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Stretching the limits of extracellular signal-related kinase (ERK) signaling — Cell mechanosensing to ERK activation

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Abstract

Extracellular signal-regulated kinase (ERK) has been recognized as a critical regulator in various physiological and pathological processes. Extensive research has elucidated the signaling mechanisms governing ERK activation via biochemical regulations with upstream molecules, particularly receptor tyrosine kinases (RTKs). However, recent advances have highlighted the role of mechanical forces in activating the RTK–ERK signaling pathways, thereby opening new avenues of research into mechanochemical interplay in multicellular tissues. Here, we review the force-induced ERK activation in cells and propose possible mechanosensing mechanisms underlying the mechanoresponsive ERK activation. We conclude that mechanical forces are not merely passive factors shaping cells and tissues but also active regulators of cellular signaling pathways controlling collective cell behaviors.

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ERK/MAP kinase signaling, Intercellular signal transmission, Mechanochemical feedback, Mechanosensing, Receptor tyrosine kinases.

Introduction

Cells utilize a range of diverse signaling mechanisms to communicate with one another, enabling them to effectively coordinate their activities and respond to changes in their environment. Understanding how signals are transmitted cell-to-cell is critical to comprehending biological regulatory systems for various cellular processes in multicellular tissues and organs. A principle that has recently emerged to govern this regulation is the interplay between mechanical forces and biochemical signals, i.e., mechanochemical feedback loops in cells [1,2]. These feedback loops involve mechanosensation at the molecular level, biochemical signal transduction, and the generation of mechanical forces, which creates a rich dynamical system of cells and molecules within the multicellular tissues.

A prime example of the cell signaling systems that form part of the mechanochemical feedback loops is the extracellular signal-related kinase (ERK)/mitogen-activated protein kinase (MAP) kinase signaling pathway, known to regulate various cellular processes, such as cell differentiation, proliferation, metabolism, and motility. Typically, the ERK/MAP kinase signaling pathway is initiated when an extracellular ligand binds to and activates the receptor tyrosine kinases (RTKs) at the plasma membrane, followed by sequential activation of RAS, RAF, MEK, and ERK [3,4]. It was previously believed that the RTKs–ERK signaling pathways were solely activated by chemical signals, such as growth factors, cytokines, and hormones. However, mounting evidence has suggested that mechanical forces can also activate this signaling pathway,

ultimately leading to the generation of cellular mechanical forces through cytoskeletal activities. In particular, recent efforts have been devoted to uncovering how molecular machinery involved in mechanosensing stimulates the ERK signaling pathways.

This review aims to discuss the current understanding of the interplay between intercellular mechanical forces and the ERK signaling pathway in multicellular tissues. First, we introduce an overview of intercellular propagation of ERK activation observed in various contexts and explain the mechanism based on mechanochemical feedback loops underlying the phenomenon. Then, we discuss recent studies that have uncovered the role of mechanical forces in activating the ERK signaling pathway, with a particular focus on the mechanosensing involved in. Finally, we propose potential avenues that need to be explored for future research.

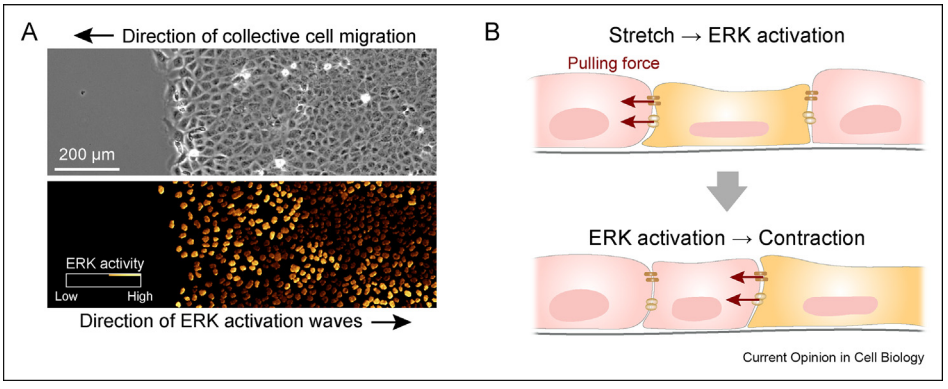
Stretch-induced ERK activation and intercellular transmission

