PLANT-DERIVED NATURAL PRODUCTS TARGETING RHO GTPASES SIGNALLING NETWORKS FOR CANCER THERAPY: A REVIEW

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Abstract

Rho GTPases are intracellular signalling molecules that involve in transducing extracellular stimuli to downstream effector of signalling pathways to elicit cellular functions. Changes in expression level of Rho GTPases and altered activities of GTPase regulators have been reported in a variety of human tumours. These modifications perturb actin cytoskeleton dynamics hence promote cancer cell development and progression. Available evidence suggests that targeting therapeutic targets in Rho GTPase signalling network may reduce the progression of cancer to metastasis stage. Pharmacological modulators of Rho GTPases have been investigated as promising chemotherapeutic intervention, which of these are natural products derived from plants. A brief overview of potential therapeutic compounds from selected plants followed by their roles in altering Rho GTPase signalling in cancer cells will be provided. There is increasing knowledge of newly discovered pharmacological modulators of Rho GTPase from natural sources to suppress cancer growth and metastasis. Future directions should emphasize on evaluating efficacies and appropriate therapeutic doses of the promising Rho GTPase modulators from plants to be used in animal models and clinical trials. Modern techniques should also be considered to improve anticancer drugs properties including increased bioavailability and localization to targeted sites.

Keywords: Rho GTPase, Actin Cytoskeleton, Cancer Treatment

Introduction

Rho GTPases are intracellular signalling molecules involved in transducing extracellular stimuli to downstream effector of signalling pathways to elicit cellular functions including regulation of cell motility, cell cycle and vesicle trafficking. Since discovery of the first Rho GTPase more than 30 years ago, over 20 Rho GTPases have been identified. In mammals, Rho GTPases are categorized into eight subgroups among which Rac1 is suggested as the founding member of one subgroup (1). The GTPases that make up these subgroups are; RhoA, RhoB and RhoC (Rho subgroup); Rac1, Rac2, Rac3 and RhoG (Rac subgroup); Cdc42, RhoQ and RhoJ (Cdc42 subgroup); RhoU and RhoV (RhoU/RhoV subgroup); RhoH (RhoH subgroup); RhoBTB1 and RhoBTB2 (RhoBTB subgroup); Rnd1, Rnd2 and RhoE (Rnd subgroup); and RhoD and RhoF (RhoD/RhoF subgroup). Amongst Rho GTPases, Rho, Rac and Cdc42 are highly conserved across eukaryotes.

RhoA, Rac1 and Cdc42, the three best-characterized Rho GTPases, have been reported to be activated in human cancer cells (2). These proteins play crucial role in cancer metastasis by regulating actin cytoskeleton in migrating cells and adhesion between cell and its extracellular matrix (3). Hence targeting Rho GTPase activation and inhibition of Rho GTPase effectors are regarded as promising therapeutic approaches in cancer treatment (4). Plant-derived compounds have been suggested as excellent candidates of chemotherapeutic drugs because of their distinct pharmacological activities and less toxic (5). This review focuses on the emerging therapeutic potential of plants that aimed at regulating Rho GTPase signalling cascade for cancer treatment.

Regulation of Rho GTPases signalling pathway

Like other small GTPases, Rho GTPases activity is typically regulated by an inactive GDP-bound and an active GTP-bound state as shown in Figure 1. The classical Rho GTPases cycle is regulated by three type of

proteins named guanine nucleotide exchange factors (GEFs), GTPase activating proteins (GAPs) and guanine nucleotide dissociation inhibitors (GDIs) (6). GEFs activate GTPases by stimulating the exchange of GDP for GTP whereas GAPs turn off GTPases activity by increasing intrinsic GTP hydrolysis and GDIs sequester inactive GTPases in the cytosol. Upon binding to GTP, the GTPases undergo conformational changes that involves reorientation of the side chains of switch I and switch II (7). Switch I and switch II domains bound to the γ-phosphate of GTP and when the GTP is hydrolysed, both switch regions relax into GDP-conformation. There are a vast number of Rho GEFs and Rho GAPs (approximately 80 and 70 respectively) identified as regulators of Rho GTPases in humans (8) and this allows many upstream pathways to influence Rho GTPase activity.

