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The Rate of Fluid Shear Stress is a Potent Regulator for Lineage Commitment of Mesenchymal Stem Cells Through Modulating $[Ca^{2+}]_i$, F-actin and Lamin A

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Abstract: Mesenchymal Stem Cells (MSCs) are recruited to the musculoskeletal system following trauma [1] or chemicals stimulation [2]. The regulation of their differentiation into either bone or cartilage cells is a key question. The fluid shear stress (FSS) is of pivotal importance to the development, function and even the repair of all tissues in the musculoskeletal system [3]. We previously found that MSCs are sensitive enough to distinguish a slight change of FSS stimulation during their differentiation commitment to bone or cartilage cells, and the internal mechanisms. In detail, MSCs were exposed to laminar FSS linearly increased from 0 to 10 dyn/cm^2 in 0, 2, or 20 min and maintained at 10 dyn/cm^2 for a total of 20 min (termed as ΔSS of 0-0', 0-2', and 0-20', respectively, representing more physiological (0-0') and non-physiological (0-2' and 0-20') ΔSS treatments). 0-0' facilitated MSC differentiation towards chondrogenic but not osteogenic phenotype. In contrast, 0-2' promoted MSCs towards osteogenic but not chondrogenic phenotype. 0-20' elicited the modest osteogenic and chondrogenic phenotypes [4]. In addition, we disclosed that 20 min of ΔSS could compete with 5 days' chemical and 2 days' substrate stiffness inductions, demonstrating ΔSS is potent regulator for MSC differentiation control [5]. We found that the ΔSS induced MSC differentiation into osteogenic or chondrogenic cells is directed through the modulation of cation-selective channels (MSCCs), intracellular calcium levels and F-actin. Here we demonstrate that the 0-2' induced significant lamin A; the 0-0' induced similar lamin A to 0-2' and 0-20' elicited less lamin A. A special ΔSS of 0-1' is found to induce osteogenic differentiation comparable to 0-2' and chondrogenic differentiation comparable to 0-0' as well as the most lamin A. Lamin A has no influence on the expression of runx2, a key transcription factor in osteogenic differentiation, but has affected the expression of sox9, a key transcription factor in chondrogenic differentiation. Our study presents evidences that the MSCs are highly sensitive to discriminate different ΔSS loads and differentiate towards the osteogenic or chondrogenic phenotype by regulating MSCCs and the subsequent $[Ca^{2+}]_i$ increase, F-actin assembly and Lamin A expression, which provides guidance for training osteoporosis and osteoarthritis patients and stresses the possible application in MSCs linage specification.

Keywords: Mechanical stimulation; osteogenic differentiation; chondrogenic differentiation

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References

1. Chen H, Chevrier A, Hoemann CD, Sun J, Lascau-Coman V et al. Bone marrow stimulation induces greater chondrogenesis in trochlear vs condylar cartilage defects in skeletally mature rabbits. *Osteoarthritis and cartilage* **2013**, 21(7): 999-1007.
2. Yueyi C, Xiaoguang H, Jingying W, Quansheng S, Jie T et al. Calvarial defect healing by recruitment of autogenous osteogenic stem cells using locally applied simvastatin. *Biomaterials* **2013**, 34(37): 9373-9380.
3. Schätti O, Grad S, Goldhahn J, Salzmann G, Li Z et al. A combination of shear and dynamic compression leads to mechanically induced chondrogenesis of human mesenchymal stem cells. *European Cells and Materials* **2011**, 22: 214-225.
4. Lu J, Fan Y, Gong X, Zhou X, Yi C et al. The Lineage Specification of Mesenchymal Stem Cells Is Directed by the Rate of Fluid Shear Stress. *Journal of cellular physiology* **2016**, 231(8): 1752-1760.
5. Yue D, Zhang M, Lu J, Zhou J, Bai Y et al. The rate of fluid shear stress is a potent regulator for the differentiation of mesenchymal stem cells. *Journal of cellular physiology* **2019**. doi: 10.1002/jcp.28296. [Epub ahead of print].