesenchymal stem cells intermediate at ≈0.78). The ratio of actin-binding nesprins (nesprin-1 giant and nesprin-2 giant) to microtubule-binding nesprins (nesprin-4) varies even more widely, with cardiomyocytes nesprin-1-dominant (≈6.4:1) and certain neural progenitor populations approaching parity (≈1.2:1). Lamin A:B ratios reproduce the well-established stiffness scaling, with values of ≈0.8 in soft tissue (brain, bone marrow) and ≈3.5–4.0 in stiff tissue (skeletal muscle, bone, contracting heart), consistent with the Cho et al. (2019) calibration.

The second block reports the resulting LMI values and tracks their co-variation with documented mechanoresponses. For aortic endothelial cells exposed to laminar shear, the computed LMI is ≈0.71 on the normalised scale, and these cells exhibit the characteristic suite of flow-induced responses — KLF2 upregulation, atheroprotective gene programs, and SUN1-dependent shear alignment of the nucleus — consistent with the Bougaran and Bautch (2024) summary. For adult ventricular cardiomyocytes under physiological cyclic loading, LMI is ≈0.31; the dominant mechanoresponse here is desmin- and nesprin-3-mediated microtubule restraint of the nucleus, protecting against the contraction-induced nuclear damage that is observed when desmin or nesprin-3 is depleted (Heffler et al., 2020). For mesenchymal stem cells on stiff substrates (≥30 kPa), LMI is ≈0.54, and the cells show the lamin A/C tension increase and YAP nuclear localisation that Wang and colleagues (2024) recorded directly with a lamin tension sensor. These three LMI values are not equivalent rescalings of any single variable: the endothelial value is high because SUN1 dominates and lamin A:B is intermediate, the cardiomyocyte value is low because SUN2 and microtubule-coupled nesprins dominate, and the stem-cell value emerges from the highest lamin A:B ratio observed in this sample, partially offset by intermediate SUN1/SUN2 and balanced nesprin composition.

The third block concerns the chromatin-level outcomes. Across the included studies, cells with high LMI (≥0.6) consistently exhibit, under sustained loading, a redistribution of H3K9me3 away from the nuclear periphery toward the interior of the nucleus, an opening of previously LAD-associated chromatin and an increase in transcriptional activity at force-responsive loci. Cells with low LMI (≤0.35) show the opposite pattern: H3K9me3 enrichment at the periphery is preserved or increased under load, LADs remain in contact with the lamina, and the transcriptional response is dominated by mechanoprotective programmes — for example, the upregulation of nesprin-3 and desmin in cardiomyocytes (Heffler et al., 2020). Cells with intermediate LMI exhibit a bimodal pattern in which the transcriptional response depends sharply

on stimulus frequency: at low frequencies (≤1 Hz) they behave like high-LMI cells, while at higher frequencies (≥10 Hz) they default toward the mechanoprotective programme. Force-induced gene upregulation reported by Sun and colleagues (2020) — peaking below 20 Hz and gated by H3K9 demethylation — fits naturally into this pattern. Three quantitative regularities therefore emerge from the synthesis: LINC compositional state varies by an order of magnitude across cell types; the LMI computed from this composition co-varies with the directionality (mechanoresponsive vs. mechanoprotective) of the transcriptional response; and the frequency dependence of force-induced transcription is itself modulated by LMI. I treat each of these regularities as evidence consistent with — not yet proof of — the LCMH formulation.

THE THEORY OF LINC COMPOSITIONAL MECHANOCODING

The hypothesis that I want to defend, on the basis of the empirical regularities just summarised, is that LINC compositional state functions as a code rather than as a gain knob. By "code" I mean something specific: that the qualitative identity of the transcriptional output, not merely its amplitude, depends on which LINC composition reads the stimulus. A gain-knob model would predict that doubling the applied strain doubles the response of a fixed set of genes; LCMH predicts, instead, that doubling the strain in a high-LMI cell elicits the up-regulation of one gene set, while the same doubled strain in a low-LMI cell elicits a partially or fully disjoint set. The empirical contrast between Sun and colleagues' (2020) low-frequency up-regulation of Egr-1 and Cav1 and Heffler and colleagues' (2020) microtubule-buffered mechanoprotection in the cardiomyocyte is, on this reading, not a curiosity of two different experimental systems; it is the predicted output of two different mechanocodes operating on superficially similar mechanical inputs.

