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SPOTLIGHT

Stretching the secretory pathway: Mechanical control of Golgi export

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How deep into the cell do mechanical signals reach? In this issue, Bhaskar Naidu et al. (https://doi.org/10.1083/jcb.202510026) show that the Golgi responds to cell-spreading force and tunes its secretory output in a loop that feeds back to support spreading.

Cells are persistent mechanical sensors. They read the stiffness of their surroundings, register the pull of neighbors, and remodel themselves in response. For decades, the search for where cells feel force centered on two structures: the plasma membrane, where receptors and ion channels meet the extracellular environment, and the nucleus, whose deformation tunes gene expression. Only recently has attention turned inward to the organelles of the secretory pathway. The ER stands at the forefront of cellular mechanotransduction, actively reshaping its export machinery in response to physical cues. While the ER itself is not yet established as a primary force-sensing organelle, its secretory framework responds directly to mechanical strain. Extracellular mechanical cues upregulate ER exit sites and COPII-dependent ER-to-Golgi transport through the GTPase Rac1 (1), while optogenetic and other perturbations that strain the ER alter its export dynamics (2), and focal adhesions and the extracellular matrix further tune the COPII machinery (3). The Golgi, too, has entered this picture, as substrate stiffness has been shown to shape its secretory output by directing cargo between secretion and lysosomal degradation through a Src-FAK-AMPK-GBF1 signaling axis (4). What was left open is how mechanical force acts on the Golgi as a physical structure, altering the membrane behavior that drives cargo export rather than the signaling that sorts it. Here, Bhaskar Naidu et al. (5) show that the Golgi is a mechanoresponsive organelle that converts the force of cell spreading into increased membrane tension and secretory carrier output, extending mechanotransduction deep into the biosynthetic pathway.

Three distinct mechanical inputs, cell spreading on integrin-engaging substrates, substrate stiffness, and equibiaxial stretch, each increase the output of post-Golgi carriers, assayed with a RUSH-based CD59 reporter and by release of the CARTS cargo PAUF. Mechanistically, these cues drive tubulin acetylation and, measured through a Golgi-localized DAG biosensor and a protein kinase D (PKD) activity reporter, raise DAG and PKD signaling at the TGN. Notably, increasing microtubule acetylation pharmacologically with tubacin is sufficient to boost carrier formation even without external force, whereas inhibiting PKD with CRT0066101 blocks carrier formation. PKD activity also raises Golgi membrane tension, measured by Halo-Flipper fluorescence lifetime imaging, and this tension feeds forward into carrier production (Fig. 1). The precise mechanisms of how tension promotes biogenesis remain open and are likely nonlinear, as excess tension inhibits the curvature required for budding.

The idea that secretion and adhesion are spatially coordinated is not itself new. Post-Golgi carriers are known to be delivered preferentially toward the leading edge of migrating cells, and Golgi orientation follows the direction of movement (6). What Bhaskar Naidu et al. establish is a graded, quantitative relationship: the more a cell spreads, the more its Golgi exports. Using reporter systems to track cargo leaving the TGN, the authors find that carrier output scales with the degree of cell spreading and with substrate stiffness, echoing earlier reports that mechanical cues reach the secretory pathway (1) and reshape metabolism through matrix stiffness (7), thus placing Golgi export downstream of the same mechanical inputs that govern adhesion and cytoskeletal tension.

Two features make the advance more than a catalogue of mechanical inputs. The first is the physical readout: rather than force acting only through a signaling cascade, the biophysical state of the Golgi, its membrane tension, is itself part of the circuit, both an output of PKD and a contributor to carrier production. The second, and most striking, is the circularity. Carrier output is not merely a consequence of spreading but is itself required to sustain it: blocking the pathway blunts both secretion and the cell's ability to spread. The Golgi thus sits inside a feedback loop rather than at the end of a linear cascade, converting a mechanical state into a secretory response that reinforces that state. The convergence on PKD is mechanistically informative. PKD has a long-established role in the biogenesis of trans-Golgi carriers, where it is recruited and activated by DAG and, through

