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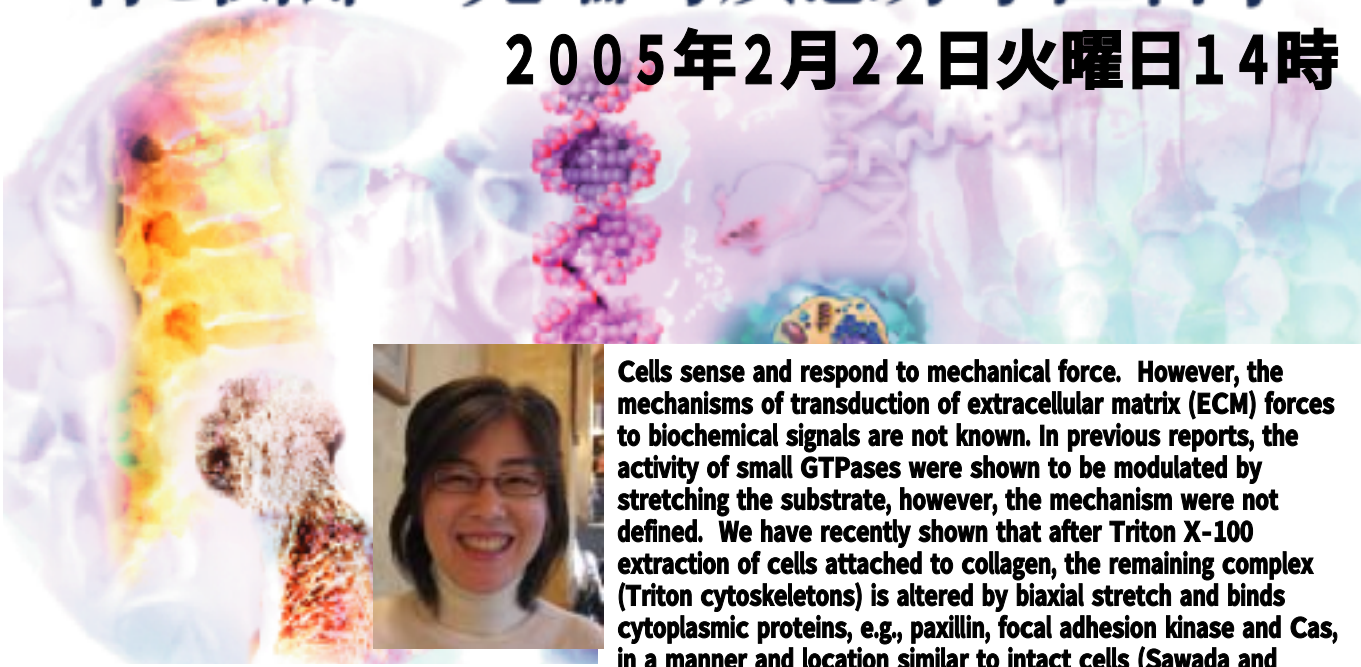
独立行政法人日本学術振興会　先端研究拠点事業　ABJS

ABJS国際セミナー（第3回）・COE共催

骨と関節の先端的疾患分子医科学

2005年2月22日火曜日14時



Activation of a signaling cascade by cytoskeleton stretch

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Cells sense and respond to mechanical force. However, the mechanisms of transduction of extracellular matrix (ECM) forces to biochemical signals are not known. In previous reports, the activity of small GTPases were shown to be modulated by stretching the substrate, however, the mechanism were not defined. We have recently shown that after Triton X-100 extraction of cells attached to collagen, the remaining complex (Triton cytoskeletons) is altered by biaxial stretch and binds cytoplasmic proteins, e.g., paxillin, focal adhesion kinase and Cas, in a manner and location similar to intact cells (Sawada and Sheetz, 2002). These findings indicate that the direct alteration rather than changes in the ionic environment can mediate force-induced binding of cytoplasmic proteins. Here we found that Triton cytoskeletons activated Rap1 upon stretch. Rap1 guanine nucleotide exchange factor, C3G was required for this activation; and C3G as well as the adapter protein, CrkII, in cell extract bound to Triton cytoskeletons in a stretch-dependent manner. CrkII binding, which was Cas-dependent, correlated with stretch-dependent tyrosine phosphorylation of proteins in Triton cytoskeletons including Cas at the contacts with ECM. These *in vitro* findings were compatible with *in vivo* observations of stretch-enhanced phosphotyrosine signals, accumulation of CrkII at cell-ECM contacts, and CrkII-Cas colocalization. We suggest that mechanical force on Triton cytoskeletons activates local tyrosine phosphorylation, which provides docking sites for cytosolic proteins, and initiates signaling to activate Rap1, i.e. force-dependent conformational changes provide a simple mechanism to transform physical force into biochemical signals.

第11回　COE海外研究者招聘セミナー

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骨・軟骨疾患の先端的分子病態生理学研究の国際的拠点形成

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