The propagation of ERK activation within multicellular tissues is an exemplary phenomenon of intercellular signal transmission. In a confinement release assay using Madin–Darby Canine Kidney (MDCK) cells, the cells migrate coherently toward the cell-free space, while the activation of ERK propagates as traveling waves in the opposite direction of cell migration, i.e., from the leading edge to the center of the monolayer cell sheet (Figure 1a) [5,6]. ERK activation waves travel for around 7 min, spanning one cell scale, across the MDCK monolayer tissue [7], which is faster than the time scales of the transcription and translation, indicating that intercellular ERK signal transmission is likely passed through the changes in molecular activities but not gene expressions in this context. The intercellular propagation of ERK activation has been observed not only in the specific setting of *in vitro* system but also in various *in vivo* physiological situations, such as tissue morphogenesis [8–10], regeneration [11], and tissue homeostasis [12–14].

In confluent epithelial tissues, cells mechanically interact with one another, pulling and pushing through cell-cell adhesions. During directed collective cell migration, mechanical signals in the form of intercellular mechanical stress are initiated by cells at the leading edge that pull neighboring follower cells and propagate throughout the constituent cells on a large scale [15,16]. The readout of this intercellular mechanical signal transmission is the wave propagations of cell deformation, such as cell extension and shrinkage along the orientation of migration [15,17], which is well-correlated with the ERK activation waves [7]. Perturbation assays have unveiled a sequence of processes whereby ERK activation triggered by cell stretch induces cellular contractile forces, pulling subsequent follower cells and evoking the propagation of ERK activation (Figure 1B) [7,18,19]. This concept is supported by the observation that depletion of α-catenin, a tension transducer that mediates binding between E-cadherin and actin filaments [20,21], abolishes organized ERK activation waves [7]. Thus, the pulling forces serve as a spatial mediator of signal transmission in this context.

How do mechanical forces trigger ERK activation? So far, biochemical assays have shown that mechanical stretch applied to various cell types activates RTKs, such as epidermal growth factor receptor (EGFR) [22,23], fibroblast growth factor receptor (FGFR) [24,25], vascular endothelial growth factor receptor [26], and platelet-derived growth factor receptor [27], as well as their downstream signaling targets. Recent studies have further shown that stretch-induced ERK activation

Figure 1



Intercellular propagation of ERK activation during collective cell migration. (**a**) Shown here are phase contrast image (upper) and ERK activity image (bottom) of migrating MDCK cells released from confinement. The cells migrate toward the free space while the ERK activation waves propagate in the opposite direction of cell migration. The images were reproduced with modifications from a previous publication [7] and have been reused with permission from Elsevier under the terms of the license number 5550100152839 granted. (**b**) ERK activation occurs when the center cell is stretched by the front cell by pulling force. Subsequently, the ERK activation generates cell contraction, which transmits the stretch-induced ERK activation to the cell behind. ERK, extracellular signal-related kinase; MDCK, Madin–Darby Canine Kidney.

plays a crucial role in physiological function under *in vivo* situations. For example, mechanical stretching of murine skin cells increases the expression of the molecules through the EGFR–ERK signaling pathway, including the transcription factor AP1 [28]. The activation of AP1 alters gene expression to control proliferation and differentiation for stem cell renewal in murine skin. Another example is that stretching the ectodermal tissue in *Xenopus* embryos activates ERK through FGFR [24]. The force-induced FGFR–ERK signaling increases the stiffness and integrity of epithelial tissues, ensuring proper morphogenesis during early development.