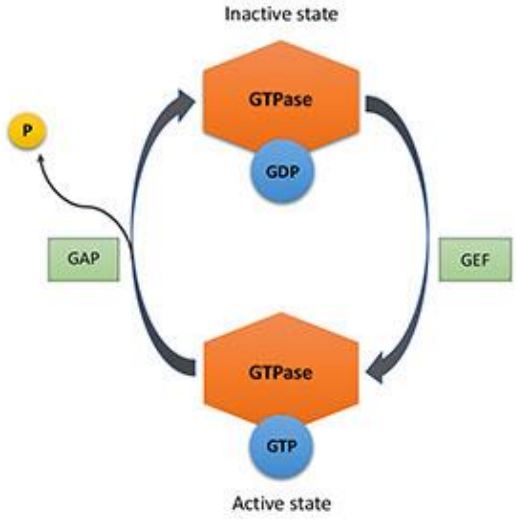

Figure 1: Rho GTPases activation cycle. Rho GTPases are activated by GEFs that promote the exchange of GDP for GTP. Activated Rho GTPases trigger the activation of downstream effectors until their activity is "switched off" by GAPs which hydrolyse the GTP and return the GTPases to their GDP-bound.

GEFs

The first mammalian Rho GEF discovered was the oncogenic protein Dbl identified in a diffuse B-cell lymphoma (9). Later, Dbl was demonstrated to specifically catalyse guanine nucleotide exchange by Cdc42 protein thus shedding light on oncogenic protein involvement in the regulation of nucleotide binding activity. Since then, more than 70 human Dbl-like Rho GEFs have been characterised. These Dbl family proteins share a region of homology of ~200 amino acid called a Dbl homology (DH) domain and an adjacent ~100 amino acid pleckstrin homology (PH) domain. The DH domain of Rho GEFs interacts with the Rho GTPases by remodelling the switch regions that subsequently alter the nucleotide binding pocket. CR1 and CR3 of the DH domain interacts with switch I while switch II directly contacts the CR3 and C-terminal helix (α6) of the DH domain. These interactions lead to disorganization of the nucleotide binding pocket and dissociation of GDP and Mg^{2+}, which then allows rebinding of GTP.

The role of the PH domain in guanine nucleotide exchange activity however is currently less well understood. While the PH domain directly interacts with Rho protein (10), the region does not directly interact with Rac1 and a crystal structure of the DH-PH domains from human Sos suggests an inhibitory function of the PH domain towards DH domain binding activity. Dedicator of cytokinesis (DOCK) family is another distinct class of Rho GEFs, which is characterised by its catalytic domain, Dock-homology region-2 (DHR-2). DOCK family lacks a Dbl domain and specifically have guanine nucleotide exchange activity only for Rac and/or Cdc42 in the Rho family (11).

GAPs

GEFs counterparts in regulating Rho GTPases activity are GAPs, which exhibit a conserved catalytic domain comprising approximately 190 amino acids containing conserved arginine residues known as the "arginine finger" (12). The Rho GAPs domain is made up of a nine α helix structure that interacts with switch I, switch II and the P-loop of Rho GTPases. The major role of Rho GAPs is to stabilize the position of glutamine 61 residue of Rho GTPases, which orients a water molecule for GTP hydrolysis. In addition, the arginine finger of Rho GAPs is placed into the Rho GTPase's active site to neutralize negative charge at the γ-phosphate for stabilization of the transition state. Substrate specificity and fine-tuning of Rho GAP catalytic efficiency in cells are suggested to be achieved through additional domains with different properties (13). However, Rho GAPs that lack these additional domains can still exert specific functions possibly through their highly variable regions at their N and C termini.

Co-ordination of GEFs and GAPs

Different GEF-GAP interactions in different regions of cells reflect the importance of balancing GEFs and GAPs activity and localization in order to tune functional levels of GTPases signalling (8). When GEFs and GAPs are present at the same place and same time, their activities can be balanced in order to achieve an optimal GTPase activity. Although a lot of attention has been directed to GTPases activation through classical GEF-GAP interactions, some of the Rho GTPases do not adapt this activation mechanism. Four Rho GTPases subgroups, RhoU/RhoV, RhoH, RhoBTB and Rnd, are always in a GTP-bound state due to high intrinsic nucleotide exchange activity or alterations in GTPase domain (14). Because these atypical Rho GTPases are unable to perform GTP-GDP exchange, their activities are regulated by other means such as the level of gene

expression or post-translational modifications (PTMs).