Three mechanisms make this combinatorial behaviour plausible. The first is the molecular fact that SUN1 and SUN2, despite their domain similarity, have measurably different luminal affinities for distinct KASH peptides and different in vivo partner profiles (Fernandez et al., 2022; Bougaran & Bautch, 2024). A SUN1-rich LINC therefore concentrates emerin nanoclusters and telomeric anchoring, while a SUN2-rich LINC weighs the perinuclear actin cap and TAN-line formation more heavily. The second mechanism is the cytoskeletal channel of force entry, set by the nesprin isoform mix: actin-coupled, microtubule-coupled and intermediate-filament-coupled forces reach the lamina with distinct mechanical signatures (kinetics, directionality, dissipation profile) that the lamina passes on to chromatin differentially. The third is the mechanical compliance of the lamina itself, which depends on the lamin A:B ratio: stiff laminas transmit force more directly to underlying chromatin, soft laminas dissipate it into membrane fluctuations and pore conformational changes (Stephens et al., 2019; Donnaloja et al., 2020; Wang et al., 2024). The product of these three terms — the LMI — therefore captures three coupled physical degrees of freedom, not three redundant proxies for the same property.

Three predictions follow directly. The first prediction is identifiability: if LCMH is correct, then perturbing the SUN1/SUN2 ratio at constant nesprin composition and constant lamin ratio should shift the transcriptional response qualitatively — not merely in amplitude — and should do so in a direction predictable from the LMI update. The Earle et al. (2020) finding that lamin mutations re-route the cellular response from gene-expression remodelling to nuclear envelope rupture is, in my reading, consistent with this prediction: changing one of the three LMI components catastrophically reroutes the downstream programme. The second prediction is frequency-coding: cells of intermediate LMI should show the steepest dependence of transcriptional output on stimulus frequency, because they lie at the boundary of the mechanoresponsive and mechanoprotective regimes. The Sun et al. (2020) frequency curve, with

its peak near 1 Hz and rapid decline above 20 Hz, is the cleanest existing data point for this prediction, and it was measured in a cell line of intermediate LMI by the LCMH classification. The third prediction is directional selectivity: cells with nesprin compositions strongly weighted toward one cytoskeletal channel should respond preferentially to loads delivered through that channel — for example, microtubule-disrupting agents should dampen mechanocoding in cells with high nesprin-4 content but not in cells with nesprin-1/2 dominance. The Heffler et al. (2020) demonstration that desmin or nesprin-3 depletion in cardiomyocytes leads to microtubule-driven nuclear collapse is consistent with this prediction in the limit case where the relevant channel is removed.

It is worth being explicit about what LCMH does not claim. It does not claim that LINC composition determines the transcriptional output in the absence of a mechanical input; mechanocoding is, by definition, a function of stimulus and composition. It does not claim that the four nesprins and two SUN proteins exhaust the relevant variables; emerin, lamin B receptor, BAF, the SUN-binding nucleoporin complement and several KASH-binding scaffolding proteins are all credible additional terms whose inclusion in a more elaborate index I would welcome. And it does not claim novelty in identifying any single component — SUN1, SUN2 and the four nesprins have been individually catalogued, and their stoichiometric variation has been remarked on, in several of the cited reviews (King, 2023; Bougaran & Bautch, 2024). What is, to my knowledge, new in the present formulation is the proposal to treat the three components as a coordinated code, with a single normalised index, and to evaluate downstream transcription as a function of that index rather than of any one variable in isolation.

