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Rho GAPs and GEFs
Controling switches in endothelial cell adhesion

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Within blood vessels, endothelial cell–cell and cell–matrix adhesions are crucial to preserve barrier function, and these adhesions are tightly controlled during vascular development, angiogenesis, and transendothelial migration of inflammatory cells. Endothelial cellular signaling that occurs via the family of Rho GTPases coordinates these cell adhesion structures through cytoskeletal remodelling. In turn, Rho GTPases are regulated by GTPase-activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs). To understand how endothelial cells initiate changes in the activity of Rho GTPases, and thereby regulate cell adhesion, we will discuss the role of Rho GAPs and GEFs in vascular biology. Many potentially important Rho regulators have not been studied in detail in endothelial cells. We therefore will first overview which GAPs and GEFs are highly expressed in endothelium, based on comparative gene expression analysis of human endothelial cells compared with other tissue cell types. Subsequently, we discuss the relevance of Rho GAPs and GEFs for endothelial cell adhesion in vascular homeostasis and disease.

Introduction

The endothelial monolayer covers the luminal side of blood and lymphatic vessels and functions as a physical barrier that preserves vascular integrity. Endothelial cells make adhesive contacts with the extracellular matrix (ECM) as well as homotypic adhesions between neighboring cells. Throughout embryonic development, strictly regulated formation and breakdown of adhesion complexes determines tissue shapes and boundaries.[1-4] In adults, these adhesions are essential to regulate and maintain the barrier function of the endothelium. Moreover, the activity and content of endothelial cell adhesion structures are highly regulated during angiogenesis and inflammatory responses.[5-8]

Cell–matrix and cell–cell adhesion complexes

Endothelial cell–matrix interactions, in particular those mediated by integrins, are crucial for vascular development and angiogenesis as they mediate adhesion to, and migration through, the vascular ECM.[5] Besides their structural anchoring role, integrins modulate angiogenic growth factor- and inflammatory cytokine-induced signaling pathways through increased receptor clustering and recruitment of signaling molecules that control cell behavior.[9,10] Changes in the composition, deposition, or rigidity of the vascular ECM are transmitted through integrin-based complexes to alter cellular signaling pathways,[11] and when such changes are prolonged they cause permanent perturbation of endothelial functions, as occurs during age-related cardiovascular disease or chronic inflammation.

The vascular barrier, required to control leakage of solutes and traffic of circulating cells, is maintained by endothelial adherens and tight junctions, which critically depend on cell–cell adhesion mediated by the VE-cadherin complex. Cell–cell adhesions are destabilized by vascular permeability factors like vascular endothelial growth factor (VEGF), thrombin, and tumor necrosis factor α (TNFα), or by transmigrating leukocytes that stimulate signaling pathways, which transiently destabilize the VE-cadherin complex.[6,8,12] When the formation of endothelial cell–cell adhesion structures is impaired, vascular permeability increases, which contributes to the pathogenesis of chronic inflammation, edema, or acute lung injury. Regulation of cell–cell adhesions also occurs at the onset of angiogenesis; angiogenic growth factors destabilize endothelial cell–cell junctions and thereby initiate sprouting from pre-existing vessels. In contrast, at later stages when new vessels are formed, cell–cell adhesions need to tighten to re-establish vessel integrity.[7,13]

Despite the spatially distinct locations of cell–ECM vs. cell–cell adhesions in endothelial cells, there is intimate crosstalk between integrins and cadherins.[14] The integrin–cadherin crosstalk largely depends on their shared signaling pathways that control adhesion, in which Rho GTPases play a central role, as well as on the organization of the actomyosin cytoskeleton that tightly associates with both cell–ECM adhesions and cell–cell junctions.[15-20] This is also clear during mechanotransduction, when integrins transmit mechanical signals from stiffening ECM toward the actomyosin cytoskeleton.[21] This, in turn, destabilizes cell–cell adhesions, and increases permeability of endothelial monolayers.[22,23] Moreover, cell–matrix and cell–cell adhesions also cluster various signaling molecules that trigger or enhance signaling by small GTPases that control the actomyosin cytoskeleton.[24-28]

Regulation of Rho GTPases in endothelial cell adhesion

In this review, we focus on the regulation of Rho GTPases. These are members of the Ras superfamily of small GTPases