Biological role of Rho GTPases in actin cytoskeleton organization

The best-known role of Rho GTPases is in the regulation of actin-containing cytoskeletal structures. Research in the 1990s characterised the role of three highly conserved members; RhoA, Rac1 and Cdc42, in actin dynamics in fibroblasts (15). This work demonstrated that activation of RhoA leads to the generation of stress fibres, which consist of actin-myosin filaments while activation of Rac1 and Cdc42 induces lamellipodia/membrane ruffles and filopodia protrusions, respectively (16). Lamellipodia are broad, sheet-like protrusions comprised of dense branched actin filaments while filopodia are long, needle-like structures made up of a bundles of actin filaments. More recent research has shown that the effects of Rho GTPases on actin assembly vary with cell type and context, so the clearly defined roles of Rho, Rac and Cdc42 originally observed in fibroblast represent a simplified view of Rho GTPases function (17). RhoA, Rac1 and Cdc42 serve as the main regulators for actin-based structures which underlie numerous cellular events including cell migration and cell growth.

Regulation of cell migration

In order to achieve efficient migration following stimulation, the formation of different actin-based structures at specific locations and times must be tightly regulated and co-ordinated by Rho GTPases and their multiple upstream and downstream signalling events (Figure 2). Cell migration involves formation of lamellipodia and filopodia protrusions at the leading edge, which is driven by Rac and Cdc42 (18). A number of GEFs have been implicated in Rac/Cdc42-dependent migration including DOCK1, P-Rex1 and Tiam1 (19). To provide anchorage and stabilization for the actin extensions, cell adhesions are formed between integrins and extracellular matrix (ECM) components.

Integrin binding to ECM leads to p21-activated kinase (PAK)-mediated paxillin phosphorylation which recruits G protein-coupled receptor (GPCR) kinase-interacting protein (GIT) to paxillin at the adhesion site (20). Since GIT binds to the RacGEF β-p21-activated kinase-interacting exchange factor (β-PIX), this triggers accumulation of GIT-PIX-PAK near the leading edge, which then promotes cell spreading via Rac1 activation by β-PIX. By contrast, RhoA is inhibited by p190RhoGAP to enhance membrane protrusions and cell migration. Since p190RhoGAP has been demonstrated to participate downstream of Rac1 signalling in the generation of reactive oxygen species (ROS), there is a possibility of Rac1 and RhoA crosstalk during cell adhesion.

