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SPOTLIGHT

FOMO no more: NOMO and calmin extend mechanobiology to the ER

Julie Heffler[1] and Jan Lammerding[1]

Research on cellular mechanotransduction has primarily focused on the cell surface and the cytoskeleton. In this issue, Naughton et al. (https://doi.org/10.1083/jcb.202505010) identify NOMO, an endoplasmic reticulum (ER)–resident protein, as a force-bearing element with crucial roles in muscle differentiation and function. In a complementary study, Merta et al. (https://doi.org/10.1016/j.celrep.2025.115502) demonstrate that calmin physically tethers ER tubules to actin filaments at focal adhesions, modulating their function.

The ability of cells to sense and respond to mechanical forces plays a crucial role in many physiological and pathological processes, ranging from development and muscle homeostasis to immune cell function and cancer metastasis (1, 2). Whereas much attention has been paid to mechanotransduction processes at focal adhesions, cell–cell contacts, and the cytoskeleton, mechanical stimuli are also transmitted to intracellular structures and organelles, where they can induce mechanotransduction events (Fig. 1 A). For example, mechanically induced deformation of the cell nucleus has emerged as a key mechanotransduction mechanism, which can lead to cPLA2-mediated cell contractility, changes in chromatin organization, and altered gene expression (3).

Two new studies from the Schlieker (4) and Henne (5) groups now offer important clues into the role of the ER in intracellular mechanotransduction. The ER is responsible for protein processing and export, lipid synthesis, calcium storage, cellular stress responses, and various other functions. The ER, whose membrane and lumen are continuous with the nuclear envelope, can be subdivided into two domains based on morphology: ER sheets and tubules. ER sheets are mostly located near the nucleus and consist of parallel membranes separated by ∼50 nm. Their luminal width is regulated by the ER spacer CLIMP-63, which bridges the ER membranes. ER tubules have a diameter of 50–100 nm and form a reticular network, predominantly in the cell periphery. They bind to microtubules and can be actively deformed and remodeled by the cytoskeleton.

The Schlieker group had previously identified nodal modulator (NOMO), a highly conserved ER-resident protein, to play a crucial role in regulating ER morphology (6). NOMO is highly expressed in striated muscle, and reduced NOMO expression is associated with congenital heart abnormalities and myotonic dystrophy type 1, a skeletal muscle disease, suggesting an unexplored mechanoresponsive function.

NOMO contains a large ER luminal domain consisting of 12 immunoglobulin (Ig)-like domains positioned like beads on a string, along with an N-terminal transmembrane domain and a short cytoplasmic domain. Using AlphaFold3 predictions, Naughton and colleagues identified a salt bridge that forms between the Ig1 and Ig10-11 domains, resulting in a compact, looped conformation (Fig. 1 B, top left). They verified the interaction of these Ig-like domains using recombinant NOMO fragments and further showed that mutations at the salt bridge interface that disrupt this interaction cause an extended conformation of NOMO, increasing its effective size from ∼12–18 to ∼40 nm. Disruption of the salt bridge interface via dominant negative overexpression of the recombinant peptides or mutation of key residues induces large voids in the ER network in cells and increases the mobility of NOMO within the ER, which is normally extremely low, suggesting stable anchoring (Fig. 1 C).

To directly test whether NOMO is subjected to mechanical forces, the authors inserted a force-sensitive TEV protease cleavage site into the NOMO luminal domain near the transmembrane domain. They found that NOMO experiences forces in the ∼5 pN range, which is similar in magnitude to molecular forces at focal adhesions or transmitted to the nucleus via the LINC complex (7, 8). Disrupting the salt bridge interface significantly reduced the force transmitted across NOMO, which the authors confirmed using a FRET-based tension sensor inserted near the transmembrane domain of NOMO. Demonstrating the context-dependent nature of the forces experienced by NOMO, Naughton et al. showed that NOMO is subjected to higher forces in migrating cells in a scratch wound assay.

These experiments convincingly demonstrate that NOMO functions as a force-bearing element in the ER via its salt bridges. However, what structures NOMO forms *in vivo*, and whether these structures

[1]Weill Institute for Cell and Molecular Biology, Meinig School of Biomedical Engineering, Cornell University, Ithaca, NY, USA.

