Archives of Biochemistry and Biophysics 586 (2015) 20–26

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

journal homepage: www.elsevier.com/locate/yabbi

Review article

Mechanoreception at the cell membrane: More than the integrins

Alexander N. Gasparski, Karen A. Beningo*

Department of Biological Sciences, Wayne State University, Detroit, MI 48202, USA

ARTICLE INFO

Article history:
Received 27 February 2015
Received in revised form
24 July 2015
Accepted 26 July 2015
Available online 1 August 2015

Keywords:
Mechanoreceptors
Mechanotransduction
Cell migration
Cell mechanics

ABSTRACT

A cell receives mechanical cues from its surrounding microenvironment and transduces this mechanical information into a biochemical signal within the cell, ultimately resulting in physiological change. Several molecules within the plasma membrane have been identified that are capable of receiving and translating a mechanical signal. Although integrins are most often discussed as the cell's primary method of mechanoreception at the cell membrane, several non-integrin mechanoreceptors have emerged over the last decade. Specifically, multiple G-protein coupled receptors, the glycocalyx, ion channels, lipid rafts and receptor tyrosine kinases have been found to translate mechanical stimuli from the environment into cellular change. This review will discuss these non-integrin mechanoreceptors associated with the plasma membrane, and their impact on cell physiology.

Contents

1. Introduction

Cells communicate with one another through both biochemical and physical means. Specifically, a cell can receive mechanical information from its surrounding environment through mechanoreception and subsequently transduce the signal internally resulting in physiological changes [1–6]. Within a biological system, stimuli of a mechanical nature can function as a ligand similar to a biochemical molecule, with both types of ligands existing in a variety of forms and combinations. Biochemical ligands can be proteins, lipids or carbohydrates while the mechanical ligands may be compressive, tensile or shear stress [7]. Each of these different forms utilize different receptors, are transduced by different pathways and result in different cellular responses [1]. Further, the biological impact of the extracellular biochemical signal is dependent on ligand concentration, receptor concentration and frequency of encounter [8]. In correlation, a mechanical ligand is dependent on the physical medium involved and can vary widely in magnitude, frequency and duration [9,10]. In a biological

* Corresponding author. Department of Biological Sciences, Wayne State University, 5047 Gullen Mall, Detroit, MI 48202, USA.
E-mail addresses: dw5087@wayne.edu (A.N. Gasparski), beningo@wayne.edu (K.A. Beningo).