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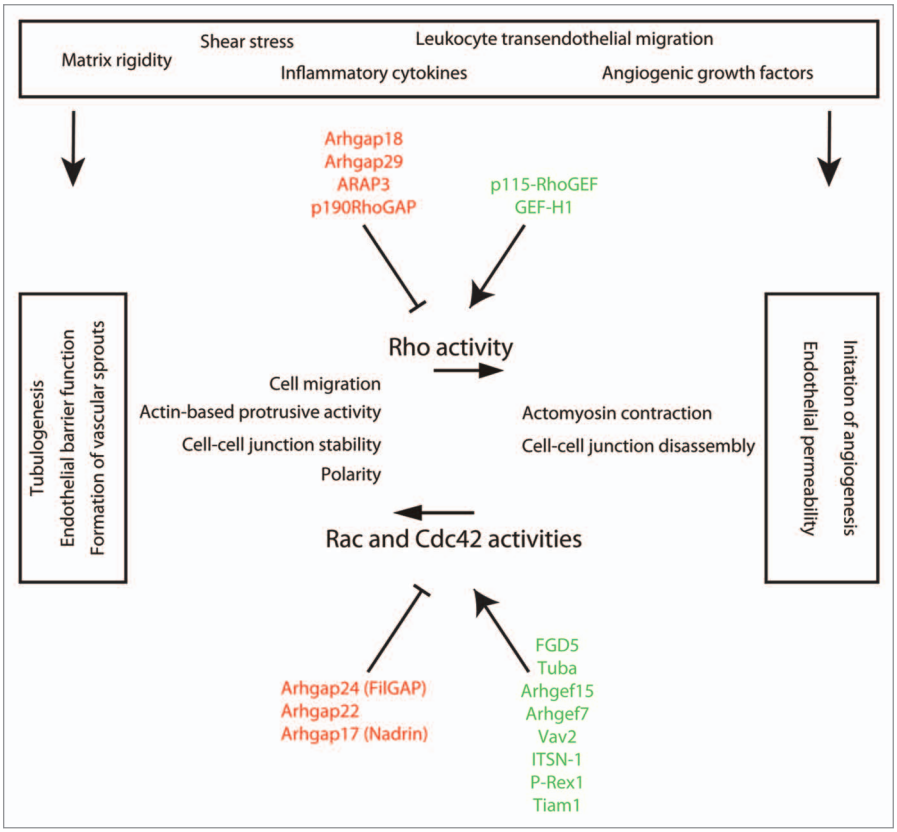

Figure 1. Endothelial functions regulated by Rho GAP and GEF activities. This simplified scheme summarizes the endothelial function of a selection of key GAPs (highlighted in red) and GEFs (highlighted in green) that control the activity of Rho, Rac, and Cdc42 in response to external cues, such as increased extracellular matrix rigidity, changes in shear stress, inflammatory cytokines, angiogenic growth factors, or signals that derive from leukocyte transendothelial migration events. Upon activation, the indicated Rho GAPs and GEFs regulate RhoA signaling toward actomyosin contractility and cell–cell junction disassembly, which underlies the onset of angiogenesis from existing vessels and induction of endothelial permeability. Activated GAPs and GEFs of Rac/Cdc42 regulate their signaling toward actin-based protrusions during cell migration or cell–cell junction stabilization, which is important for endothelial barrier function and formation of vascular sprouts. The control of activity of Cdc42 regulates cellular polarity and lumen formation during tubulogenesis.

