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HIGHLIGHTS

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Biotechnology smart control over stem cell fate commitment at nanoscale

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In the landscape of desirable stem-cell-based regeneration, the fate of cell is directed by orchestrated dialog between nanoscale subcellular receptors and biointerfacial niches [1]. This bottom-up development manner has inspired a great many nanogeometric [2] and nanotopographic [3] material-based biointerfaces promising for regenerative medicine. These previous studies shed light on the critical role of nanoscale cell-surfaces interactions in guiding cell fate, but those biointerfaces with properties static in time often inadequately mimic the active control manner of nature life. Although several elaborated dynamic interfaces have enabled successfully influence of cell behavior with adjusting surface chemistry [4] or stiffness [5]. The performance and design of those artificial biointerfaces lagged behind natural niches that can provide reversibly physical and chemical stimuli. It is still a great challenge to establish a nich-like nano-biointerface to scale down the regulation for trigging cell function.

In a recent publication of *ACS Nano*, Professors Xuliang Deng, Shutao Wang and Yan Wei have developed a smart polypyrrole (Ppy) nano-biointerface, which is promising to provide dynamic nanoscale stimuli to precisely target cell osteogenic lineage for bone regeneration [6]. The key design of this interface is the reversible nanotubes/nanotips transition in response to electrochemical redox switching. Upon exposure to a reducing potential, anions in the surrounding electrolytes enter the Ppy and cause it to expand [7] to occupy the spaces within the nanotubes, resulting in nanotips. Upon exposure to an oxidising potential, ions exit Ppy which contracts [8] to unoccupy the inner space of nanotips, yielding nanotubes. Accompanied with this morphology variation, significant surface water contact angle and surface adhesive forces changed. This transition between highly adhesive hydrophobic nanotubes and poorly adhesive hydrophilic nanotips could act as dynamic attachment/detachment stimulus. In this way, they have achieved a smart surface that can provide reversible nanoscale stimuli *via* electrochemical redox switching between nanotubes and nanotips.

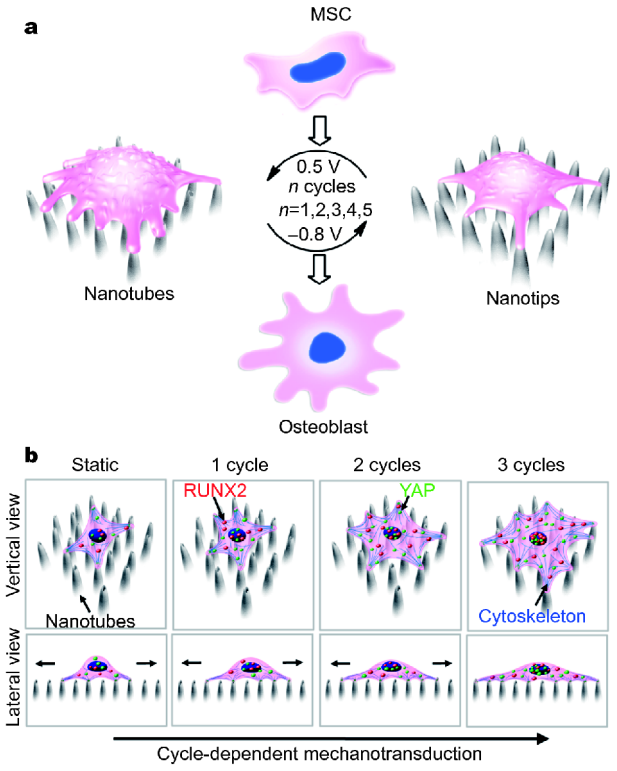

Figure 1 Schematic illustration of electrochemical switchable nanotubes/nanotips transition of Ppy arrays guiding stem cell fate commitment. (a) The nanotubes/nanotips transition can guide MSCs cell adhesion at nanoscale and direct osteogenic differentiation in response to multiple cycles of electrochemical redox switching. (b) The nanotubes/nanotips transition activates both structural and molecular signaling underlying MSCs mechanotransduction. Reprinted with permission from [6]. Copyright 2017, American Chemical Society

