Spontaneous symmetry breaking in spreading fibroblasts requires RACK1 that integrates FAK, p190A-RhoGAP and ERK2 signaling

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Abstract

The spreading of adhering cells is a morphogenetic process during which cells break the radial symmetry and adopt migratory polarity with spatially segregated protruding cell front and non-protruding cell rear. The asymmetrical shape and migratory polarity develop spontaneously; however, it is unclear how these events, which are both complex and stochastic, are organized and regulated. We found that in radially spreading cells symmetry breaking commences with the development of discrete non-protruding regions characterized by large but sparse focal adhesions and long peripheral actin bundles. The establishment of the non-protruding static region specifies the distally oriented protruding cell front and thus determines the polarity axis and the direction of cell migration. The central role in controlling and organizing spontaneous symmetry breaking plays scaffold protein RACK1 that enables cells to form non-protruding cell rear. Mechanistically, RACK1 promotes adhesion-mediated activation of ERK that in turn suppress p190RhoGAP signaling by reducing p190RhoGAP membrane localization. The depletion of p190RhoGAP is restricted to prospective cell rear where it spatially correlates with the establishment of large focal adhesions and formation of non-protruding cell region. Since integrin-mediated cell adhesion activates both ERK and p190RhoGAP signaling we propose that adhesion induces antagonistic signaling circuit. In this system, sustained and localized ERK signaling is required for the spatially restricted depletion of membrane-associated p190RhoGAP resulting in reduced actin polymerization, actomyosin bundles formation and cell rear formation.