that act as molecular switches controlling the actomyosin cytoskeleton and cell adhesion.[29,30] The regulation of Rap GTPase signaling and its role in endothelial cell adhesion will be discussed in detail elsewhere (Pannekoek et al., Cell Adhesion and Migration, this issue). Small GTPases cycle between active GTP-bound and inactive GDP-bound conformations. This cycle is regulated by guanine nucleotide exchange factors (GEFs) that activate, and GTPase activating proteins (GAPs) that inactivate Rho GTPases.[31] Rho GTPases, comprising 20 family members, transduce signals from receptors on the plasma membrane to intracellular effector proteins. The best-studied Rho GTPases regulating cell adhesion are Rho, Rac, and Cdc42. Differences in the spatiotemporal activation of these Rho GTPases is particularly important as they locally drive the formation of actin fibers, stimulate actomyosin contraction, or promote polymerization of branched actin in membrane protrusions through effector proteins such as Rho-associated kinase (ROCK), Diaphanous-related formins (Dia), or Arp2/3, respectively.[32,33] In endothelial cells, vascular permeability factors, for instance thrombin or TNFα, regulate RhoA to enhance actomyosin contraction and remodeling of cell–cell adhesions, supporting immune cells to cross the endothelium, and reach inflamed tissue. Another example of growth factor-induced regulation of Rho GTPases is the activation of Rac1 by VEGF and basic fibroblast growth factor (bFGF) to generate protrusions in leading endothelial tip cells that guide newly formed sprouts during angiogenesis.[34-36] Many other studies show that RhoA-mediated signaling stimulates actomyosin contractility and weakens the endothelial barrier function, whereas increased Rac1-mediated signaling improves barrier function (reviewed in detail in refs. 34 and 36) (**Fig. 1**). In general, during angiogenesis, activation of RhoA-mediated actomyosin contractility underlies the onset of sprout formation from pre-existing vessels, whereas Rac1 and Cdc42 signaling contribute to migration and invasion of sprouts by stimulating membrane protrusions (**Fig. 1**).[35]

Given the fact that Rho GTPase signaling, and especially their local and time-dependent activation-inactivation cycle, is crucial for endothelial cells to maintain vascular barrier function and control dynamic cell behavior during angiogenesis and inflammation, it is surprising that we know so little about the specific role of their regulators, the GAPs and GEFs, in endothelial cell adhesion.

Endothelial GAPs and GEFs

The Rho GEF family, also called the Dbl family, consists of approximately 80 members. The GEF proteins usually contain a Dbl homology (DH) domain and a pleckstrin homology (PH) domain that is important for plasma membrane localization, where the activation of Rho GTPases takes place. GEF DH domains interact with Rho GTPase switch regions, modifying their conformation, resulting in release of GDP. This allows free GTP to bind the GTPase, inducing the switch to the active conformation. The Rho GAPs, comprising approximately 65 members, enhance the intrinsic GTP hydrolysis activity of Rho GTPases and stabilize the GDP-bound switch regions.[31,37]

The known functions of several endothelial Rho GAPs and GEFs fit in a simplified scheme where they control activation of Rac and Cdc42 GTPases to establish actin-based protrusions during cell migration, cell–cell junction stabilization, or cell polarization in response to external cues (**Fig. 1**). These processes are particularly important for the formation of new vascular sprouts, during endothelial barrier formation or tube/lumen formation of developing vessels, respectively. Many of the known RhoA regulators control RhoA activity toward

actomyosin contraction and concomitant cell–cell junction destabilization, which underlies the onset of angiogenesis and is the major cause for endothelial permeability induction. Because of their overlapping functions, the question arises whether Rho GAPs and GEFs have non-redundant roles during regulation of endothelial cell adhesion. Here, we will provide a complete overview of all the Rho GAPs and GEFs that are highly expressed in endothelial cells, as well as ubiquitously expressed GAPs and GEFs with known endothelial functions, followed by a discussion on the individual relevance of these regulators for endothelial cell adhesion in vascular homeostasis and disease. This overview shows that Rho GAPs and GEFs contain many overlapping functions, but clearly also have distinct and local functions in endothelial cells.

