Similarities and Differences of RhoGDI1 and RhoGDI2

Subjects: Oncology

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RhoGDI1 and RhoGDI2 (guanine nucleotide dissociation inhibitor (GDI)) have been implicated in multiple human cancers through their involvement in cancer cell migration, invasion and metastasis and, thus, are regarded as attractive targets for cancer biology. RhoGDI2 has largely remained in RhoGDI1′s shadow because of its lower abundancy and more restrained distribution.

RhoGDI2 1 RhoGDI1 2 Rho GTPases 3 cancer 4

1. Introduction

Rho GTPases are highly conserved members of the Ras superfamily, which are best known to organize the actin and microtubule cytoskeleton thereby defining the cell shape and migration. They also control a wide variety of signaling pathways that regulate crucial biological processes such as vesicle transport, cell division and gene transcription [1][2][3]. Rho GTPases cycle between an active GTP-bound form and an inactive GDP-bound form. This activity is regulated by three classes of proteins: guanine nucleotide exchange factors (GEFs) catalyze the exchange of GDP for GTP to activate the GTPase; whereas GTPase-activating proteins (GAPs) increase the intrinsic GTP hydrolysis rate of the GTPase and inactivate it; and guanine nucleotide dissociation inhibitors (GDIs) sequester the GDP-bound form of GTPases in the cytosol to prevent their activation by GEFs or ubiquitin-mediated degradation (**Figure 1**) [4]. Aberrant signaling of Rho GTPases and their regulators is commonly found in many human cancers and has been attributed to several mechanisms [5][6][7][8][9][10].