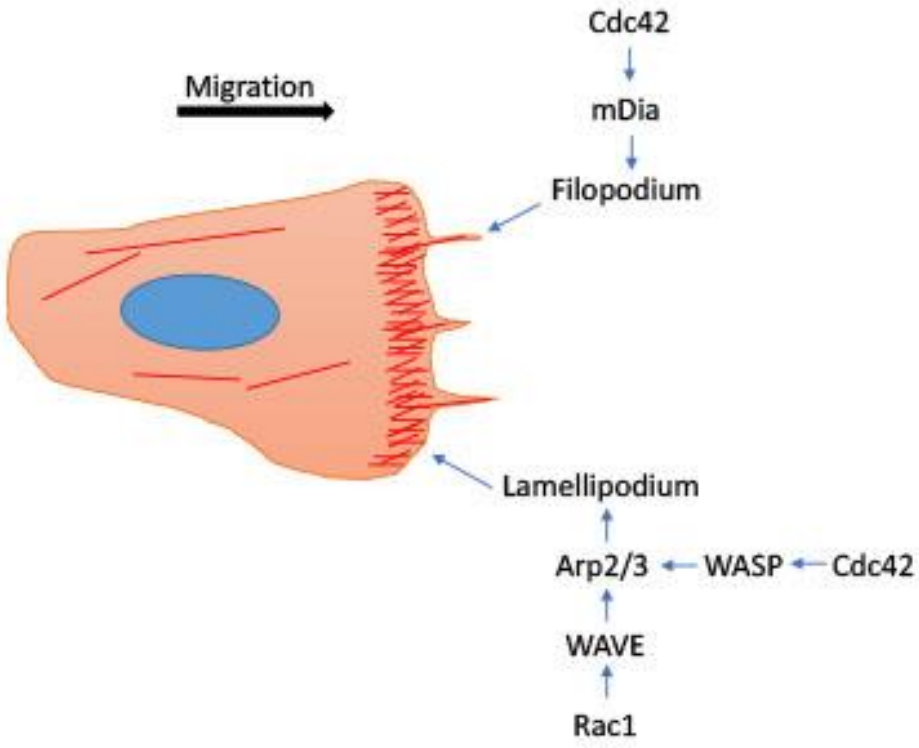

Figure 2: Rho GTPases in the regulation of cell migration. Cdc42 regulates the formation of filopodium that acts as sensors to navigate the migration direction. Rac1 induces the formation of lamellipodium that extend the cell

forward and promotes formation of cell adhesion.

Other Rac effector proteins, such as formins, have been demonstrated to participate in cell migration (21). Formin-like protein 1 (FMNL1) binding to the GTP-bound form of Rac via its FH3 region regulates organization of actin cytoskeleton for adhesion and chemotaxis of macrophages. Other formins such as FH1/FH2 domain-containing protein 1 (FHOD1) interact with the polybasic domain in the Rac1 C-terminal domain and consequently induces transcription of genes necessary for motility, such as cfos and β-actin. The Rac-FHOD1 interaction not only triggers FHOD1 recruitment into the membrane ruffles and lamellipodia, but also induces the formation of actin stress fibres mediated via ROCK (22).

At a later stage of adhesion, where Rac1 activation reaches a maximum level, its activity is suppressed through the action of RacGAP1 and filamin A-associated GAP (FilGAP). This is achieved via filamin A (FLNa) and IQ-motif-containing GTPase activating protein 1 (IQGAP1) binding to active β1 integrin, which in turn recruits RacGAP1 to hinder activation of Rac1 (23). FilGAP localizes at the lamellae and upon its activation by ROCK phosphorylation, FilGAP inactivates Rac thus leading to suppression of leading edge protrusion and enhanced cell retraction. Inhibition of Rac1 activation gradually increases RhoA activity that promotes stress fibres formation and FA maturation through the activity of Rho-specific GEFs such as Rgnef (p190RhoGEF), GEF-H1 and p115RhoGEF (24). RhoA activity at the cell rear induces cell contraction through actomyosin contractility which provides tension for tail retraction and allows cell to move forward.

Cell cycle progression

Eukaryotic cells undergo cell division that consists of four distinct phases named as G1, S, G2 and M. G1 phase is characterised by a stage where cellular contents except chromosomes starts to duplicate in response to stimuli, followed by DNA synthesis in S phase and cell checkpoints prior to division in G2 phase. When the G2 phase is complete, cell undergoes mitosis (M phase) which involves positioning of centrosome, generation of mitotic spindles, sister chromatids separation and ends with cell division. Rho, Rac and Cdc42 are key regulators in cell cycle progression particularly during the G1 and M phases. In early G1 phase, Rac induces transcription of cyclin D1, a crucial sensor and integrator of extracellular stimuli, that activates cyclin-dependent kinase 4 in promoting cell cycle progression (25). Rac is regulated by both integrins and E-cadherin and acts through the Nuclear factor-κB (NF-κB) pathway to stimulate cyclin D1 transcription. Production of cyclin D1 in mid G1 phase requires activation of sustained extracellular signal-regulated kinase (ERK) signalling which is achieved through suppression of Rac by Rho, demonstrating the importance of Rac and Rho activity in controlling the correct level of cyclin D1 production within G1 phase (26). Cdc42 has been found to be involved in both early G1 phase cyclin D1 and late G1 phase cyclin E production.

Natural products targeting Rho GTPases signalling

Hemsleya amabilis is a popular homeopathic plant in China that has been used for centuries to treat illnesses including inflammation, ulcers, jaundice and tuberculosis (27). The potential of *H. amabilis* in treating cancer has been demonstrated through *in vitro* studies using various types of cancer cells such as mouse hepatocellular carcinoma H22, human lung cancer NCI-H1299 and human prostate cancer (28). Tumour cell growth was significantly suppressed following treatment with cucurbitacin IIa (Cu IIa), a triterpene isolated from *H. amabilis* extract. The finding was consistent when Cu IIa administered via intravenous injection in hepatoma H22-bearing mice such that the treatment inhibited tumour development and shrunk the size of the tumour in a dose-related manner.