Proposed mechanisms of mechanosensing to ERK activation

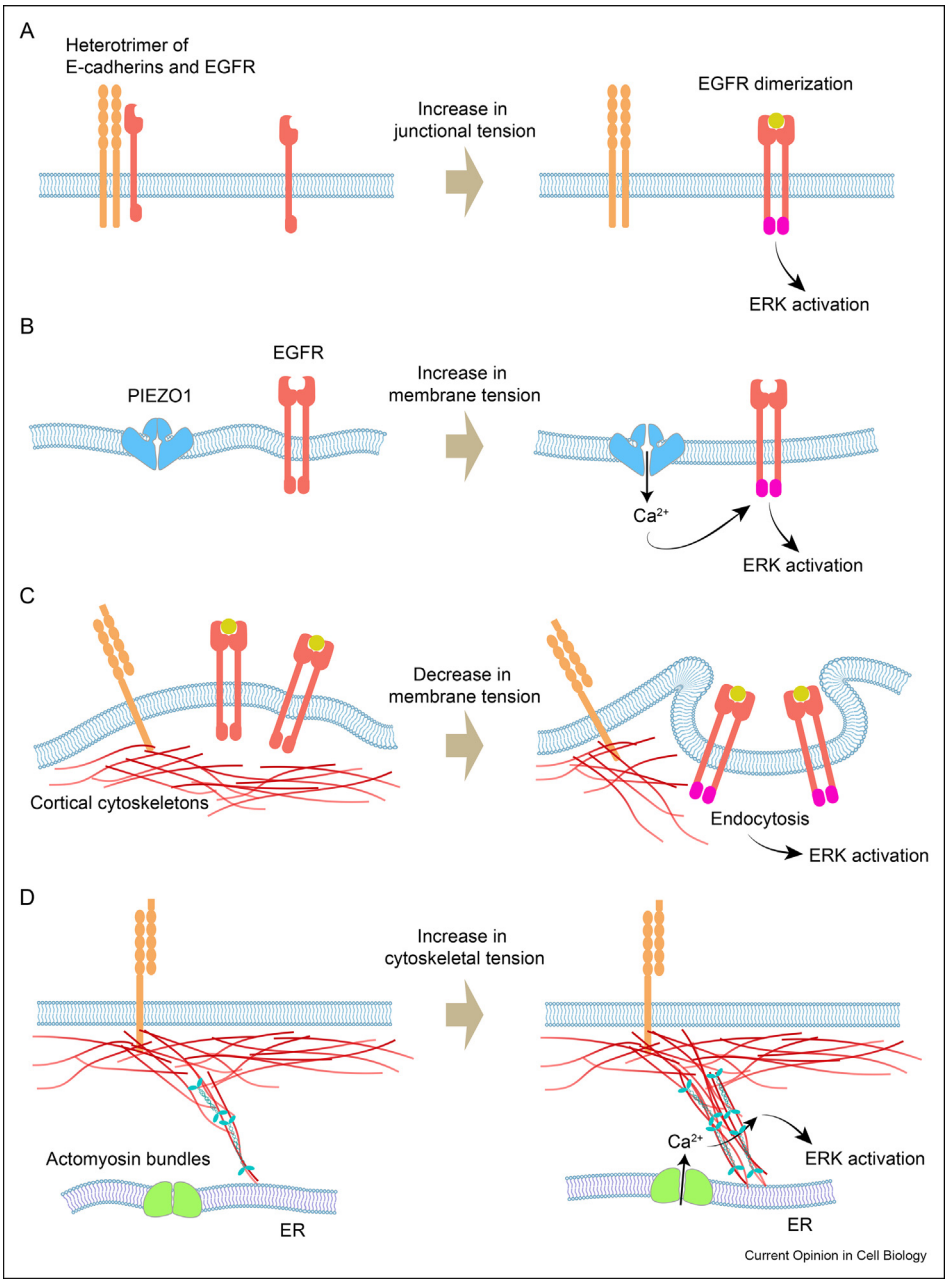
Although the mechanosensing mechanisms underlying ERK activation remain unclear, several scenarios have emerged from recent studies. One feasible scenario suggests that tensile stress at the cell–cell junction elicits EGFR activation by releasing the complex formation of E-cadherin and EGFR (Figure 2a). Previous studies showed that E-cadherin associates with EGFR and thereby regulates ERK [29–31], but the details of the underlying regulatory mechanism remain elusive. Sullivan et al. demonstrated using epithelial cell lines that E-cadherin and EGFR form heterocomplexes, most likely heterotrimers consisting of two E-cadherins and one EGFR, at the plasma membrane, and the mechanical disruption of these complexes by increased junctional tension activates ligand-dependent signaling [32]. E-cadherin forms constitutive cis dimers at the plasma membrane, regulated by p120 catenin bound to the intracellular region [33], indicating that E-cadherin tends to sequester EGFR monomers to prevent EGFR from homodimerization and activation under weak junctional tension. Once junctional tension arises, homophilic E-cadherin bonds dissociate from EGFR, resulting in EGFR dimerization and its binding to EGF, which eventually leads to the activation of ERK. In the context of directed collective cell migration, pulling forces from one cell to the follower cell would increase junctional tension, activating the EGFR–ERK pathway. Shear forces that occur when two unaligned forces pull or push against each other on adjacent plasma membranes could also be a mechanical stimulant, as they trigger E-cadherin-mediated EGFR activation and its signal transduction [34]. Still, how mechanical forces disrupt the E-cadherin–EGFR complexes at the plasma membrane needs to be further investigated.