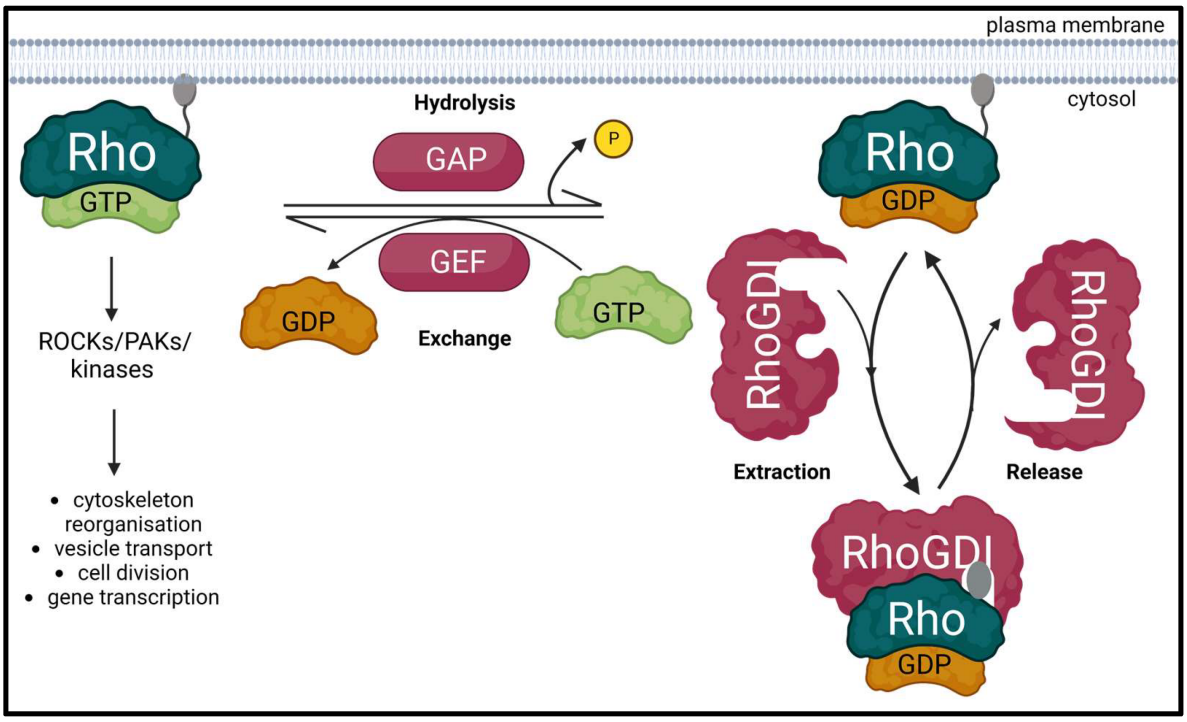

Figure 1. Schematic diagram of the Rho GTPase regulatory cycle. Inactive Rho GTPase is dissociated from its GDP and uptakes GTP to get activated through a process promoted by the Rho guanine exchange factors (RhoGEFs). Active GTP-bound Rho GTPase can then interact with its effectors such as Rho-associated coiled-coil containing kinases (ROCKs), PAK family of serine/threonine kinases (PAKs) and other kinases to participate in various biological processes. This interaction ceases when Rho GTPase-activating proteins (RhoGAPs) stimulate the hydrolysis of the bound GTP to GDP, thereby inactivating the Rho GTPase. The inactive GDP-bound form of Rho GTPase is free to bind to and be sequestered by Rho guanine nucleotide dissociation inhibitors (RhoGDIs). This induces their relocation to the cytoplasm, prevents their ubiquitin-mediated degradation and regulates the activation of Rho GTPases by GEFs. Created with BioRender.com (accessed on 28 January 2023).

To this date, nearly 85 RhoGEFs and 66 RhoGAPs have been identified for nearly 20 Rho GTPase family members, wherein, in stark contrast, only three human RhoGDIs have been identified so far: RhoGDI1 (or RhoGDIα), RhoGDI2 (or RhoGDIβ or D4-GDI or Ly-GDI) and RhoGDI3 (or RhoGDIγ) [8]. All three reside exclusively in the cytoplasm wherein RhoGDI1 is ubiquitously expressed [11][12]. RhoGDI2 was initially believed to be expressed specifically in hematopoietic cells [13][14] but subsequently has also been found in various other cell types and tissues, including cancer cells [8]. RhoGDI3 is primarily expressed in the brain, lung, kidney, testis and pancreas where it targets the Golgi, and shows specificity towards RhoB and RhoG [15].

RhoGDI1 and RhoGDI2 have been implicated in multiple human cancers through their involvement in cancer cell migration, invasion and metastasis and, thus, are regarded as attractive targets for cancer biology [8]. RhoGDI2 has largely remained in RhoGDI1′s shadow because of its lower abundancy and more restrained distribution. It is, however, starting to garner more attention due to discoveries hinting that RhoGDI2 may play more complex roles in multiple human cancers and many key cellular processes.

2. RhoGDI1 and RhoGDI2: Similarities and Differences

RhoGDI1 was the first RhoGDI to be discovered in rabbit intestine and bovine brain cytosol in 1989 and is widely considered to be the prototype of RhoGDIs. Subsequently, corresponding human cDNA was isolated and a RhoGDI protein was also identified in yeast [11]. Leffers et al. characterized RhoGDI2 and found that it was largely expressed in hematopoietic cells [16]. RhoGDIs interact with the GDP-bound Rho GTPases and extract Rho GTPases from the membrane to regulate them from undergoing the GDP/GTP exchange cycle. [17]. The N-terminal domain of the RhoGDIs interacts with the switch 1 and switch 2 regions of GDP-bound Rho GTPases which prevents the exchange of GDP for GTP and therefore keeps them in their inactive form [18][19], whereas the C-terminal domain also contributes towards their inhibition by extracting Rho GTPases from the membrane [17][20].

RhoGDIs may also shuttle inactive Rho GTPases towards membranes leading to their activation [17][21]. Moreover, RhoGDIs can protect its interacting Rho GTPases from proteasomal degradation [22], demonstrating that RhoGDIs are not merely inhibitors for Rho GTPases but also have a key role in their regulation and signaling. Quite expectedly in view of these functions, both the RhoGDIs are involved in the regulation of multiple biological processes such as actin cytoskeletal organization, cell migration and immune response [23][24][25][26]. As mentioned previously, they are also implicated in many human cancers where they can either be upregulated or downregulated (**Table 1**).

Table 1. Expression of RhoGDI1 and RhoGDI2 in human cancers. Biphasic, up and then down.

Cancer	RhoGDI	Regulation	Reference(s)
Colorectal cancer	RhoGDI1	Up	[27]
	RhoGDI2	Up	[28]
Breast cancer	RhoGDI1	Up	[29]
	RhoGDI2	Up	[30][31]
		Biphasic	[32][33]
Hepatocellular carcinoma	RhoGDI1	Down	[34]
	RhoGDI2	Up	[35]
Bladder cancer	RhoGDI1	Down	[36]
	RhoGDI2	Down	[37]
Ovarian cancer	RhoGDI2	Down	[38][39]
Hodgkin's lymphoma	RhoGDI2	Down	[40][41]
Gastric cancer	RhoGDI2	Up	[42][43]

