論文の内容の要旨

論文題目　細胞形態と RhoGTPase

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RhoA plays a pivotal role in regulating cell shape and movement. It has been shown that protein kinase A (PKA) inhibits RhoA signaling and thereby induces characteristic morphological change, cell rounding. This has been considered to result from cAMP-induced phosphorylation of RhoA at S188, which increases the affinity of RhoA to RhoGDIα, induces stable RhoA-RhoGDIα complex, and sequesters RhoA to cytosol. Although nearly stoichiometrical phosphorylation of RhoA has been demonstrated biochemically, only few reports have detected phosphorylation of endogenous RhoA in intact cells. In cardiac fibroblast, we have observed that even cells transfected with constitutively active and phosphoresistant RhoA (RhoA-G14V/S188A) shows cAMP-induced cell rounding when RhoGDIα is coexpressed. Knockdown of RhoGDIα by siRNA cancels cAMP-induced cell rounding. Although cell rounding recovers when RhoGDIα-WT are expressed in these cells, it does not recover when RhoGDIα-S174A are expressed. We further found that PKA phosphorylates RhoGDIα at S174 and phosphorylation of RhoGDIα (but not that of RhoA) is likely to induce the formation of active RhoA-RhoGDIα complex. These data suggest that phosphorylation of RhoGDIα at S174 plays an essential role in PKA-induced inhibition of RhoA signaling and morphological change in cardiac fibroblasts. Our results thus reveal a principal molecular mechanism underlying Gs/cAMP-induced crosstalk to Gq/G13/RhoA signaling