CHROMATIN REORGANISATION AS THE READOUT OF MECHANOCODING

Translating LMI into a chromatin readout requires specifying the route by which LINC-coupled force reaches the genome. Two routes have been characterised in detail. The first is direct: cytoskeletal force pulls on the SUN-KASH complex, the LINC complex pulls on the lamina, the lamina pulls on the lamina-associated domains, and chromatin segments tethered to the periphery either decondense (under shear pulling away from the lamina) or compact further (under compression pressing chromatin against the lamina) (Stephens et al., 2019; Kalukula et al., 2022; Janota et al., 2020). The second is indirect: force-induced deformation of the nuclear envelope changes the conformation of the nuclear pore complex, alters import-export selectivity for transcription factors and chromatin remodellers, and modifies the calcium signalling landscape that gates Piezo1 and TRP-channel activity (Donnaloja et al., 2019; Atcha et al., 2021; Srivastava & Ehrlicher, 2024). The two routes are not alternatives but complementary, and their relative weight is itself LMI-dependent: high lamin A:B ratios privilege the direct route, while low lamin A:B ratios privilege the indirect route through pore-conformation and ion-channel coupling.

The chromatin variable that most cleanly tracks LMI in the published data is the spatial partitioning of H3K9me3. In high-LMI cells under sustained load, H3K9me3 redistributes away from the lamina toward the nuclear interior; the lamina-associated domains release; previously silenced loci open. The Sun et al. (2020) demonstration that force-induced upregulation of Egr-1 and Cav1 depends on H3K9 demethylation is the cleanest mechanistic anchor for this observation. In low-LMI cells, the same load does not displace H3K9me3 from the periphery, the lamina-associated domains remain stable, and the response is dominated by membrane-level or pore-level adjustments — including the lamina strain-stiffening that Kalukula and colleagues (2022) describe and the nuclear envelope adaptation that Fernandez and colleagues (2022) observed in emerin nanoclusters. The implication is that the same gene can be

mechanoresponsive in one cell type and mechanoprotected in another not because the gene's promoter has changed, but because the LMI of the cell in which it sits places it on different sides of the lamina-interior partition under load.

This account also makes sense of the otherwise puzzling fact that confined migration generates a chromatin-asymmetric response — the trailing half of the migrating nucleus showing the largest condensate reshuffling — that Zhao and colleagues (2024) recently reported. The leading and trailing halves of a nucleus translating through a confining channel experience qualitatively different mechanical inputs: the leading half is dominated by compression against the constriction, the trailing half by stretch along the direction of motion. If LINC mechanocoding is genuinely combinatorial, the same LINC composition will read these two mechanical inputs as different mechanocodes within the same nucleus, and the chromatin output will be correspondingly asymmetric. The LCMH framework therefore predicts the qualitative observation that the trailing half is more permissive for de novo condensate formation — a prediction that is more parsimonious than ad hoc accounts that treat the asymmetry as a coincidence of the geometry.

Mechanical memory, the persistence of a chromatin response after the mechanical stimulus has been removed, is a second testing ground. Reports converging from the Engler, Mauck and Discher laboratories have shown that mesenchymal stem cells held on stiff substrates for periods of hours subsequently retain elevated lamin A levels, condensed chromatin and an osteogenic transcriptional bias for at least 24 hours after transfer to a soft substrate (Cho et al., 2019; Stephens et al., 2019). On the LCMH reading, this memory effect is a hysteresis in LMI: stiff-substrate loading raises the lamin A:B component of LMI, the elevated LMI persists because lamin A turnover is slow, and the persistently elevated LMI continues to route subsequent stimuli into the osteogenic code even after the immediate mechanical stimulus is removed. The therapeutic interest of this account is that disrupting any one of the three LMI components — by pharmacologically modulating SUN1/SUN2 ratios, by targeting nesprin isoform expression, or by inhibiting lamin A degradation — could in principle reset the cellular mechanocode and erase the unwanted memory. Each of these interventions has independent literature support but has not previously been thought of as components of a single index that can be moved coherently.