Correspondence to Jan Lammerding: jan.lammerding@cornell.edu.

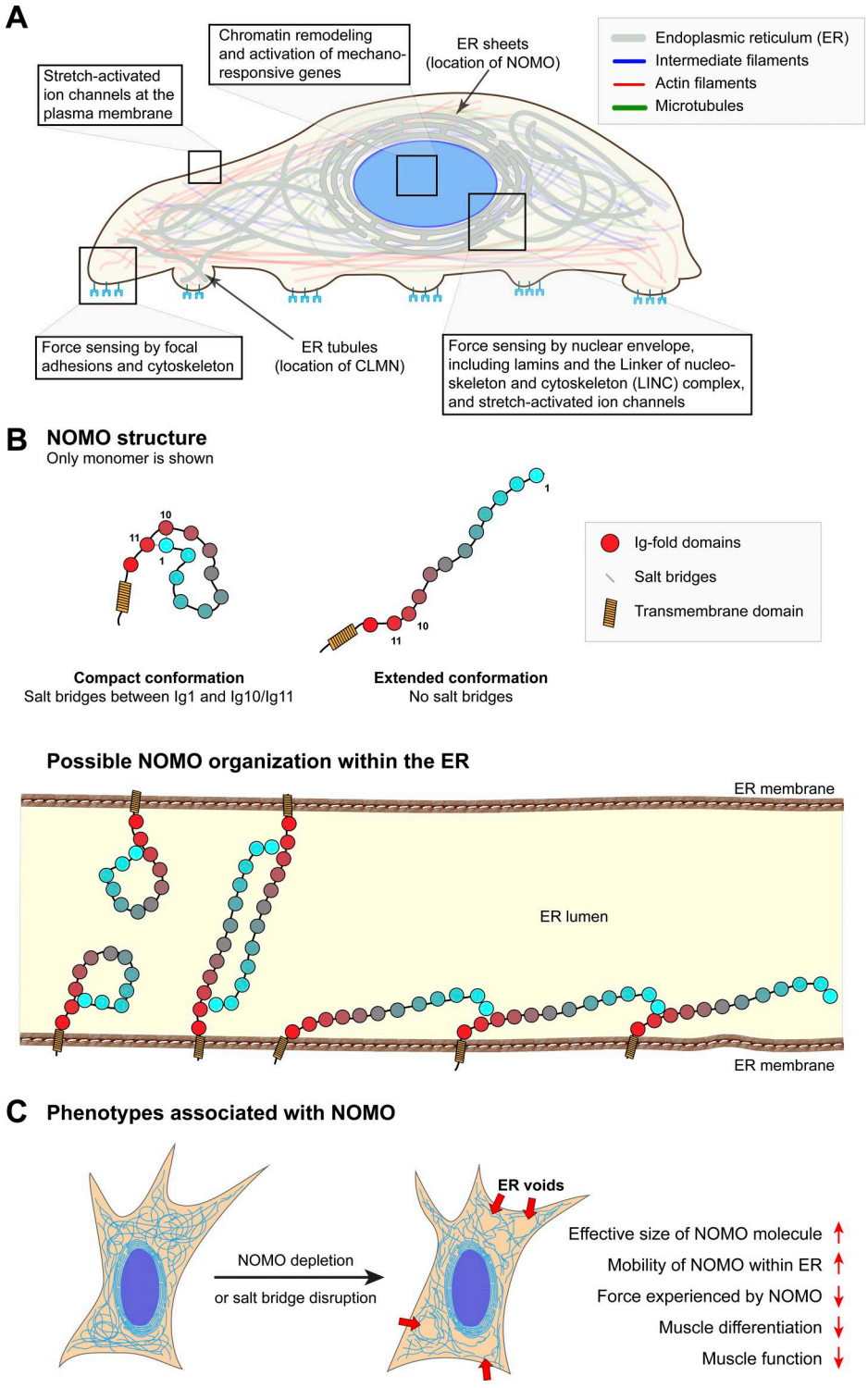

Figure 1. **Emerging role of NOMO and ER mechanobiology. (A)** Overview of key cellular mechanotransduction and force-bearing elements, including focal adhesions, the plasma membrane, cytoskeleton, nuclear envelope, and nuclear interior, along with the emerging role of the ER. **(B)** Schematic structure of the ER protein NOMO in its compact form, in which the Ig-like domains Ig1 and Ig10-Ig11 interact via salt bridges, and in the extended form when the salt bridges are disrupted (top). Numbers indicate the position of the Ig-like domains. The bottom panel shows different putative forms in which NOMO could be organized within the ER, including those with intramolecular salt bridges (left) and intermolecular salt bridges (center and right). Note that NOMO is predicted to form dimers, independent of the salt bridges, but for simplicity, only monomers are shown here for most configurations. **(C)** Phenotypes associated with NOMO depletion or when disrupting the interface required to form Ig1-Ig10/11 interactions. These include voids in the ER network (red arrows), increased mobility of NOMO within the ER, and muscle defects.

not only modulate intermolecular force transmission but also respond to applied forces and induce downstream signals have yet to be resolved. For example, NOMO dimers could span the width of the ER to sense forces transmitted across the lumen, or NOMO could dimerize or multimerize on the same side of a tubule, allowing it to sense tension along the ER surface (Fig. 1 B, bottom). It also remains to be determined whether the force transmission is based on intra- or intermolecular NOMO salt bridges.

Naughton et al. offer some clues into the biological function and the role of the NOMO salt bridges. They show that mutation of the salt bridge interface impairs the differentiation of mouse myoblasts into myotubes, and silencing of the NOMO homolog *nra-4* in *Caenorhabditis elegans* leads to motility defects, suggesting impaired muscle function. For now, it remains unanswered how the load-bearing ability of NOMO contributes to its function in muscle. Defects in ER morphogenesis are sufficient to impair motor axon function and general development in other organisms (9, 10), but in the present study, ER perturbation by depletion of CLIMP-63, Rtn3, or calnexin did not alter myoblast differentiation, indicating that the effect of NOMO cannot be solely attributed to defects in ER morphology. This opens the intriguing scenario that NOMO plays a crucial role in mechanosensing, particularly in differentiating muscle cells, with the precise mechanism and downstream effectors awaiting further exploration.