Identifying Rho GAPs and GEFs that are highly expressed in endothelium

Many potentially important Rho regulators have not yet been studied in endothelial cells in detail. To uncover which GAPs and GEFs are highly expressed in endothelium, and therefore, may be relevant for regulation of endothelial cell adhesion, we performed comparative gene expression analysis using genome-wide mRNA profiles of human umbilical vein endothelial cells (HUVECs) that were deposited in the NCBI-GEO database (http://www.ncbi.nlm.nih.gov/gds). Expression levels of Rho GAPs and GEFs were determined based on 17 Affymetrix arrays derived from nine independent and well-defined expression studies available in the public domain. The absolute expression values were related to their levels in many other "normal" human tissues. For this, we used the Roth-504 Affymetrix data set ("The Human Body Index"), the largest normal human tissue data set in the public domain. It contains 504 high-quality genome-wide transcription profiles representing 95 different human tissues, including low-passage, non-stimulated, non-recombinant HUVECs (see **Table S1** and legends for details concerning the complete gene expression analysis and calculations). The comparison revealed that 17 different Rho GAPs and 20 Rho GEFs are highly expressed in HUVECs (**Fig. 2**), at levels over 5-fold increased compared with other tissues. Because the results suggest that these highly expressed GAPs and GEFs are important, we will first discuss their role in endothelial cell adhesion. Obviously, regulation of Rho GTPase signaling and adhesion is not only a matter of transcriptional control, and we will therefore also discuss the role of other Rho GAPs and GEFs that are ubiquitously expressed and described to regulate important endothelial functions.

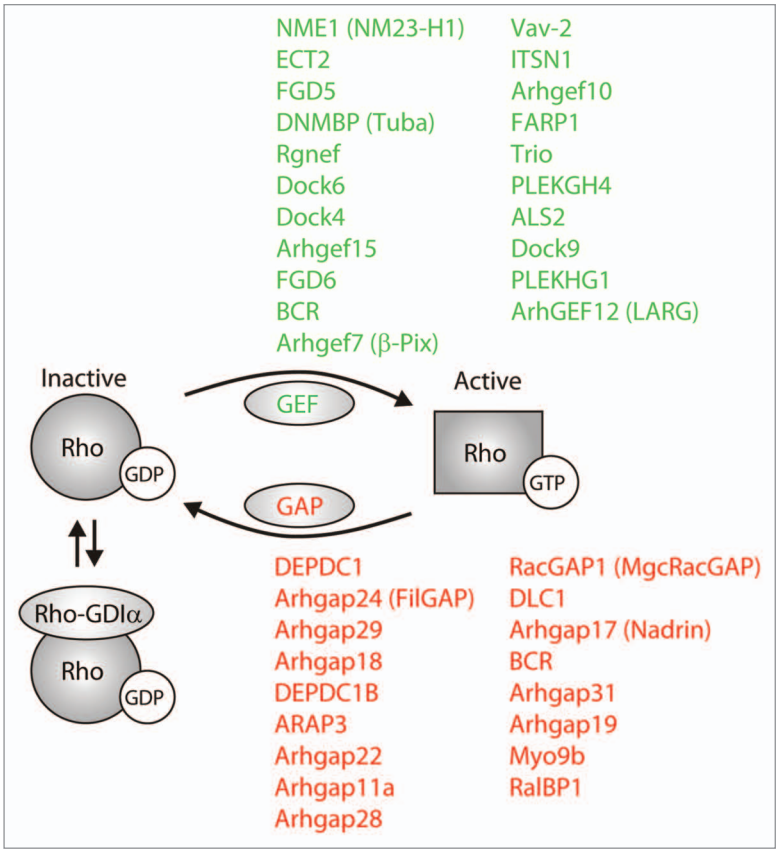

Figure 2. Regulation of Rho GTPase activity by endothelial-enriched GEFs and GAPs. A schematic representation of Rho GTPase regulation by GEFs (green), GAPs (red), and GDIs. Listed are GEFs and GAPs that are above 5-fold higher expressed in endothelial cells compared with cells from other tissues. Rho-GDIα is the only GDI that is strongly expressed in HUVECs.

