key regulator of vesicle trafficking. This complex consists of Par3, Par6 and atypical PKC (aPKC), which are conserved proteins that regulate cell polarization from worms to mammals. Here we show that loss of the polarity protein Par3 is associated with Alzheimer's disease pathogenesis. Knockdown of Par3 promotes amyloidogenic APP processing and increases Aβ generation, while overexpression of Par3 promotes non-amyloidogenic APP processing. We further show that Par3 regulates APP trafficking by promoting its targeting to the recycling pathway, while knockdown of Par3 leads to lysosomal targeting of APP. Unexpectedly, we found that Par3 also regulates the trafficking of the β-secretase BACE1. However, loss of Par3 does not seem to cause a global disruption of vesicular trafficking. Rather, Par3 regulates APP and BACE1 trafficking through two distinct mechanisms. While Par3 regulates APP trafficking through the small GTPase Rac, it promotes BACE1 retrograde trafficking to the TGN by recruiting aPKC, which phosphorylates BACE1 on the C-terminus. Finally, we found that Par3 protein level is decreased in both human AD brain samples and a mouse AD model, and treatment of neurons with Aβ leads to a decrease in Par3. This suggests that there exists a vicious cycle in the AD brain where Aβ leads to a decrease in Par3, which then causes APP and BACE1 convergence in the lysosomes, leading to a further increase in Aβ generation. Taken together, our studies reveal a novel role for the polarity protein Par3 in AD pathogenesis through a two-pronged mechanism that involves regulation of APP and BACE1 trafficking.

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Mechanochemical feedback regulates the dynamics of the PAR system in C. elegans zygotes.

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The interplay between regulatory biochemistry and cell mechanics is critical for a broad range of morphogenetic changes. Cell mechanics can induce transport via growth and flow-fields, which in turn affect concentration-fields of regulators. Such systems exhibit an intrinsic feedback-architecture between regulators of cell mechanics and mechanical deformation. While we anticipate that this feedback between biochemistry and cell mechanics is widespread in Morphogenesis, there are few examples that are studied with respect to their potential for generating spatiotemporal patterns.

Here we establish at a quantitative level that PAR polarization of *C. elegans* zygotes represents a coupled mechanochemical system. Using Fluorescence Recovery After Photobleaching (FRAP) and RNA interference (RNAi), we first demonstrate that the biochemistry in form of the PAR domains feeds back on the mechanics by establishing and maintaining a non-muscle myosin II (nmy-2) gradient. Additionally, we characterize the effect of the polarity cue associated with the centrosome of the male pronucleus on the local myosin concentration at the posterior pole. We show that it induces a reduction in myosin concentration and thereby triggers the onset of cortical flows. Furthermore we measure the

spatiotemporal profile of the anterior and posterior PAR concentration, the myosin II concentration and the induced flow-field.

Finally, we capture the feedback-architecture of the coupled actomyosin – PAR system in a quantitative model, based on coupling a thin film active fluid description of cortical mechanics [1] to a reaction-diffusion PAR patterning system [2]. We show that this mathematical model can quantitatively recapitulate the spatiotemporal profile of PAR polarity establishment. Furthermore, we demonstrate that the model predicts the existence of a threshold in cortical flow velocity, which separates the non-polarizing and the polarizing regime and confirm the existence of this threshold velocity in the living *C. elegans* zygote.

Taken together, we show that the spatiotemporal chain of events that constitute PAR polarization in *C. elegans* can be described quantitatively in terms of a coupled, active mechanochemical pattern generating system.

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[2] Goehring, N. W. et al. Polarization of PAR Proteins by Advective Triggering of a Pattern-Forming System. Science **334**, 1137–1141 (2011).

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An Instructive Role for C. elegans HMR-1/E-cadherin in Translating Cell Contact Cues into Cortical Polarity.

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Early embryonic cells in many species polarize radially by distinguishing their contacted and contact-free surfaces. The homophilic adhesion protein E-cadherin is required for contact-induced polarity in many cells. However, it is not clear whether E-cadherin functions instructively as a spatial cue, or permissively by ensuring adequate adhesion so that cells can sense other contact signals. In *C. elegans*, radial polarity begins at the four-cell stage, when cell contacts restrict the PAR polarity proteins to contact-free surfaces. We previously identified the RhoGAP PAC-1 as an upstream regulator that is required to exclude PAR proteins from contacted surfaces of early embryonic cells. PAC-1 is recruited specifically to sites of cell contact and directs PAR protein asymmetries by inhibiting the Rho GTPase CDC-42. How PAC-1 is able to sense where contacts are located and localize to these sites is unknown. We show that HMR-1/E-cadherin, which is dispensable for adhesion, functions together with HMP-1/α-catenin, JAC-1/p120 catenin, and the previously uncharacterized linker PICC-1/CCDC85/DIPA to bind PAC-1 and recruit it to contacts. Furthermore, we show that ectopically localizing the intracellular domain of HMR-1/E-cadherin to contact-free surfaces of cells recruits PAC-1 and depolarizes cells, demonstrating that HMR-1/E-cadherin plays an instructive role in polarization. Our findings identify an E-cadherin-mediated