Cancer	RhoGDI	Regulation	Reference(s)
Pancreatic cancer	RhoGDI2	Up	[44][45][46]
Melanoma	RhoGDI2	Up	[47]
Lung cancer	RhoGDI2	Down	[48][49]
Osteosarcoma	RhoGDI2	Down	[50][51]
Leukemias	RhoGDI2	Down	[52][53]

ively) are completely divergent, RhoGDI 1 and 2 show 73.6% identity for the remaining C-terminal sequence (**Figure 2**). RhoGDI1 and RhoGDI2 interact with and form complexes with the classical Rho GTPases, i.e., RhoA, RhoC, Rac1, Rac2, Rac3, RhoG and Cdc42 [19][54][55][56]. However, the interaction potency of RhoGDI2 with Cdc42 is 10–20 folds lower than that of RhoGDI1. Platko et al. observed that a single residue (Ile 177 in RhoGDI1/Asn 174 in RhoGDI2) is responsible for this difference in their affinity for Cdc42 [57].

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P52565  MAEQEPTAEQLAQIAAENEEDEHSVNYKPPAQKSIQEIQELDKDDESLRKYKEALLGRVA      60
P52566  MTEKAPEPH---VEEDDDDELDSKLNYKPPPQKSLKELQEMDKDDESLIKYKKTLLGDGP      57
        *:*: *  .       :::* : .:***** ***::*:**:******* ***::***

P52565  VSADPNVPNVVVTGLTLVCSSAPGPLELDLTGDLESFKKQSFVLKEGVEYRIKISFRVNR      120
P52566  VVTDPKAPNVVVTRLTLVCESAPGPITMDLTGDLEALKKETIVLKEGSEYRVKIHFKVNR      117
        * :**:.****** *****.*****: :*******::**:::***** ***:** *:***

P52565  EIVSGMKYIQHTYRKGVKIDKTDYMVGSYGPRAEEYEFLTPVEEAPKGMLARGSYSIKSR      180
P52566  DIVSGLKYVQHTYRTGVKVDKATFMVGSYGPRPEEYEFLTPVEEAPKGMLARGTYHNKSF      177
        :****:**:*****.***:**: :******** ********************:*  **

P52565  FTDDDKTDHLSWEWNLTIKKDWKD   204
P52566  FTDDDKQDHLSWEWNLSIKKEWTE   201
        ****** *********:***:*.:
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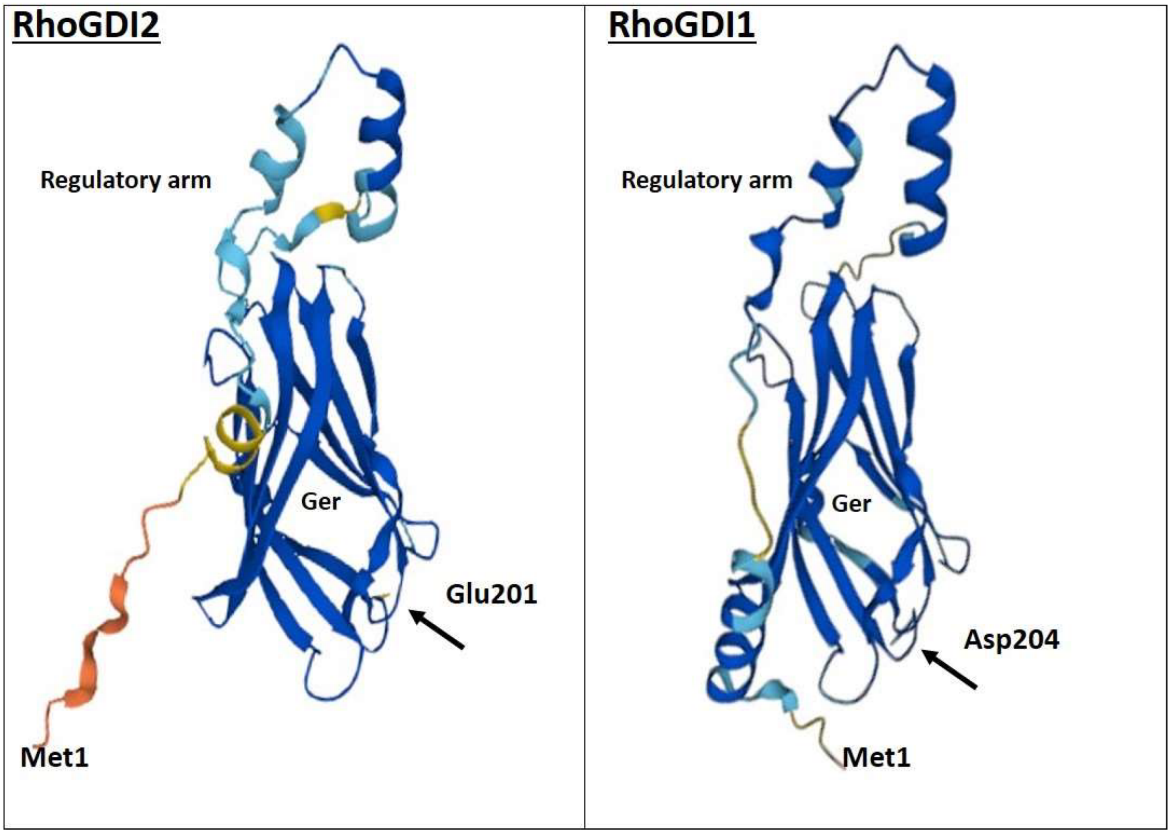
(**A**)



