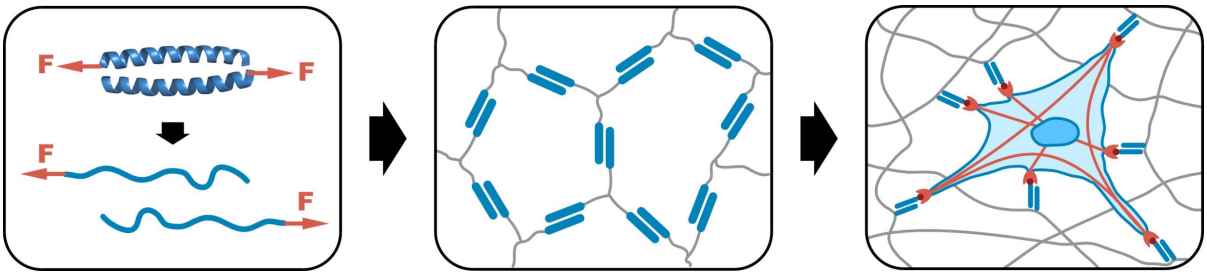
Coiled Coils as Molecular Force Sensors
from molecular mechanisms towards applications in biology and materials science

Laura M. Wolfthaler[1], Melis Goktas[2], Patricia Lopez Garcia[2], Zeynep Atris[2], Angelo Valleriani[3], Russell J. Wilson[1,2], Kerstin G. Blank[1,2]

[1]Johannes Kepler University, Biomolecular and Selforganizing Matter, Linz, Austria
[2]Max Planck Institute of Colloids and Interfaces, Mechano(bio)chemistry, Potsdam, Germany
[3]Max Planck Institute of Colloids and Interfaces, Biomaterials, Potsdam, Germany

laura.wolfthaler@jku.at

Cells sense the mechanical properties of the extracellular matrix (ECM) and use this information to regulate a wide range of functions. It is widely acknowledged that mechanical signals play a crucial role in directing cell fate; however, measuring cell-generated forces at the cell-ECM interface with high spatiotemporal resolution remains a major challenge. To determine the single-molecular forces acting at the cell-ECM interface and within engineered ECM mimicking materials, we developed a library of coiled coil (CC)-based molecular force sensors (MFSs). CCs are abundant folding motifs in many cytoskeletal and ECM proteins where they possess crucial mechanical function. CCs are therefore primed to act as mechanical building blocks in 2D and 3D cell biology applications.



Using atomic force microscope-based single-molecule force spectroscopy, we show that the CC response to shear forces depends on helix length and stability, hydrophobic core packing and force loading geometry [1-5]. Building on this knowledge about CC sequence-structure-MECHANICS relationships [5-7], we have established a library of CCs with tunable mechanical properties. For 2D cell culture systems, CC-MFSs were equipped with the cell-adhesive ligand RGDS. While fibroblasts initially adhered on RGDS-MFS-containing and RGDS control surfaces, their spreading behavior diverged after 60 to 120 min, with observable differences in cell shape, spreading area and cytoskeleton organization. Towards developing 3D cell culture systems, CC-MFSs are utilized as physical crosslinks within hydrogels. Varying molecular CC characteristics, we show that CC thermodynamics and kinetics determine hydrogel properties in the linear viscoelastic range, while bond rupture forces define the yield stress and strain. With the goal of visualizing mechanical cell-material interactions in real-time, our key next step is the integration of a fluorescence readout that reports on the molecular state of CC-MFSs. Our CC-MFS library contributes to the growing toolkit of MFSs, paving the way for innovative 2D and 3D biomaterials that visualize, probe and modulate cell-matrix interactions.

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