The roles of Rho GTPase GAPs in endothelium

Highly expressed GAPs

Arhgap24 (FilGAP) and Arhgap22

Among the highest expressed Rho GAPs (**Table 1**) are Arhgap24 (also known as FilGAP, over 25-fold overexpressed in HUVECs as compared with other tissues) and its close relative Arhgap22 (~11-fold upregulation), both designated as GAPs for Rac1 that are involved in Rho–Rac antagonistic signaling.[38] The third member of this protein family, Arhgap25, is never expressed in HUVECs (**Table S1**). Activation of Rho GTPases at membrane protrusions or at cell–cell adhesions strongly depends on the activity of other Rho GTPases as they suppress each other's signaling capacity through downstream mediators including ROS, p190RhoGAP, and FilGAP family members.[39-41] RhoA-mediated activation of ROCK induces phosphorylation of FilGAP at membrane protrusions, and stimulates its Rac GAP activity. The localization of FilGAP is dependent on its interaction with the cytoskeleton and integrin-associated protein filamin A, which controls cell protrusion activity and cell spreading on ECM-coated surfaces.[41,42] Importantly, the complex of FilGAP with filamin A forms a cytoskeletal mechanosensing unit: when mechanical-exerted forces or myosin-dependent contractile forces increase tension on filamin A, its interaction with FilGAP and local FilGAP activity is lost, whereas the interaction with integrins increases.[43] This may, in part, explain the force-dependent activation of Rac at integrin-based adhesions that depends on the relocation of FilGAP by filamin A.[44] A slightly truncated isoform of FilGAP that lacks the PH domain, called RC-GAP73 or p73RhoGAP, is also expressed in endothelial cells. This isoform is recruited

Table 1. Rho GAPs

Gene name	Alternative names	Relative expression in HUVEC	Rho GTPase targets	Function
DEPDC1	DEP.8; SDP35; DEPDC1A; DEPDC1-V2	40.60		
ARHGAP24	FilGAP, RC-GAP72, RCGAP72, p73, p73RhoGAP	25.86	Rac1, Cdc42	Regulates endothelial cell migration, tubulogenesis and angiogenesis.[46]
ARHGAP29	PARG1, RP11–255E17.1	24.97	RhoA	Regulates endothelial adhesion, spreading and polarization during vascular lumen formation and endothelial barrier function.[53, 54.]
ARHGAP18	MacGAP, SENEX, bA307O14.2	21.52	RhoA	Role in endothelial capillary tube formation and barrier protective function.[56]
DEPDC1B	XTP1; BRCC3	20.19		
ARAP3	CENTD3, DRAG1	16.69	RhoA	Adhesion and migration of endothelial cells during (lymph) angiogenesis.[59,63,64]
ARHGAP22	RhoGAP2, RhoGap22, p68RacGAP	11.16	Rac1	Role in endothelial capillary tube formation.[48]
ARHGAP11a	GAP (1–12); rho GTPase-activating protein 11A; rho-type GTPase-activating protein 11A	10.73		
ARHGAP28	Rho GTPase activating protein 28	10.14		
RACGAP1	CYK4, HsCYK-4, ID-GAP, MgcRacGAP	9.97	Rac1, Cdc42	
DLC1	Deleted in Liver Cancer 1, ARHGAP7, HP, STARD12, p122-RhoGAP	7.54	RhoA, RhoB, RhoC, Cdc42	
ARHGAP17	PP367; RICH1; WBP15; MST066; MST110; NADRIN; PP4534; RICH1B; MSTP038; MSTP066; MSTP110	7.39	Rac1, Cdc42, RhoA	
BCR		7.39	RhoA, Rac, Cdc42	
ARHGAP31	AOS1, CDGAP	6.47	Rac1, Cdc42	
ARHGAP19	rho GTPase-activating protein 19	6.40	RhoA	
MYO9B	myosin-Ixb, CELIAC4, MYR5	5.87	RhoA	
RALBP1	RIP1, RLIP1, RLIP76	5.20	Rac1, Cdc42	Role in tumor-associated angiogenesis.[98]

Rho GAP and GEF genes with high and robust mRNA expression in HUVECs. These tables show the highest expressed GAPs (**Table 1**) and GEFs (**Table 2**) in HUVECs. For each gene, the expression value of the highest expressed transcript is shown in the 3rd column, which is relative to the average expression level in Roth-504. mRNA expression in HUVECs was determined by analysis of Affymetrix U133 Plus 2.0 mRNA genome-wide expression profiles in the public domain. All studies at the NCBI Gene Expression Omnibus (GEO) website (http://www.ncbi.nlm.nih.gov/gds/) on low-passage, non-stimulated, non-recombinant HUVECs with data normalization using the MAS5.0 algorithm (Affymetrix Inc., Santa Barbara, CA) were included. A total of 9 different studies comprising 17 arrays were used for expression analysis, an additional 2 studies comprising 12 arrays were used as validation. Relative gene expression was determined by comparing the average expression over all 17 HUVEC sets with the average expression in all 504 arrays representing 95 different normal human tissues in the Roth "Human Body Index," the largest study on normal human mRNA expression (NCBI GEO: GSE7307). Only Rho regulatory genes with high expression in 14 or more of the 17 data sets analyzed are shown. The probe-sets shown for each gene detected the highest and widest expression, but all valid probe-sets were analyzed and used for expression analysis. The TranscriptView visualization tool (http://r2.amc.nl) was used to validate probes: probes had to target a unique, anti-sense position in an exon of the target gene. Gene and splice variant specificity was verified by NCBI GENE and BLAST analysis. Full information on the gene expression calculations, probe validations, and GEO studies can be found in **Table S1**. The Rho GTPases that are targeted by these GAPs and GEFs are indicated in column 4. Column 5 summarizes the known endothelial functions of each Rho regulator including references.

