The International Journal of Biochemistry & Cell Biology 44 (2012) 2233–2237

Contents lists available at SciVerse ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

Signalling networks in focus

Biophysical signals controlling cell fate decisions: How do stem cells really feel?

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ARTICLE INFO

Article history:
Received 30 July 2012
Received in revised form 4 September 2012
Accepted 5 September 2012
Available online 12 September 2012

Keywords:
Stem cell
Biophysical
Forces
Cytoskeleton
Transcription
Differentiation

ABSTRACT

Self-renewal and differentiation are fundamental stem cell fate decisions, which are essential for normal tissue development, homeostasis, and repair. Extracellular signals, including mechanical and biophysical forces, play an important role in directing the behaviour of a variety of stem and progenitor cells, and recent studies have provided new insights into the molecular mechanisms of these responses. While integrin receptors transmit forces from the extracellular matrix to the cell, the actin cytoskeleton and Rho-GTPases, mediate downstream signal transduction. To affect stem cell fate, however, these signalling cascades must ultimately be transduced into specific transcription responses. Serum response factor (SRF) and yes-associated protein (YAP) are two examples of mechano-sensitive transcription factors, which have recently been implicated in epidermal and mesenchymal stem cell differentiation. Significant challenges for future studies will likely include measuring the relevant biophysical forces experienced by cells *in vivo* and translating the current knowledge into regenerative therapies.

Signalling network facts

- Biophysical cues and forces from the external environment regulate fate decisions for many different stem and progenitor cells.
- Integrin-mediated adhesion to the extracellular matrix is a central component of force transmission to the cell.
- Cytoskeletal tension and Rho-GTPase activity sense biophysical cues and mediate lineage selection in mesenchymal stem cells.
- SRF and YAP/TAZ are downstream transcriptional regulators of various biophysical stimuli.
- Molecular level understanding of stem cell mechano-sensing is critical for developing effective biomaterials and therapies for regenerative medicine.

1. Introduction

Extracellular signals from the surrounding microenvironment, including soluble factors, cell–cell interactions, and cell–matrix interactions play an essential role in coordinating many basic cell functions, such as proliferation, migration, and differentiation. This is especially true for stem and progenitor cells, where fate decisions must be executed in the right time and place for normal development and tissue function (Watt and Hogan, 2000). The ability to self-renew and differentiate defines all types of stem cells, and the process of differentiation involves a regulated series of transitions from committed progenitors to terminally differentiated cell types.

While much work has focused on the role of biochemical signalling in the regulation of stem cell function, only recently have we begun to appreciate the influences of biophysical and mechanical forces. Like their biochemical counterparts, physical cues act in many different forms, including dynamic or static deformations of the ECM (Fig. 1A), matrix elasticity (Fig. 1B), topographic cues (Fig. 1C), intercellular tension (Fig. 1D), hydrostatic pressure (Fig. 1E), and fluid shear (Fig. 1F). In this review, we will provide an overview of the biophysical regulation of stem cell fate and the key signalling pathways involved in mechanotransduction. We will also highlight the current challenges and on-going issues for dissecting the mechanisms of cellular mechano-sensing and discuss how these concepts may be translated into regenerative therapies. The primary focus will be on biophysical cues from the extracellular matrix (ECM), but it is important to note that cells can experience many different types of physical stimuli.

2. Function: biophysical regulation of stem cell behaviour

A large proportion of stem cell mechanotransduction studies have focused on mesenchymal stem cells (MSCs), most likely because these cells are an attractive source for regenerative

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http://dx.doi.org/10.1016/j.biocel.2012.09.003