Another central question is how intracellular forces are transmitted to the ER. New insights into this question come from a recent study by the Henne laboratory (5). Merta and colleagues de-orphanize the previously poorly characterized protein calmin (CLMN), demonstrating that it acts as a physical tether between the tubular ER and actin filaments at focal adhesions. Using a proximity-labeling technique with endogenously-tagged proteins specific to either ER sheets, tubules, or the nuclear membranes, the authors identified CLMN as an ER tubule–specific transmembrane protein. They found that CLMN contains a cytoplasmic pair of actin-binding calponin homology (CH) domains. These CH domains are closely related to those of nesprins, which form part of the LINC complex that transmits forces between the nucleus and the cytoskeleton (11, 12). CLMN's localization and CH domains allow it to recruit ER tubules to focal adhesions by stably interacting with actin filaments at the basolateral surface. The reason for the specificity of CLMN to a subset of actin fibers remains to be resolved. Depletion of CLMN promoted peripheral actin bundling, increased the number of focal adhesions by reducing adhesion disassembly, and reduced cell motility. CLMN depletion also reduced intracellular calcium bursts, whereas CLMN overexpression increased calcium burst events, revealing a crucial role of CLMN in modulating calcium dynamics by perturbing ER–plasma membrane contact sites. It is intriguing to speculate whether CLMN depletion or overexpression could alter the forces experienced by NOMO and other ER structures, which could further modulate mechanotransduction processes in the ER.

Taken together, the publications by the Schlieker and Henne groups offer exciting new insight into the mechanobiology of the ER. The identification of NOMO as a force-bearing structure in the ER is the first direct evidence that the ER is under mechanical force in cells and that ER-resident proteins might use mechanical feedback to maintain ER morphology and function. The work by Merta et al. paints a complementary picture by revealing how ER tubules interact with force-bearing cytoplasmic structures, providing a mechanism by which ER proteins such as NOMO may receive mechanical input. Although many details of ER mechanotransduction—and the crosstalk of these mechanisms with other cellular mechanosensing processes—remain to be resolved, these studies highlight the rapidly growing field of organelle mechanobiology and stimulate exciting follow-up questions about how mechanical forces influence diverse aspects of cell biology. The fear of missing out (FOMO) for the ER (and other organelles) is thus no more.

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