Review

Rho GTPase regulation by miRNAs and covalent modifications

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To date, most studies of Rho GTPase regulation have focused on the classic GTPase cycle – GTP binding and hydrolysis – controlled by guanine nucleotide exchange factors (GEFs), GTPase-activating proteins (GAPs) and GDP-dissociation inhibitors (GDIs). Recent investigations have unveiled important additional regulatory mechanisms: microRNA (miRNA) regulating post-transcriptional processing of Rho GTPase-encoding mRNAs; palmitoylation and nuclear targeting affecting intracellular distribution; post-translational phosphorylation, transglutamination and AMPylation impacting Rho GTPase signaling; and ubiquitination controlling Rho GTPase protein stability and turnover. These modes of regulation add to the complexity of the Rho GTPase signaling network and allow precise spatiotemporal control of individual Rho GTPases. This review discusses these 'unconventional' modes of regulation and their contribution to cellular function, focusing on post-transcriptional and post-translational events beyond the classic GTPase cycle regulatory model.

An overview of the Rho GTPase regulatory cycle

The Rho GTPases, which belong to the Ras superfamily of 20–30 kDa GTP-binding proteins, include at least 20 members in higher eukaryotes that can be subdivided into six groups: the Rho subfamily (RhoA, RhoB, RhoC); the Rac subfamily (Rac1, Rac2, Rac3, RhoG); the CDC42 subfamily (CDC42, Wrch1, TC10, Chp, TCL); the Rnd subfamily (Rnd1, Rnd2, Rnd3); the Rho BTB subfamily (RhoBTB1, RhoBTB2, RhoBTB3); and the Miro subfamily (Miro1, Miro2) [1,2]. These proteins function in multiple cell processes including gene expression, cytoskeletal dynamics, survival, cell division, cell adhesion, polarity, and vesicle trafficking [1–4]. Dysfunctional Rho GTPase-regulated signaling underlies multiple forms of cancer, neurological abnormalities, immunological disorders and several other diseases [5–10]. Although a subset of Rho GTPases is constitutively active, most act as molecular switches, cycling between the active, GTP-bound form and the inactive, GDP-bound form. Their activities can be influenced by multiple types and levels of spatiotemporal regulation that places them in the context of a vast intracellular signaling network [11–17]. On activation, each Rho GTPase may interact with several effector targets leading to physiologic responses.

Rho GTPases can be activated by intrinsic or extrinsic cues, setting off a signaling cascade [1,3,15]. In response to stimulatory signals, individual Rho GTPase activities are controlled by the GTP/GDP ratio and subcellular distribution in the cell through the joint action of multiple regulatory molecules: GEFs, which activate Rho GTPases by promoting GDP-to-GTP exchange; GAPs, which inactivate the GTPases by enhancing intrinsic GTP hydrolysis activity; and GDIs, which bind prenylated GDP-bound Rho proteins, allowing translocation of Rho GTPases between membranes and cytosol [11–14,17] and protecting Rho GTPases from degradation [18]. This molecular switch regulatory mechanism forms the classic 'GTPase cycle' model (GTP binding/GTP hydrolysis), which has been the subject of extensive reviews [15–17].

Adding to the complexity of the GTPase cycle, recent studies have revealed 'unconventional' mechanisms for the regulation of Rho GTPase signaling activities. These include post-transcriptional regulation by microRNAs (miRNAs), intracellular distribution by lipid and nuclear translocation signals, post-translational modifications via phosphorylation, transglutamination and AMPylation, and protein stability controlled by ubiquitination (Figure 1). In this review, we discuss these additional modes of Rho GTPase regulation, focusing on post-transcriptional regulation and post-translational covalent modifications. We present evidence that these mechanisms, combined with the GTPase cycle, are important for maintaining physiological levels of Rho GTPase activity in cells.

miRNA regulation of Rho GTPase expression

To date, more than 1500 miRNAs have been identified in human cells [19]. These short, non-coding RNA molecules play crucial roles in diverse physiological, developmental and pathological processes by controlling gene expression post-transcriptionally. In conjunction with Argonaute protein, miRNAs can silence target genes by either suppressing translation or degrading mRNA – in the former case, by partially complementing the 3′ untranslated region (UTR) of cognate mRNAs to suppress protein synthesis [20–22]. By regulating one or more mRNA targets, individual miRNAs can direct a developmental switch or tissue-specific gene expression [20–22]. Through targeting