http://dx.doi.org/10.1016/j.abb.2015.07.017
0003-9861/

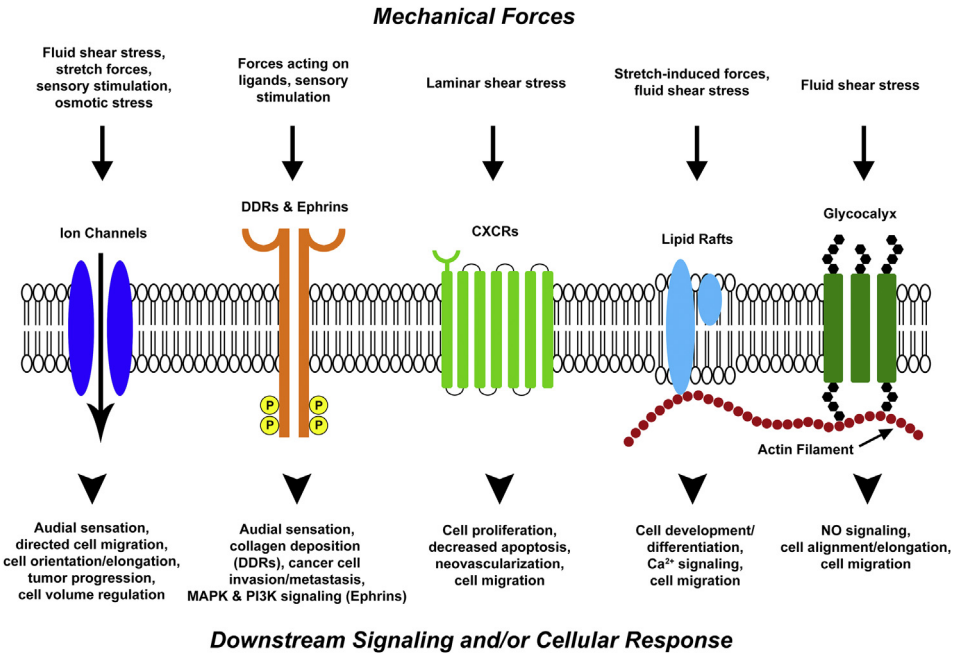

Fig. 1. Non-integrin mechanoreceptors in the plasma membrane. Ion channels, DDRs and ephrin, RTKs, CXCRs, lipid rafts and the glycocalyx have all been found to receive mechanical signals from the environment and transduce the signal across the plasma membrane. While some members of these receptor families act in collusion with the integrins or cadherins, others are entirely independent. Two examples of complexes that may act with the integrins or cadherins are the VEGFR and the lipid rafts. In the figure VEGFR functions in complex with β-catenin and cadherin, and examples of the lipid raft proteins could include integrin β-1 as well as caveolin and syndecan. Whether cooperatively or independent of cadherin and integrin, these mechanoreceptors participate in the conversion of the mechanical signal to biochemical signals that trigger multiple signaling cascades within the cell culminating in a physiological response, such as migration.

context, mechanical stimulation can present itself as vascular shear stress [11], mechanical strain brought on by the elasticity of the surrounding tissue or as compressive force due to hydrostatic changes, to name a few [12,13]. With all of these options, it stands to reason that like biochemical ligands, mechanical forces have been found to affect cells in many different ways. A well-characterized example of this diversity of effects is found within the vasculature where fluid shear stress on endothelial cells, impacts differentiation, growth and migration, which ultimately results in the modulation of the vascular system as a whole [14–17].

Given the significance of mechanical input to proper physiological function, it is not surprising that a number of cell surface molecules capable of receiving mechanical input have emerged. The most notorious being the integrins and cadherin families of transmembrane receptors that mediate cell-ECM interactions and cell–cell interactions respectively [18]. While much emphasis is still placed on understanding these two receptors in mechanoreception, a number of other membrane molecules have also been implicated. Some of these transduce the mechanical signal independently of integrins and cadherins while others either function directly or cooperatively with these main receptors to produce the downstream physiological response. Currently several comprehensive reviews can be found on integrin and cadherin-based mechanotransduction [5,19–23]. However in this review we limit our focus to non-integrin or cadherin molecules that receive mechanical signals at the plasma membrane, we further describe their ultimate impact on cell behavior and specifically migration Fig. 1.

2. G-protein coupled receptors

2.1. CXCR

The chemokine receptors CXCR1 and CXCR2 are transmembrane receptors located on a limited number of cell types including endothelial cells. CXCR1 and CXCR2 are G-protein coupled receptors that are essential for cell migration in response to the chemokine interleukin-8 (CXCL8) [24]. A number of studies provide correlative evidence that CXCR1 and CXCR2 receptors may function as mechanoreceptors. For instance, upon exposure to laminar shear stress, both mRNA and protein expression of CXCR1 and CXCR2 increases in endothelial cells. Further, in response to shear stress, these receptors will redistribute on the surface of endothelial cells, suggesting they respond to mechanical cues. Additionally, variable levels of shear stress resulted in a dose dependent response in suppression of the rate of wound closure in a scratch wound assay when CXCR1 and CXCR2 activity was inhibited with inhibitory antibodies [25].

Upon binding of the CXCL-8 ligand to the receptors, Rho and Rac signaling pathways are activated leading to reorganization of the actin cytoskeleton [26] and increased motility [27]. Interestingly, the expression of the CXCL8 ligand itself can be induced by shear stress on the endothelial cell, thus self-promoting cytoskeleton reassembly and cell migration [25,28]. As such, knockdown of CXCR1 and CXCR2 generates actin stress fibers and phosphorylation of ERK1/2 in melanoma cells, culminating in decreased cell migration [29]. Nonetheless, despite this evidence, it is unclear whether CXCL-8 directly mediates the CXCR1 and CXCR2 response to shear stress or if co-factors or secondary receptors, potentially even the integrins are involved [25,30].

Given the capacity for mechanoreception of these receptors, it is also an intriguing possibility that CXCR1 and CXCR2 could enhance the progression of cancer via their mechanoreceptive properties. It is already known that both receptors influence growth, motility and invasiveness of malignant melanoma both *in vitro* and *in vivo*. For example, overexpression of CXCR1 and CXCR2 in mice melanoma models leads to enhanced tumor growth resulting from increased proliferation and neovascularization, and decreased apoptosis. *In vitro* overexpression of CXCR1 and CXCR2 generates a ~2-fold