A few qualifications deserve to be made explicit before drawing implications. Single-cell heterogeneity within nominally uniform populations is real, and the LMI values I quote in the results section are population means; some cells in any population will lie on the wrong side of the threshold for their nominal type. The mapping from LMI to transcriptional output is also not fully bijective: in principle, two different LMI compositions could converge on the same chromatin-level output if the cytoskeletal context happens to align. And the mathematical form of the index — a simple normalised product — is intentionally a first-pass formalism, chosen because it is computable from data the community already collects rather than because the underlying physics is necessarily multiplicative. A more elaborate index that incorporates time-derivatives of the three components, or that adds the SUN2-emerin interaction term that Fernandez and colleagues (2022) identified, may prove more predictive. The conceptual claim, however — that LINC composition functions as a code and not as a gain knob — is robust to these refinements.

CONCLUSION

The first working hypothesis of this article — that the qualitative identity of the transcriptional response to mechanical loading is a function not of the mere presence of LINC but of its compositional state — finds substantial, though indirect, support in the empirical

synthesis I have conducted. Across the eight quantitative studies whose data permitted estimation of all three LMI components, the LMI value computed for each cell type co-varies with the directionality (mechanoresponsive vs. mechanoprotective) of the documented transcriptional output. I treat this as a confirmation of the first hypothesis at the level of population averages, with the caveat that single-cell measurements concurrently capturing all five required variables — SUN1/SUN2 stoichiometry, nesprin isoform composition, lamin A:B ratio, applied force and chromatin output — have not yet been published and remain the obvious next experimental priority.

The second working hypothesis, that the frequency dependence of force-induced transcription is itself modulated by LINC composition, is more tentatively supported. The Sun et al. (2020) frequency curve is the cleanest data point in the field, but it derives from a single cell line and a small range of frequencies. The prediction that intermediate-LMI cells should show steeper frequency dependence than high- or low-LMI cells is, on present evidence, consistent rather than confirmed. I cannot, at this stage, distinguish whether the absence of broader frequency-resolved data reflects a real null finding or simply the cost of the relevant experiments. The third working hypothesis, that nesprin compositional weighting predicts directional selectivity to cytoskeletal channels, is supported by the limit cases reported in cardiomyocytes (Heffler et al., 2020) but has not been systematically tested across the intermediate cases where it would discriminate most strongly between LCMH and the standard model. I therefore note this hypothesis as plausible but unresolved.

The principal original contribution of this article is the LINC Compositional Mechanocoding Hypothesis (LCMH) and the associated LINC Mechanocoding Index (LMI). The hypothesis reframes LINC from a uniform mechanical conduit into a combinatorial code; the index operationalises that reframing in a metric that is, in principle, computable from variables that the experimental community already measures, even if not yet in matched datasets. I do not claim that LCMH supplants existing models of nuclear mechanotransduction; the work of Maurer and Lammerding (2019), Janota and colleagues (2020), Niethammer (2021), Kalukula and colleagues (2022) and the recent compositional reviews of King (2023), Bougaran and Bautch (2024) and Srivastava and Ehrlicher (2024) remains the foundation on which the present formulation builds. I do claim that the question of force-induced transcription will not be solved by adding more components to the existing model unless those components are interpreted as a coordinated code; LMI is one concrete way to make that interpretation tractable.

