Cyclooxygenase and cyclic AMP -dependent protein kinase regulate actin organization and cell motility

Honor L Glenn, *University of Massachusetts Amherst*

Abstract

Cell adhesion to an extracellular matrix plays a critical role in many aspects of normal cell function. Cells display various modes of interaction with the extracellular matrix; they may attach and spread, become immobilized, or become motile. These cellular responses are regulated by intracellular signals, which modify the organization of the cytoskeleton. One common characteristic of malignantly transformed cells is alteration in one or more aspects of adhesion. Most notably, cancer cells often display enhanced motility and there is a positive correlation between cell mobility and metastatic potential in situ. HeLa cells, a cell line derived from a cervical carcinoma, were used as a model system for this investigation. It has been shown, in HeLa cells, that cell attachment to a gelatin-coated substrate results in the release of arachidonic acid, which is metabolized by lipoxygenase. A subsequent cascade of lipid second messengers activates protein kinase C, which triggers actin polymerization leading to cell spreading. This work employed inhibitor studies, and biochemical analysis to elucidate a parallel branch of arachidonic acid signaling that reorganizes the actin cytoskeleton into small bundles. This branch of the pathway is initiated by cyclooxygenase, which generates prostaglandins and causes the downstream activation of cyclic AMP-dependent protein kinase. The results suggest that arachidonic acid functions at a branch point in signaling to the cytoskeleton. The lipoxygenase branch provides polymerized actin; the actin filaments then act as a substrate for the cylooxygenase branch to generate actin bundles. These actin bundles were shown to associate with myosin and small adhesion complexes. Activation of cyclooxygenase signaling and the subsequent cytoskeletal organization were found to increase cell motility. Overexpression of the small GTPases rho and cdc42, also induces cell crawling, and these signaling molecules seem to interact with cyclooxygenase in directing organization of the cytoskeleton. In sum these results suggest that faulty regulation of arachidonic acid signaling can result in the pathological cell motility that characterizes the most aggressive cancers. ^

Subject Area

Cellular biology

Recommended Citation