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On this smart nano-biointerface, outstanding biological outcomes were achieved. One key finding is the cause-effect relationship between the cycles of dynamic nanoscale stimuli and the extent of stem cell osteogenic differentiation. From one to three cycles, the continuously increased fluorescence intensities of osteogenic proteins bone morphogenetic protein 2 (BMP2) and bone sialoprotein (BSP) indicated that mesenchymal stem cells (MSCs) differentiation was gradually biased towards osteogenesis. Then, the significantly upregulated osteogenic gene expression and the obvious osteoid formation further demonstrated that three cycles of dynamic nanotubes/nanotips transition obviously promoted osteogenic differentiation with effectiveness comparable to that of chemical agents. The other key finding is that the authors clearly pointed out the mechanism of the dynamic nanoscale stimuli inducing MSCs osteogenesis relay on intracellular mechanotransduction initiated by dynamic MSCs adhesion. The morphology observation, fluorescence profiles and statistical analysis demonstrated that the nanotubes/nanotips transition can favor and disrupt MSCs' adhesion at nanoscale. To explore how the cell-surface interaction was further transduced by MSCs, they directly observed downstream intracellular signaling transduction. With increasing cycles of nanotubes/nanotips transition, actin filaments organization and cell spreading areas gradually increased to facilitate the conversion of external stimuli into nuclear signals. Besides structures, they also found the dynamic nanoscale stimuli could activate the nuclear-translocation of mechanotransducer YAP to promote intra-nuclear RUNX2 transcription. Taking together, they demonstrate that the electrochemically switching of Ppy array between nanotubes and nanotips can result in alternating surface adhesion, which can strongly initiate intracellular mechanotransduction, mediated by YAP/RUNX2, cytoskeleton-organization, and MSCs osteogenesis independent of surface stiffness and additional chemical inducers.

This is the first such design with dynamic nanoscale contact guidance cues that can activate central cellular response in a pointwise way to significantly enhance the extent of osteogenic differentiation. This study, permitting dynamic transduction of nanoscaled physical inputs into biological outputs, provides an alternative way to classical cell culture substrates and chemical inducing agents for stem cell differentiation. This concept of designing smart nano-biointerfaces can be extended to other stimuli-responsive nanomaterials friendly to stem cell for further tissue regeneration.

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1 Dalby MJ, Gadegaard N, Oreffo ROC. Harnessing nanotopography and integrin–matrix interactions to influence stem cell fate. Nat Mater, 2014, 13: 558–569
2 Chen CS. Geometric control of cell life and death. Science, 1997, 276: 1425–1428
3 McMurray RJ, Gadegaard N, Tsimbouri PM, *et al.* Nanoscale surfaces for the long-term maintenance of mesenchymal stem cell phenotype and multipotency. Nat Mater, 2011, 10: 637–644
4 Das RK, Gocheva V, Hammink R, *et al.* Stress-stiffening-mediated stem-cell commitment switch in soft responsive hydrogels. Nat Mater, 2016, 15: 318–325
5 Chaudhuri O, Gu L, Klumpers D, *et al.* Hydrogels with tunable stress relaxation regulate stem cell fate and activity. Nat Mater, 2016, 15: 326–334
6 Wei Y, Mo X, Zhang P, *et al.* Directing stem cell differentiation *via* electrochemical reversible switching between nanotubes and nanotips of polypyrrole array. ACS Nano, 2017, 11: 5915–5924
7 Gandhi MR, Murray P, Spinks GM, *et al.* Mechanism of electromechanical actuation in polypyrrole. Synth Met, 1995, 73: 247–256
8 Smela E. Conjugated polymer actuators for biomedical applications. Adv Mater, 2003, 15: 481–494