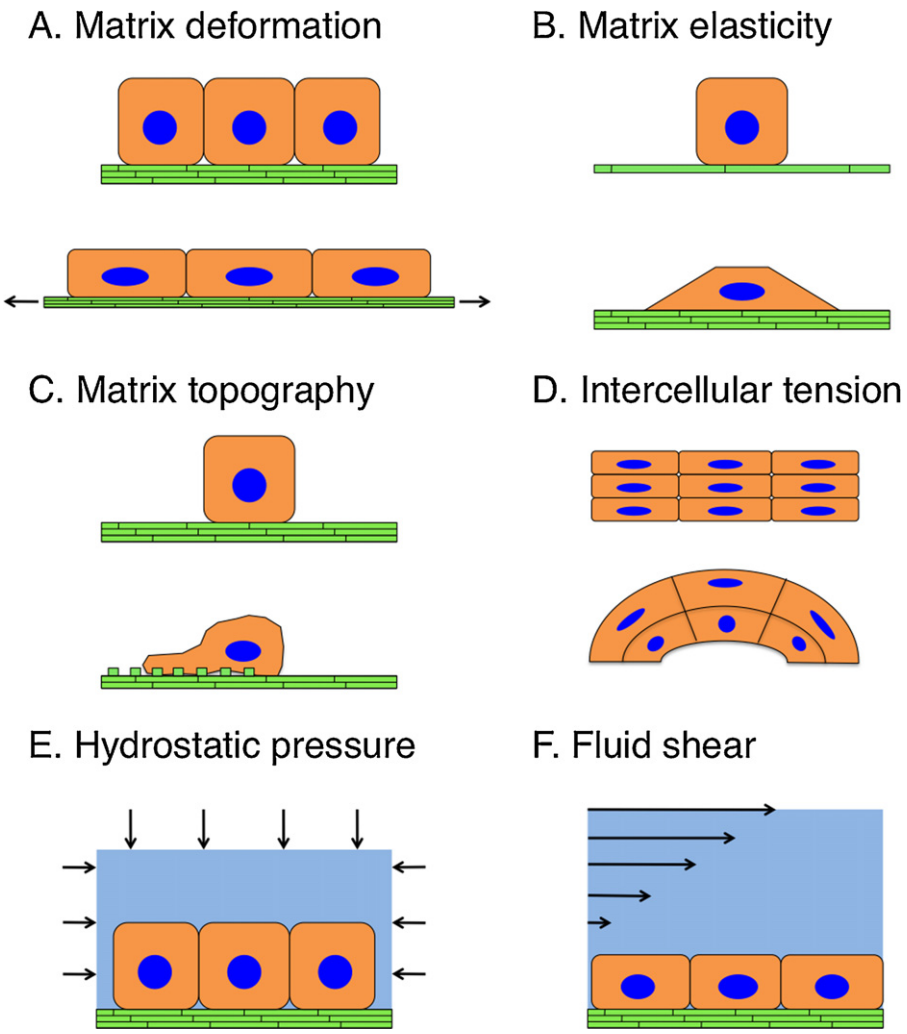

Fig. 1. *Types of biophysical stimuli experienced by cells.* Biophysical cues and mechanical forces can be exerted on stem cells in a variety of different ways. (A) Static or dynamic deformations of the ECM can stretch or compress attached cells. (B and C) Cells can also sense changes in the stiffness or topography of the ECM. (D) Movement and deformation of multi-cellular structures also exerts forces *via* intercellular adhesion. (E and F) Cells surrounded by blood or interstitial fluids experience hydrostatic pressures and shear forces.

medicine and because mesenchymal tissues, such as bone, cartilage, and muscle, have a primarily mechanical function. It has also been recognised for many years that mesenchymal tissues can adapt to changing mechanical environments (Carter et al., 1998), and a number of studies have employed bioreactors and controlled mechanical loading to enhance extracellular matrix production and the development of engineered mesenchymal tissues (Buschmann et al., 1995). More recently, this approach has been extended to MSCs for directing their differentiation along specific lineages, and in general, the cellular response appears to match the type of forces experienced *in vivo* (Engler et al., 2006). For example, tensile strains (Simmons et al., 2003) and fluid shear (Arnsdorf et al., 2009) promote osteogenesis, while compressive loading (Mauck et al., 2006) and hydrostatic pressure (Angele et al., 2003) elicit a more chondrogenic response. Although these types of studies clearly demonstrate the utility of biophysical stimuli for tissue engineering purposes, it is difficult to tease out the molecular mechanisms and fundamental effects on cell fate within such complex, 3D environments.

In contrast to the large scale, mechanical loading experiments described above, micro- and nano-fabrication techniques provide a means for applying more precise biophysical cues to single cells. By increasing the adhesive area (McBeath et al., 2004) or stiffness (Engler et al., 2006) of the underlying matrix, several studies have shown that cell spreading and cytoskeletal tension promotes osteogenic over adipogenic differentiation in MSCs. Furthermore, the role of biophysical stimuli on MSC differentiation depends on the biochemical context. When stimulated with TGF β, cell spreading instead switches the lineage selection from chondrocyte to smooth muscle cell differentiation (Gao et al., 2010). Thus, the interactions between mechanical and biochemical signals offer stem cells many options for directing differentiation along specific lineages.

Recent findings also indicate that surface topography, both at the micro- and nano-scale, influences MSC behaviour. Alignment of cells along micro-scale ridges can enhance myogenic differentiation and myotube formation (Charest et al., 2007), and high-throughput approaches have revealed that increasing the height or decreasing the size of topographical features enhances osteogenesis, while shape and spacing have a lesser effect (Lovmand et al., 2009). At the nano-scale, feature alignment and ordering is a critical regulator of MSC expansion *versus* osteogenesis (McMurray et al., 2011).

Beyond MSCs, physical cues can influence tissue homeostasis and repair through their effects on resident progenitor cells. Muscle stem cells display increased self-renewal and survival when cultured on soft (12 kPa) hydrogels, and expansion on these soft