(**B**)

Figure 2. Comparison of primary and tertiary structures of human RhoGDI1 and RhoGDI2. (**A**) Protein sequences were compared using EMBL-EBI's Clustal Omega tool. The accession numbers are as follows: human RhoGDI1, P52565 and human RhoGDI2, P52566. Identical residues are indicated by asterisks; substitutions for amino acids possessing highly similar or somehow similar characteristics are indicated by double and single dots, respectively. The highly divergent extreme N-terminal domains are enclosed in the red box. RhoGDI2 is phosphorylated at Y24, S31 and Y153 by β2 integrin-related kinases Src, c-Abl and Syk in response to PSGL-1 antibody ligation. On the contrary, RhoGDI1 is phosphorylated at S45, S48 and T52 by calcium-dependent protein kinase CPK3. (**B**) Predictions of the 3D structure of RhoGDI1 and RhoGDI2 are from the AlphaFold project (AF-P52565-F1 and AF-P52566-F1, respectively). Confidence regarding the 3D structure corresponding to different parts of the proteins is

provided by color code, with dark blue representing the highest confidence and orange the lowest confidence. Ger: pocket accommodating the geranylgeranyl moiety of the Rho GTPases.

Several other proteins that are not part of the Rho GTPase family have been found to interact with RhoGDI 1 or 2 or both, mainly through high throughput experiments. Upon examining Uniprot (https://www.uniprot.org (accessed on 23 January 2023)) and Biogrid (https://thebiogrid.org (accessed on 23 January 2023)) databases, the interactors of both RhoGDIs can be extrapolated. Both RhoGDI 1 and 2 have been found to interact with ubiquitin-fold modifier 1 (UFM1), small ubiquitin-like modifier 4 (SUMO4), U2 small nuclear RNA auxiliary factor 2 (U2AF2) and DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 (DDX58). However, RhoGDI1 interacts with Cullin3, whereas RhoGDI2 does not. RhoGDI1 also interacts with EWS RNA-binding protein 1, ezrin, moesin and radixin. On the other hand, RhoGDI2 interacts with RhoGEF Vav1, whereas RhoGDI1 is unable to do so. RhoGDI2 also interacts with acyl-CoA thioesterase 7, B cell CLL/lymphoma 6 and cadherin1. Perhaps the differences in functions of both RhoGDIs may be attributed to their interactions with different proteins that do not belong to the Rho GTPase family.

Mouse models were used to identify the respective functions of RhoGDI 1 and 2. Yin et al. generated RhoGDI2-null mice to explore its functions in lymphocytes. They observed that there were no abnormalities in lymphoid development and immune responses. However, in vitro cultivation of B and T cells from these mice showed de-regulated interactions and other impaired phenotypes. They inferred that RhoGDI2 regulates Rho GTPases in lymphocyte survival and responsiveness, wherein the absence of RhoGDI2 can be compensated in vivo by other Rho GTPase regulatory proteins [26]. It was later shown that RhoGDI1-null mice display abnormalities in the kidneys and reproductive system in adulthood and that levels of RhoGDI2 expression did not change in WT and RhoGDI1-null mice [58]. Double knockouts of RhoGDI 1 and 2 were then generated in order to get a better insight into their specific and shared functions. These mice are characterized by aberrant homeostasis of lymphocytes and an increased eosinophil population. T cells derived from the mice display defective in vitro proliferation and development and lower levels of CD3 expression. These results show that RhoGDI 1 and 2 share similar functions and can partly substitute for each other in lymphocytic migration and development [59].

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