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Review

Mechanobiology of mesenchymal stem cells: Perspective into mechanical induction of MSC fate

Jin Hao [a], Yueling Zhang [a], Dian Jing [a], Yu Shen [a], Ge Tang [a], Shishu Huang [a,b], Zhihe Zhao [a,*]

[a] Department of Orthodontics, State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, West China School of Stomatology, Sichuan University, Chengdu 610041, China

[b] Department of Orthopaedics and Traumatology, The University of Hong Kong, Hong Kong 649490, China

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ABSTRACT

Bone marrow-derived mesenchymal stem and stromal cells (MSCs) are promising candidates for cell-based therapies in diverse conditions including tissue engineering. Advancement of these therapies relies on the ability to direct MSCs toward specific cell phenotypes. Despite identification of applied forces that affect self-maintenance, proliferation, and differentiation of MSCs, mechanisms underlying the integration of mechanically induced signaling cascades and interpretation of mechanical signals by MSCs remain elusive. During the past decade, many researchers have demonstrated that external applied forces can activate osteogenic signaling pathways in MSCs, including Wnt, Ror2, and Runx2. Besides, recent advances have highlighted the critical role of internal forces due to cell–matrix interaction in MSC function. These internal forces can be achieved by the materials that cells reside in through its mechanical properties, such as rigidity, topography, degradability, and substrate patterning. MSCs can generate contractile forces to sense these mechanical properties and thereby perceive mechanical information that directs broad aspects of MSC functions, including lineage commitment. Although many signaling pathways have been elucidated in material-induced lineage specification of MSCs, discovering the mechanisms by which MSCs respond to such cell-generated forces is still challenging because of the highly intricate signaling milieu present in MSC environment. However, bioengineers are bridging this gap by developing platforms to control mechanical cues with improved throughput and precision, thereby enabling further investigation of mechanically induced MSC functions. In this review, we discuss the most recent advances that how applied forces and cell-generated forces may be engineered to determine MSC fate, and overview a subset of the operative signal transduction mechanisms and experimental platforms that have emerged in MSC mechanobiology research. Our main goal is to provide an up-to-date view of MSC mechanobiology that is relevant to both mechanical loading and mechanical properties of the environment, and introduce these emerging platforms for tissue engineering use.

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1. Introduction

Advancement of stem cell-based tissue engineering strategies for treatment of disease, injury and aging related conditions relies on the ability to direct stem cells toward specific lineages in a safe and effective manner. The promise of stem cells in tissue engineering is highlighted by the successful transplantation of stem cells for treatment of blood diseases, autoimmunity, and musculoskeletal disorders. During orthodontic treatment, osteoporotic bone loss is one of the major diseases that affect the process of tooth movement [1], and it is due to increased osteoclastic activity and decreased osteoprogenitor number. Therefore, potential therapeutics for osteoporosis are to replenish osteoprogenitors using bone marrow mesenchymal stem cells (MSCs) in both dental and general applications [2].

Despite considerable progress in our understanding of MSC behaviors and functions, we have only a limited knowledge on how to precisely direct the differentiation and self-renewal of MSCs. Over the last decade, a majority of studies in this field pertain to biochemical cues and signaling events controlling MSC functions. However, recent advances have elucidated that mechanical signals are also critical regulators of MSC behavior. Our previous work has also indicated that applied forces (or mechanical loading), including tension, compression, stress, and

* Corresponding author at: State Key Laboratory of Oral Diseases, West China College of Stomatology, West China Hospital of Stomatology, Sichuan University, 14#, 3rd Section, Renmin South Road, Chengdu 610041, China. Tel./fax: +86 28 85503645.

E-mail address: zhzhao@scu.edu.cn (Z. Zhao).

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hydrostatic pressure, can remarkably affect the maintenance and lineage specification of MSCs [3–5]. More recently, MSCs have also been found to be maintained and regulated by internal microscopic forces that occur when contracting cells pull on surrounding extracellular matrix (ECM) and on each other, which are also called cell-generated forces [6]. Current understanding believes that diverse mechanical signals between and within *in vivo* niches combine to regulate stem cell fate, however, the mechanisms are still obscure [7]. Systematic research of these mechanisms has been hampered by the limited accessibility to *in vivo* niches and the combinatorial nature of various non-additive cues.

In this review, we recount the external mechanical force induced MSC mechanobiology, and discuss the interactions between cell-generated forces with MSC lineage specification. We also summarize key experimental evidence of mechanically directed MSC lineage specification by both forces and pose important unanswered questions in this field. There is a difference between mesenchymal stem cells and multipotent stromal cells, which express a different repertoire of surface markers [8]. For the purposes of this review, we use "MSC" in lieu of either.

2. The effects of applied forces on mesenchymal stem cell functions

Biological tissues are normally subjected to multiple dynamic mechanical forces including fluid shear stress, hydrostatic compression, mechanical tension, bending, and compression (Table 1) [9]. These mechanical forces are applied throughout all stages of the development in living tissues and regulate various functions of MSCs [10]. The critical roles of applied forces in the maintenance and growth of tissues indicate they are needed for full committal and differentiation of MSCs within mature tissues [11]. The following subsections will focus on the response of MSCs to distinct applied forces, and discuss the mechanosensing mechanism of force-induced mechanotransduction.

