Group 1.1

# Spatio-Temporal Integration of Cell Signaling

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## Stretch induced shape remodeling in endothelial cells: how the cell can detect amplitude and direction of forces and covert these signals to shape formation

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Regulation of directed shape formation is essential in synapse and spine formation in neurons. However, its molecular mechanism, which requires spatiotemporal integration of cell signaling, is completely unknown. We employed stretch induced shape remodering in endothelial cells as a model system toward building up a mathematical model for the spatiotemporal integration in directed shape formation in cells.

**RESULTS**

Endothelial cells *in situ* exhibit a spindle like shape aligning their long axis along the vessel running, but they will lose this characteristic shape when cultured in dish. However, they recover their original shape when subjected to uniaxial cyclic stretch that mimics circumferential cyclic stretch in the vessel **(Fig.1)**. For understanding of this intriguing phenomenon, we first have to know the signal flow from the mehcanosensor (*e.g.* SA channel) to shape determinant components (cytoskeletons and focal contact including integrins) **(Fig.2)**.

We have approached this problem by investigating how the cells can detect amplitude and direction of applied forces and link these information to their shape change. We found that the shape change requires increases in the intracellular $Ca^{2+}$ concentration mediated by SA channels and following tyrosine phosphorylation of focal proteins, including FAK, Cas, and paxillin **(Fig.3)**. However, as the distribution of the increased $Ca^{2+}$ was spatially uniform, this signal cannot tell the direction of forces to the cell. As the stress fibers (bundle of actin filaments) align their orientation depending on the direction of applied forces **(Fig.4)**, we suspected that stress fibers and associated integrins may be a force direction sensor of the cell **(Fig. 5)**. To test this hypothesis, we visualized dynamics of integrins in living cells, and found that integrin dynamics (endocytosis and exocytosis) was strongly modulated by the stress conveyed along the stress fibers **(Fig.6)**. It is suggested that cytskeleton/integrin complex works as a direction-sensor for applied forces as well as an actuator in the shape remodeling **(Fig.7).**

**CONCLUSION**

Thus cells are equipped with two different mechanosensors, one is for the amplitude and the other the direction of forces, which signals are integrated at focal adhesions at particular positions inducing a directed cell shape changes. Based on above results, we are currently collecting more quantitative data and constructing a mathematical model that can simulate directed shape formation.

**Fig.1**

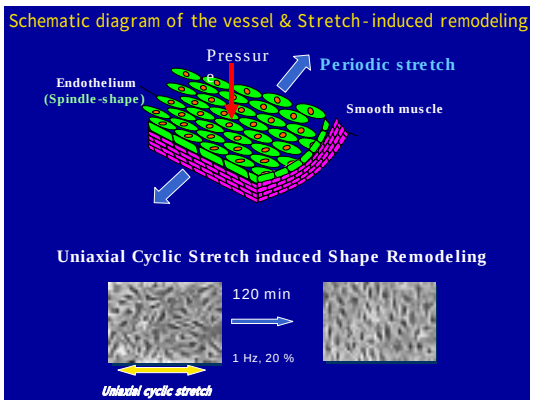


**Fig.2**

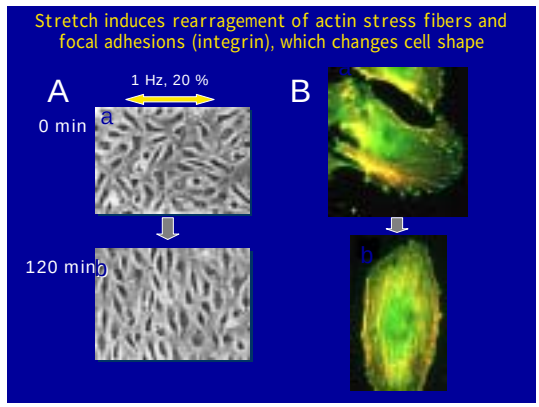


**Fig.3**

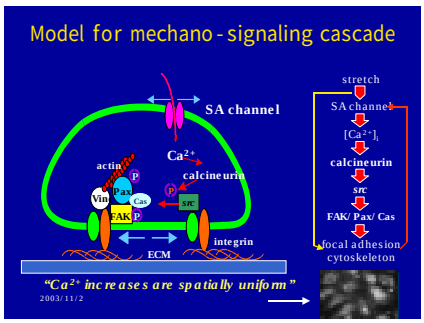


**Fig.4**

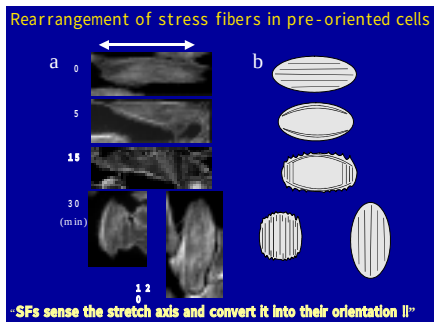


**Fig.5**

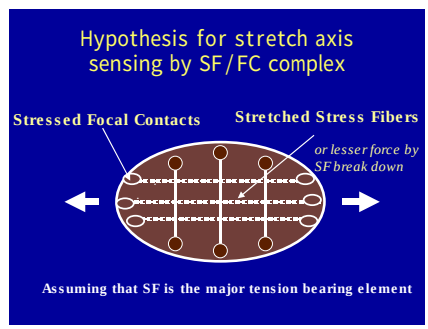


**Fig.6**

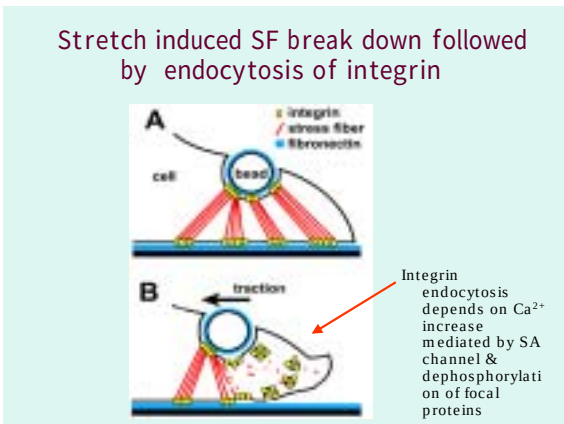


**Fig.7**