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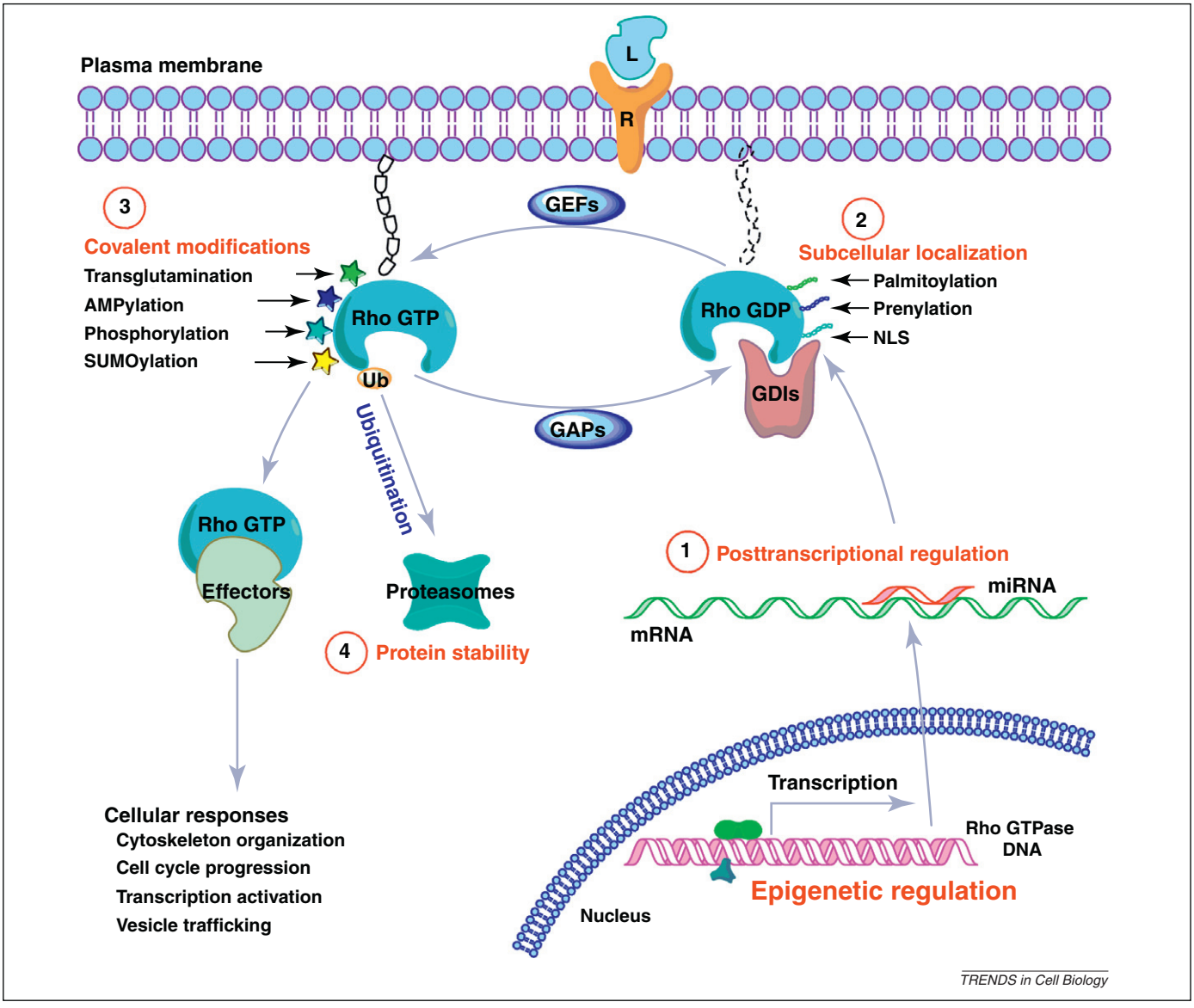

Figure 1. Overview of Rho GTPase regulatory mechanisms. GEFs, GAPs, and GDIs are the classic regulatory components controlling the GTP binding/GTP hydrolysis GTPase cycle and signaling activities of Rho GTPases. GEFs activate Rho GTPases by catalyzing the exchange of bound GDP for GTP, whereas GAPs stimulate the hydrolysis of GTP by active Rho-GTP species thereby inactivating Rho GTPases. RhoGDIs can bind to prenylated GDP-bound Rho proteins and allow translocation of Rho-GDP between membranes and the cytosol. 'Unconventional' regulatory modes are also involved in controlling Rho GTPase activities and cellular functions. First, epigenetic modifications of chromosomal DNAs and miRNAs of Rho GTPases can regulate the expression of Rho GTPases, at pre- and post-transcriptional levels. Second, palmitylation, prenylation, and nuclear localization signals (NLSs) of a subset of Rho GTPases can target them to their proper intracellular compartments to execute cell functions. Third, post-translational covalent modifications, including phosphorylation, transglutamination, AMPylation, and SUMOylation, can induce constitutive activation or inactivation of Rho GTPases or change their activities. Fourth, Rho GTPase activation could be counterbalanced by loss of active Rho GTPases at the protein level through the ubiquitin–proteasome system (UPS). Combined, these regulatory mechanisms contribute to the spatiotemporal modulation of the signaling strength of Rho GTPases in diverse cellular processes, with an impact on actin and microtubule dynamics, cell adhesion, cell cycle progression, cell survival, gene expression, polarity establishment and membrane transport.

and regulating Rho GTPase-encoding mRNAs, numerous miRNAs have been implicated in the regulation of gene expression of Rho GTPases (Table 1), thereby influencing pathophysiologic functions such as cardiac function, neuronal differentiation, and tumorigenesis.

Rho GTPases, RhoA, and Cdc42 in particular, figure prominently in cardiac development and hypertrophy, and recent studies suggest that miRNAs contribute to their regulation. For example, miR-133 is downregulated in mouse models and human patients with cardiac hypertrophy, and inhibits cardiac hypertrophy by targeting RhoA and Cdc42, which control cytoskeletal and myofibrillar rearrangements during hypertrophy, suggesting its potential therapeutic application in heart disease [23]. Similarly, miR-1, which targets Cdc42, is negatively regulated by the homeobox transcription factor Tinman in the fly and its mammalian homolog Nkx2-5 in the mouse, both of which are involved in heart development and function [24]. miRNA targeting of Rho GTPases also regulates neuronal differentiation. miR-124, which is expressed in developing and adult neurons, regulates axon growth by suppressing Cdc42 and Rac1 expression [25].

Alterations in Rho GTPase gene expression levels, rather than constitutive mutations, often are associated with tumorigenesis and cancer progression. The cause of such an expression change may be attributed, at least in part, to

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