Table 1
Effects of applied force induced MSC functions.

Force types	Cell source	Culture	Mechanical parameter	Discoveries
Fluid flow				
[25]	C3H/10T1/2	2-D Fibronectin coated glass slide	Parallel plate, 1 h, 1 Hz, peak shear of 10 dyn cm^{-2}	Increased Runx2, PPARγ, Sox9, RhoA and ROCK II regulates osteogenesis
[26]	Rat marrow	2-D glass slide	Parallel plate, 24 h, shears of 5–20 dyn cm^{-2}	Increased markers of cardiomyogenesis
Hydrostatic pressure				
[27]	Porcine marrow	1 or 4% agarose	4 h day^{-1}, 21 day, 1 Hz, 10 MPa	Increased chondrogenic markers in 4% gels only
[28]	Porcine marrow and fat pad	2% agarose	4 h day^{-1}, 35 day, 1 Hz, 10 MPa	Increased sGAG synthesis, suppressed mineralization in bone marrow
Compression				
[29]	Porcine marrow	2% agarose or fibrin	3 h day^{-1}, 21 or 42 day, 1 Hz	Day 21: decreased markers of chondro/myogenesis in both gels; Day 42: increased chondrogenic markers in fibrin gels
[30]	Porcine marrow	1% or 4% agarose	1 h day^{-1}, 7, 14 or 21 day, 1 Hz, 10% strain	Increased chondrogenic markers in 4% gels compared to 1% gels
Tension				
[31]	Rabbit marrow	Silicon wafer	3 day, 0.26 Hz, 3% and 10% strain	Increased ALP and α-SMA
[32]	Rat tendon	Col-coated silicone	0.5 Hz, 0%, 4% or 8% strain	Increased BMP2, ALP expression and calcium deposition

2.1. Mechanobiology of applied force induced mesenchymal stem cell functions

Several studies have indicated the ability of mechanical cues to steer MSC fate decisions [12,13]. It has been convincingly demonstrated that tensile forces induce osteogenic differentiation and compression forces induce chondrogenic differentiation [4]. With hydrostatic pressure and uniaxial compression, MSCs showed enhanced chondrogenic expression [12,14], while application of tensile strain enhanced osteogenic expression [15]. In addition, tensile strain has also been found to direct the spatial rearrangement of human MSCs to form knob-like three-dimensional (3-D) structures [16], suggesting that mechanical cues may influence cell migration. Moreover, an *in vivo* study has shown that high-frequency mechanical signals (90-Hz, 0.2-g peak acceleration, and 15 min) inhibited the adipogenesis of bone marrow-derived MSC (BMSC) markedly [17]. Although whether this observation can be attributed to tensile forces is unknown, it does suggest that mechanical loading can be crucial regulator of MSC differentiation (Fig. 1a). Recently, effects of cyclic mechanical stimulation on osteogenic differentiation of human intraoral MSCs were analyzed [18]. 10% cyclic tensile strain (0.5 Hz) enhanced the activity of alkaline phosphatase (ALP) and calcium deposition. Similar to tensile strain, fluid shear stress (FSS) has also been found to regulate osteogenic differentiation of MSCs [19]. With FSS, MSCs showed enhanced expression of osteopontin, bone sialoprotein, osteocalcin, collagen 1A1, transforming growth factor-β1 (TGF-β1), bone morphogenetic proteins (BMP-2, BMP-4, BMP-7), and vascular endothelial growth factor A (VEGFA) [20]. In addition, MSCs exposed to oscillatory fluid flow for 3 h at 1 Hz, with a peak shear stress of 0.1 Pa, have shown increased expression of Sox9, Runx2, and peroxisome proliferator-activated receptor-γ (PPAR-γ) [21], demonstrating their ability to regulate lineage-specific transcription factors in MSCs.

Besides differentiation, mechanical forces are capable of regulating other biological processes in MSCs. Oscillatory fluid flow, with a fluid volume of $38 \times 10 \times 0.28$ mm (1 Hz), leads to increased proliferation, and intracellular calcium mobilization of MSCs through MAPK signaling, and changes in flow rate at a constant peak shear stress are associated with decreases in MSC proliferation, while variations in peak fluid flow had no significant effect [22]. Continuous uniaxial cyclic strain (0.17 Hz) results in rat BMSC apoptosis through activation of L-type voltage-activated calcium channels and c-Jun N-terminal kinase (JNKs) signaling [23]. Furthermore, a study has found that strain can induce myogenic differentiation instead of osteogenic differentiation of BMSCs [24], suggesting that tensile stress can drive MSCs down one or more lineages.

2.2. Molecules linking applied forces with mesenchymal stem cell functions

As described previously, applied forces serve as critical regulators of MSC functions. Understanding how MSCs sense and respond to applied forces is an area of intense research.

MSCs are capable of taking those 'outside-in' signals and transduce into the nucleus, and then affect protein activity and gene expression. Such response may change the surrounding environment of cells, thus causing 'inside-out' signals. Numerous cell membrane proteins have been identified in such mechanosensing mechanisms. Ion channels, for example, have been identified to

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