Table 2. Rho GEFs

Gene name	Alternative names	Relative expression in HUVEC	Rho GTPase targets	Function
NME1	NB; AWD; NBS; GAAD; NDKA; NM23; NDPKA; NDPK-A; NM23-H1	21.68		
ECT2	ARHGEF31	19.95	RhoA, Rac1, Cdc42	
FGD5	ZFYVE23	16.42	Cdc42	Involved in VEGF-induced endothelial cell adhesion signaling, cell-cell junction stabilization and associated with vascular development.[52, 118–120.]
DNMBP	TUBA; ARHGEF36; RP11–114F7.3	12.63	Cdc42	
RGNEF	RIP2; p190RHOGEF	12.08	RhoA	
DOCK6	AOS2, ZIR1	8.45	Rac1, Cdc42	
DOCK4	WUGSC:H_GS034D21.1	8.36	Rac1, Rac2	
ARHGEF15	E5; ARGEF15; Ephexin5; Vsm-RhoGEF	8.29	Cdc42, RhoA	Mediator of VEGF-induced retinal angiogenesis.[57,134]
FGD6	FYVE, RhoGEF and PH domain-containing protein 6	7.49		
BCR		7.39	RhoA	
ARHGEF7	β-pix, RP11–494P5.1, COOL-1, COOL1, Nbla10314, P50, P50BP, P85, P85COOL1, P85SPR, PAK3, PIXB	7.32	Rac1, Cdc42	Mediator of VEGF-induced permeability.[138]
VAV2	vav 2 guanine nucleotide exchange factor	7.23	Rac1, RhoA, RhoG, Cdc42	Mediator of growth factor- or mechanotransduction-induced signaling in control of cell-cell adhesion, migration and angiogenesis.[141-143,145,147,148]
ITSN1	ITSN, SH3D1A, SH3P17	7.18	Cdc42	Pro-survival mediator and promotes vascular integrity.[150,151]
ARHGEF10	GEF10	7.00	RhoA, RhoB, RhoC	
FARP1	RP11–111L24.1, CDEP, PLEKHC2, PPP1R75	6.43	Rac1	
TRIO	ARHGEF23, tga	6.43	Rac1, RhoG, RhoA	Regulator of endothelial docking structures during transmigration of leukocytes.[160]
PLEKHG4	ARHGEF44, PRTPHN1, SCA4	6.26	Rac1, Cdc42, RhoA	
ALS2	ALSJ; PLSJ; IAHSP; ALS2CR6	6.25	Rac1	
DOCK9	RP11–155N3.2, ZIZ1, ZIZIMIN1	5.93	Cdc42	
PLEKHG1	D10Ertd733e, Gm521, mKIAA1209	5.53		
ARHGEF12	Larg, RO2792	5.08	RhoA, RhoC	Mediator of Semaphorin 4D and S1P-induced endothelial signaling.[165,166]

to both integrin- and cadherin-based adhesion complexes, regulates the actomyosin cytoskeleton in a GAP-dependent manner,[45] and is important for angiogenesis, based on studies in 3D culture models and in vivo.[46] Arhgap22 was described to regulate tumor cell invasive behavior,[47] and a PH-domain truncated isoform of Arhgap22, p68RacGAP, was shown to be