Another proposed mechanism involves receptor-mediated endocytosis triggered by plasma membrane tension. Rosenblatt et al. recently proposed that an increase in membrane tension can activate Piezo1, known as a mechanosensitive channel [35], giving rise to EGFR endocytosis and subsequent downstream signaling (Figure 2b) [36]. Intriguingly, the internalization of EGFR induced by Piezol-mediated Ca2+ influx may not rely on canonical EGFR autophosphorylation but instead on Src-family kinases and p38-dependent non-canonical EGFR phosphorylation. This mechanism could account for ERK activation via stretch-induced Piezo1 in controlling the maintenance of cell density in confluent epithelial tissues [37] as well as during directed collective cell migration.

Notably, membrane tension, which can be modulated by mechanical stretching or relaxing, regulates endocytosis [38] and ERK activity. For example, De Belly et al. demonstrated that a decrease in membrane tension during cell spreading causes increased endocytosis of FGF signaling components, resulting in ERK activation necessary for exit from naive pluripotency in mouse stem cells [39]. The activation of ERK by membrane tension is not only restricted to the FGFR pathway but also could extend to other RTK signaling pathways, given the dynamic interplay and feedback between membrane tension and endocytic activity [40]. For instance, overexpression of Rab5a, which regulates endocytosis, has been shown to enhance EGFR endocytosis and subsequent ERK activation in epithelial cells, switching from solid to liquid behaviors in cell collectives [41,42]. This observation is reminiscent of the concept of the mechanochemical feedback that integrates membrane tension, ERK activation through EGFR endocytosis and cellular force generation, which needs to be addressed in the future. It appears that this regime does not align with the stretch-induced ERK activation discussed earlier, particularly viewed at the entire cell scale. Nevertheless, the plasma membrane of a cell could be stretched by adjacent cells exerting local pulling forces, leading to the separation of the membrane from cortical cytoskeletons and the generation of the excess flabby membrane at the subcellular scale. This, in turn, prompts a decrease in membrane tension and the subsequent receptor internalization-mediated signal transduction to the ERK activation (Figure 2c).

Lastly, the mechanosensing mechanism associated with ERK activation may involve cell organelles that are physically connected to actin fibers. In both epithelial and fibroblast cells, mechanical stretch builds up actomyosin fiber bundles, which align along the orientation of the applied tensile forces, and results in ERK activation, of which magnitude is dependent on the tension in the actomyosin fibers [43]. In smooth muscle cells, mechanical stretch triggers ERK activation via Ca2+ ion channels located on the endoplasmic reticulum membrane. This process requires tension in actin fibers, but not in microtubules [44]. These findings suggest that tensile stress along actin fibers, coupled with non-muscle myosin, may play a role in the mechanosensing in response to cell stretch in order to trigger the ERK activation in cells (Figure 2d).