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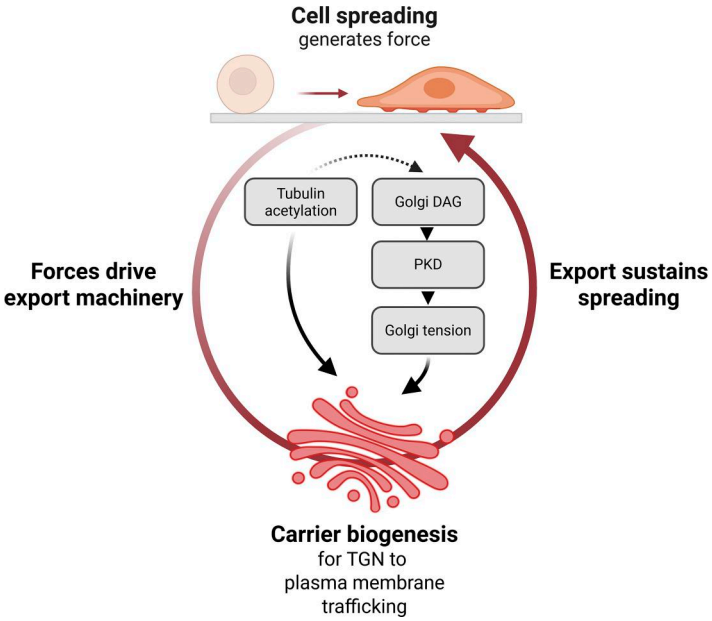

Figure 1. **Mechanical control of Golgi secretory output.** Cell spreading on the extracellular matrix generates force that is relayed to the Golgi and increases the biogenesis of post-Golgi transport carriers. These mechanical cues drive tubulin acetylation and Golgi DAG production, which activate PKD at the TGN to promote carrier biogenesis. PKD activity also increases Golgi membrane tension, which in turn feeds forward into carrier production. Tubulin acetylation may additionally promote Golgi DAG production (dashed arrow). Carrier output is itself required to sustain cell spreading, establishing a reciprocal loop between adhesion and Golgi export. Created in BioRender. Hausser, A. (2026) https://BioRender.com/5a1jf7z.

downstream phosphoinositide kinases, controls the fission of nascent carriers from the TGN for delivery to exocytic hotspots at the cell surface (8, 9). By showing that mechanical force feeds into this same node, Bhaskar Naidu et al. connect mechanotransduction to a canonical secretory effector, implying that force tunes a pre-existing secretory module rather than a dedicated, force-specific one.

The work opens several inviting directions. Because secretory output is read here from the number of carriers present at fixed times, a natural next step is to resolve the underlying kinetics directly: live imaging of carrier budding and fusion, for instance by TIRF microscopy, would convert these snapshots into rates and reveal how force reshapes the balance between carrier formation and delivery. The signaling axis itself warrants closer dissection. Acute or genetic perturbation of individual nodes will map how mechanical input is relayed to PKD, and micropatterning could separate the contributions of spreading, tension, and adhesion, which covary in most assays. A deeper question concerns what the carriers deliver to sustain spreading. PKD-dependent export is required to maintain focal-adhesion area per cell, yet it does so without altering the amount of active β1 integrin, similar to the stiffness-induced increase in focal-adhesion area, which also occurs independently of changes in active β1 integrin. Golgi export therefore appears to support adhesion growth through a route independent of integrin activation, with the responsible cargo still to be identified. The most exciting prospect is the disease setting, where tissue stiffness is itself pathologically altered. In breast cancer cells, increasing matrix stiffness has already been shown to enhance tubulin acetylation and reorganize the Golgi (10), placing the very effector Bhaskar Naidu et al. highlight under stiffness control in a tumor context. A Golgi that raises its secretory output in response to force could, in turn, feed the matrix remodeling that stiffens tissue further, suggesting that cancer cells might exploit this loop to sustain their own progression. The same self-reinforcing logic could operate in fibrosis, where progressive matrix stiffening and secretory activation likewise drive the disease. Establishing whether this loop is active in physiological and pathological tissue, and identifying the cargoes that carry its output, will determine how far a mechanically tuned Golgi shapes processes from development to disease.

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