Surface Curvature Differentially Regulates Stem Cell Migration and Differentiation via Altered Attachment Morphology and Nuclear Deformation

Abstract

Signals from the microenvironment around a cell are known to influence cell behavior. Material properties, such as biochemical composition and substrate stiffness, are today accepted as significant regulators of stem cell fate. The knowledge of how cell behavior is influenced by 3D geometric cues is, however, strongly limited despite its potential relevance for the understanding of tissue regenerative processes and the design of biomaterials. Here, the role of surface curvature on the migratory and differentiation behavior of human mesenchymal stem cells (hMSCs) has been investigated on 3D surfaces with well-defined geometric features produced by stereolithography. Time lapse microscopy reveals a significant increase of cell migration speed on concave spherical compared to convex spherical structures and flat surfaces resulting from an upward-lift of the cell body due to cytoskeletal forces. On convex surfaces, cytoskeletal forces lead to substantial nuclear deformation, increase lamin-A levels and promote osteogenic differentiation. The findings of this study demonstrate a so far missing link between 3D surface curvature and hMSC behavior. This will not only help to better understand the role of extracellular matrix architecture in health and disease but also give new insights in how 3D geometries can be used as a cell-instructive material parameter in the field of biomaterial-guided tissue regeneration.

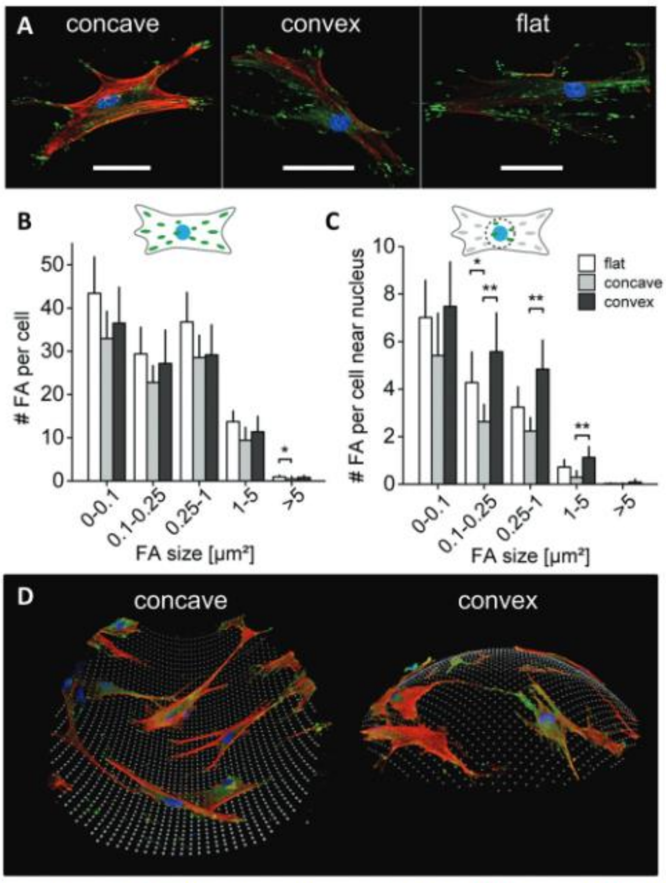

Figure 3. Curvature driven alterations in cell attachment. A) Representative immunohistochemical images of vinculin (green) identifying focal adhesions, F-actin (red) and nuclei (blue) for hMSCs on concave and convex spherical surfaces ($\kappa = 1/175\ \mu m^{-1}$), and a flat surface after 2 d in expansion medium. Scale bar 50 µm. B) Number of total amount of focal adhesions (FAs) per cell, divided into different focal adhesion size classes. C) Number of focal adhesions per cell near the nucleus for the same focal adhesion size classes as in (B). No significant differences were found in the total amount and size of focal adhesions per cell on the different structures. However, near the nucleus a significant lower number of focal adhesions (size $> 0.1\ \mu m^2$) was found in cells in concave surfaces. Mean ± 95% confidence interval. $^*P < 0.05$, $^{**}P < 0.01$. D) 3D reconstruction of immunohistological stained cells (F-actin in red, FAs in green, and nuclei in blue) on a concave and convex surface. Cells on concave surfaces showed an upward stretched cell morphology where a substantial part of the cell body is not attached to the surface. Cells on convex surfaces were fully attached to the surface.