Figure 2



Possible mechanosensing mechanisms that lead to ERK activation. (**a**) Increase in junctional tension triggers EGFR dimerization and binding with the ligands through dissociation of heterotrimer of two E-cadherins and one EGFR. (**b**) Increase in membrane tension opens PIEZO1, leading to Ca2+-mediated non-canonical EGFR activation. (**c**) Decrease in membrane tension caused by separation of plasma membrane from cortical cytoskeletons enhances endocytosis, leading to the receptor–ligand complex internalization. (**d**) Increase in cytoskeletal tension along with actomyosin bundles elevates ER membrane tension, resulting in Ca2+-mediated ERK activation. EGFR, epidermal growth factor receptor; ERK, extracellular signal-related kinase

Conclusions and perspectives

This review examines specifically potential mechanosensing mechanisms that respond to cell stretching, leading to the stimulation of the ERK signaling pathway in multicellular epithelial tissues. While the mechanosensing and transduction pathways mediated through cell–extracellular matrix adhesions have been extensively studied [45,46], mechanochemical regulatory

systems resulting from cell-cell interactions have only recently been explored from a tissue mechanobiology perspective as discussed in this review. Consequently, there are many avenues and challenges that could be taken to delve deeper into further investigation. Moving forward, we highlight the following points that need to be addressed.

First, further technological advancement in the simultaneous measurement of force and signal activity is required to gain a comprehensive insight into how, when, and where mechanical forces are exerted on and signals are transduced in cells. Although state-of-the-art technologies have enabled high-resolution mapping of time-varying mechanical fields [47,48], the continued development of force measurement *in situ* conditions will provide a vivid and quantitative picture of the input properties for mechanochemical feedback systems.

Second, mechanical force is not the sole determinant factor to trigger the cell signaling systems as discussed earlier, and thus understanding in detail the state of receptor molecules is essential when a mechanical force acts as the input in signal transduction. In particular, it depends on the types of receptors and cells whether the presence or absence of ligands is necessary to function as a mechanosensing unit. For example, the binding of EGF to EGFR is necessary in the regime where disruption of E-cadherin−EGFR complexes induces ERK activation [32]. Additionally, stretch-induced ERK activation waves in MDCK cells require proteinase activity of ADAM (a disintegrin and metalloproteinase) contributing to the ectodomain cleavage of EGF-family proteins [7,12], suggesting that EGF ligands are essential for the mechanotransduction of ERK activation. As the EGFR ligands, such as EGF and HBEGF, have redundancy in generating ERK activation waves [49], those ligands could be involved in presetting for the mechanical forces to work as a trigger cue of the signaling system. On the other hand, evidence has shown that FGF is dispensable for force-induced FGFR activation in *Xenopus* embryos [24], although the molecular mechanism is still unclear. This observation may pave the way for the discovery of a novel mode of receptor activation and signal transduction, possibly by connecting with an intriguing report that dimerized FGFR undergoes phosphorylation even without the ligands [50].

Lastly, it is fascinating to explore the interplay between intracellular signals originating from different inputs and their integration to achieve specific cellular behaviors. In this review, we have highlighted stretch-induced ERK activation as a mechanism for intercellular propagation of ERK activation. However, an alternative mechanism based on ligand−receptor interaction may be involved in generating spatiotemporal patterning of ERK activity during physiological processes. For instance, ERK activity propagates in the scale bone tissues during the regeneration and development of zebrafish [11], where the ERK activation waves take about an hour to travel across a single cell length; the timescale of ERK activation waves in zebrafish scale bone is much slower due to the involvement of gene expression than the case in MDCK cell monolayers. Despite the significant differences in the timescale of events, these signal activation mechanisms need not be mutually exclusive. We expect further studies to contrast the characteristics of each mode [19] and to understand their cooperativity through experiments and theory. From a broader perspective, it is important to investigate how the network circuit design and reaction timescale of intracellular signals from different inputs are adaptively integrated to regulate cellular behavior. Furthermore, exploring crosstalk between ERK signaling and other mechanical cues, such as the stiffness of cell substrate [51], will aid in developing a comprehensive understanding of the mechanochemical regulatory systems.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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* of special interest
** of outstanding interest

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