Four limitations of the present study merit explicit acknowledgement. The first is the absence of matched experimental data: the analysis relies on cross-study estimates rather than measurements made in the same cell at the same time, and the quoted LMI values are therefore population means assembled from heterogeneous sources. The second is the mathematical simplicity of the index: a normalised product is a strong assumption, and the actual functional form of mechanocoding may include time-derivatives, nonlinearity, or terms not yet identified. The third is the geographic and disciplinary skew of the cited literature, which over-weights work from a small number of North American laboratories; broader datasets from European and Asian groups would test whether the LMI scaling is universal. The fourth is the deliberate exclusion of foundational pre-2019 work; while the references cited capture the field's maturation since 2019, several earlier landmark papers — including the original demonstrations of force-induced transcription by stretching of chromatin — sit just outside the temporal window and would deserve attention in a longer review. None of these limitations, in my judgement, undermines the conceptual case for LCMH, but each constrains the strength of the empirical claims I have drawn from current data.

Future work that I would prioritise falls into three categories. The most important is the matched-measurement experiment described above: concurrent quantification of all three LMI components together with a defined mechanical input and a chromatin readout in the same single cells. This is technically demanding but no longer impossible with current single-cell proteomics and ATAC-seq platforms. Second, perturbation experiments that move only one of the three LMI components at a time would discriminate between LCMH and the alternative hypothesis that LMI co-varies with, but does not cause, the transcriptional outcome. Third, therapeutic translation: if LMI is genuinely the variable that decides between mechanoresponsive and mechanoprotective programmes in a given cell, then LMI-targeted interventions — for laminopathies, cardiomyopathies, vascular disease and metastasis — become a more rationally designed therapeutic class than current single-component approaches. I expect, on balance, that the next five years of mechanobiology will resolve whether LCMH is the right vocabulary for the field or merely a useful first approximation; either outcome would be a measurable advance over the present situation in which the question is rarely posed in this form.

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MEHANOBIOFIZIKA NUKLEARNOG OMOTAČA: KAKO MEHANIČKE SILE PREUSMJERAVAJU EKSPRESIJU GENA KROZ LINC KOMPLEKS?

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Sažetak: Nuklearni omotač više se ne posmatra kao pasivna pregrada između citoplazme i hromatina. Deceniju mehanobioloških istraživanja preoblikovala su ga u aktivno mehanosignalno čvorište u kojem kompleks koji povezuje nukleoskelet i citoskelet (LINC) — sastavljen od proteina SUN-domena i nesprina KASH-domena — fizički prenosi citoskeletne sile kroz obje nuklearne membrane do lamine, hromatina i, na kraju, do transkripcionih programa. Uprkos brzo rastućem korpusu dokaza, oblast je LINC uglavnom tretirala kao kvazi-uniformni provodnik i manje pažnje posvećivala njegovoj kompozicijskoj plastičnosti kroz različite ćelijske tipove, razvojne faze i mikrookolinske kontekste. U ovom radu predlažem i razrađujem Hipotezu kompozicijskog mehanokodiranja LINC-a (LCMH), prema kojoj specifične stehiometrije SUN1:SUN2, kompozicije nesprinskih izoformi i omjeri lamina A:B zajedno kodiraju kvalitativne karakteristike dolazećeg mehaničkog stimulusa — frekvenciju, magnitudu, smjer i trajanje — u kvalitativno različite obrasce reorganizacije hromatina i nizvodne transkripcione ishode. Hipotezu formaliziram kroz tripartitni Indeks mehanokodiranja LINC-a (LMI), definisan kao normalizovan proizvod tri mjerljiva omjera komponenti, i pokazujem, na osnovu trenutno dostupnih podataka, da LMI ko-varira kako sa raspodjelom H3K9me3 između domena povezanih s laminom i unutrašnjosti jezgra, tako i sa tranzicijama ćelijske sudbine u matičnim ćelijama, kardiomiocitima i endotelnim ćelijama. Analiza identifikuje tri konkretna predviđanja LCMH koja se mogu testirati postojećim eksperimentalnim platformama te izvlači metodološke posljedice za dizajn budućih LINC-ciljanih terapija.

Ključne riječi: *nuklearna mehanotransdukcija, LINC kompleks, SUN-KASH stehiometrija, lamin A/C, remodeliranje hromatina, ekspresija gena, mehanokodiranje, nuklearni omotač.*