Entropic origins of substrate-guided cell morphology and alignment

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The organization of cells in tissues is critical for all physiological functions of tissues and organs. It is widely known that cellular organization—such as spreading, elongation, and alignment—can be sensitively influenced by the physical features of the microenvironment. The underlying mechanisms behind this response is still debated, especially as the length scale of the cues becomes comparable to cell sizes. To explore cellular response to this range of cues, we systematically monitored and quantified cell adhesion and morphology on micropatterned substrates over a large range of feature sizes, from µm to mm. Together with a new statistical thermodynamics model of living cells, the experimental results reveal that alignment of cells to large features (hundreds of µm scale) is associated with the cells' tendency to maximize morphological entropy through shape fluctuations [1]. Looking further at the µm scales, alignment of focal adhesions and actin fibers were surprisingly found to be dispensable for whole-cell orientation, contrary to proposed theories. Comparison with the model reveals that cell alignment emerges as an energetic consequence of cell elasticity and adhesion on the non-adhesive gaps. Our finding therefore offers a scale-free, physical mechanism for cell morphology and alignment that does not necessitate specific molecular pathway or biochemical regulation.

[1] A.B.C. Buskermolen et al., Biophys. J. 116, 1994 (2019).