Further investigation showed irreversible severe clustering of F-actin and changes in cell morphology of Cu IIa-treated cancer cells, suggesting alteration in Rho GTPase pathway (28). Following Western blots analysis, it was found that RhoA phosphorylation at serine 188 was decreased in the cancer cells treated with Cuc IIa. However, serine 71 phosphorylation of Rac1/Cdc42 was not changed, indicating inactivation of Rac1/Cdc42. Hence the result confirmed altered RhoA signaling by Cuc IIa treatment. Cucurbitacin B and cucurbitacin IIb are other triterpenoid compounds derived from Cucurbitaceae plants, which also have been reported to interfere actin dynamics by altering expression of actin-regulating factors in Rho GTPase pathways (29).

Persimmon, *Diospyros kaki*, is widely cultivated throughout East Asia region mainly in Korea, China and Japan. The plant belongs to Ebenaceae family and has been utilised in traditional Chinese medicine practice to cure diseases such as sore throat, diabetes and hypertension. Leaves of *D. kaki* contain abundance bioactive compounds such as flavonoids and terpenoids. Treatment with ethanol extract of *D. kaki* leaves (EEDK) as lower as 0.1 μg/mL induces cytotoxic effects and prevents colony formation in human liver carcinoma cells HepG2 (30). By using fluorescent resonance energy transfer (FRET)-based biosensors, they found that the EEDK-induced cell death is regulated by platelet-derived growth factor receptor (PDGFR) pathway, which activates various downstream pathways that are important for cell survival, proliferation and migration (31).

Ras-related C3 botulinum toxin substrate (Rac) is one of PDGFR downstream effectors that forms Rac-GTP complex in its activated state in order to regulate the formation of lamellipodia during cell motility (32). HepG2 cells treated with EEDK promotes Rac activity, which is reflected with increased in Cyan fluorescent protein (CFP)/FRET emission ratio. Previous study by Kato and co-workers had reported the hyperactivation of Rac in metastatic prostate cancer that is responsible for the migration of cancer cell during invasion (32). Following Rac activation by EEDK in HepG2 cells, JNK pathway is also found to be activated that later results in cellular death (30). Upon investigation on the mechanism of action, it has been demonstrated that JNKs downstream transcription factors; AP-1 and p53, involve in EEDK-induced cell death.

An alkaloid extracted from *Coptidis rhizoma*, berberine, has been reported to effectively induce apoptosis and inhibit tumorigenic growth of human nasopharyngeal carcinoma (NPC) cell line *in vitro* and *in vivo* (33). The inhibitory action of berberine on NPC cells growth is found to be mediated by inhibiting STAT3 activation while supressing Rho GTPases that leads to inhibition of cell migration and invasion. Previous work using GST pull-down assay showed that RhoA, Cdc42 and Rac1 activation was repressed by berberine in a dose-related manner (34). This finding is consistent with the inhibition of stress fibre formation when visualized by phalloidin staining, suggesting berberine interrupts key players involve in the regulation of cytoskeletal dynamics.

Conclusion

Given the important role in the regulation of actin cytoskeleton, targeting Rho GTPases is a promising strategy to combat cancer especially in the development and metastasis stage. Pharmacological inhibition of cancer cells growth and migration can be highly beneficial to suppress their survival and prevent invasion into surrounding tissues. Bioactive compounds derived from plants have been demonstrated to exhibit potential therapeutic activities and used for years to treat various diseases in many traditional practices. This review summarized potential anticancer drug candidates from several plants that target Rho GTPase regulatory activities to result in altered cytoskeletal dynamics thus inhibits cancer progression. Further work is warranted to understand better the roles of Rho GTPase downstream effectors in order to identify compensatory feedback mechanism that may restrain the success of therapy. In addition, the potential use of plant-derived natural products that target Rho GTPase regulatory pathway with other chemotherapeutic agents should also be studied in the future.

Competing interests

Author declares that there is no conflict of interest.

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