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RNA-seq reveals diverse effects of substrate stiffness on mesenchymal stem cells

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RNA-seq reveals diverse effects of substrate stiffness on mesenchymal 1 2 stem cells 3 Max Darnell^{1,2}, Luo Gu^{1,2,3}, David Mooney^{1,2,*} 4 5 1. Harvard John A. Paulson School of Engineering and Applied Sciences, Cambridge, MA 02138 6 2. Wyss Institute for Biologically Inspired Engineering, Cambridge, MA 02138 7 3. Department of Materials Science and Engineering, Institute for Nanobiotechnology, Johns 8 Hopkins University, Baltimore, MD 21218 9 10 * Corresponding Author **Keywords:** mesenchymal stem cells; RNA-seq; systems biology; alginate; 11 12 transcriptome; immune response 13 14 Abstract 15 Substrate stiffness has been recognized as an important regulator of cell fate and 16 function, but an understanding of the full extent of processes affected by stiffness is 17 lacking as its transcriptome-wide effects have not been mapped. This limited 18 understanding has restricted the contexts in which engineers can employ stiffness as 19 an engineering design parameter. To address these limitations, we performed RNA-20 seq on mesenchymal stem cells (MSCs) cultured in alginate hydrogels over a range 21 of moduli to broadly map the transcriptome-wide changes associated with stiffness 22 sensing. We found a large number of stiffness-sensitive genes, and that many genes 23 respond to stiffness in nonlinear ways. Informed by these differential expression 24 results, we explored a hypothesis related to current MSC clinical activity, and found 25 that stiffness can regulate the expression of MSC immunomodulatory markers in 26 response to cytokine stimulation. Overall, these results reveal previously unknown 27 features of MSC stiffness response and demonstrate the value of coupling -omics 28 approaches with biophysical experiments. 29 30 31 For almost two decades, engineers and biologists have studied the effects of adhesion substrate properties on cell phenotype $^{[1,2]}$. Over that time, approaches to control and 32 33 study these features have evolved, revealing myriad ways in which cells sense and respond to their culture substrates^[3]. For instance, Tekin et al found significant 34 transcriptome-wide changes associated with 2D versus 3D tissue culture^[4]. Within 3D 35 36 cell culture, material characteristics such as adhesion ligand composition and density^[5-7], time-dependent material properties^[5, 8], nanoscale topography^[9], and degradability^[10], 37

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