Table 3. Non-enriched Rho regulators with known endothelial function

Gene name	Alternative names	Function
ARAP1	**CENTD2**	**Highly enriched in renal vasculature.[207]**
ARHGAP35	**GRF-1, GRLF1, P190-A, P190A, p190ARhoGAP, p190RhoGAP**	**Modulates cell adhesion and F-actin organization to protect barrier function and mediates transcriptional control of retinal angiogenesis.[105-110]**
ARHGAP5	**GFI2, RhoGAP5, p190-B, p190BRhoGAP**	**Extracellular matrix degradation.[208]**
OCRL	**RP3–454M7.1, INPP5F, LOCR, NPHL2, OCRL-1, OCRL1**	**Expressed in Schlemm's canal ocular endothelial cells.[209]**
PIK3R1	**AGM7, GRB1, p85, p85-ALPHA**	**Regulates migration of endothelial tip cells during zebrafish angiogenesis and controls lymphangiogenesis in mice.[210,211]**
PIK3R2	**MPPH, P85B, p85, p85-BETA**	**Negatively regulates VEGF signaling in sprouting angiogenesis and vascular integrity.[212]**
STARD13	**RP11–81F11.1, ARHGAP37, DLC2, GT650, LINC00464**	**Mediates endothelial adhesion and migration and suppresses experimentally-induced angiogenesis in mouse models.[79]**
ARHGEF1	GEF1, LBCL2, LSC, P115-RHOGEF, SUB1.5	Inducer of endothelial permeability via regulation of cell adhesion.[174-178]
ARHGEF11	RP11–356J7.2, GTRAP48, PDZ-RHOGEF	Mediator of Semaphorin 4D-induced endothelial signaling in adhesion and migration.[165]
ARHGEF17	P164RHOGEF, TEM4, p164-RhoGEF	Important for endothelial migration and monolayer integrity via cytoskeletal-dependent regulation of cell adhesion.[180,181]
ARHGEF2	RP11–336K24.3, GEF, GEF-H1, GEFH1, LFP40, P40	Regulator of endothelial permeability induced by agonists or by mechanical strain.[183,184]
ARHGEF26	CSGEF, HMFN1864, SGEF	Regulator of endothelial docking structures during transmigration of leukocytes.[186,187]
ARHGEF4	ASEF, ASEF1, GEF4, STM6	Involved in experimentally-induced angiogenesis in mouse models.[202]
ARHGEF6	RP3–527F8.4, COOL2, Cool-2, MRX46, PIXA, α-PIX, alphaPIX	Regulator of endothelial migration and adhesion.[213]
DOCK1	RP11–82L9.1, DOCK180, ced5	Regulates polarized membrane protrusions and endothelial migration during vascular development.[188,189]
ELMO1	CED-12, CED12, ELMO-1	Regulates polarized membrane protrusions and endothelial migration during vascular development.[188,190]
FGD1	RP1–112K5.1, AAS, FGDY, MRXS16, ZFYVE3	Regulates TGF-β-induced endothelial podosome formation and extracellular matrix degradation.[214]
ITSN2	PRO2015, SH3D1B, SH3P18, SWA, SWAP	Caveola endocytosis.[152]
PLEKHG5	RP4–650H14.3, CMTRIC, DSMA4, GEF720, Syx, Tech	Regulator of endothelial cell migration, cell-cell adhesion and angiogenesis.[86-88]
PREX1	P-REX1	Regulator of cell adhesion, Weibel-Palade body secretion, and required for inflammation-induced permeability.[191,193,194]
PREX2	6230420N16Rik, DEP.2, DEPDC2, P-REX2	Regulator of endothelial cell migration.[192]
TIAM1	T-lymphoma invasion and metastasis-inducing protein 1; TIAM-1	Regulation of endothelial cell-cell adhesion and redox signaling.[145,197-201]
VAV3	VAV-3; guanine nucleotide exchange factor VAV3; vav 3 oncogene	Mediator of ephrin-induced angiogenesis and tumor-associated angiogenesis.[147,148]

Non-enriched Rho regulators with known endothelial function. This table shows the GAPs (bold) and GEFs (unbold) that are not specifically enriched in endothelium based on gene expression analysis, but which are, based on literature, known to function in endothelial cells. Gene name, alternative names and a summary of their endothelial function including references are shown.

specifically expressed in endothelial cells, where it controls tube formation on matrigel.[48] Thus, inhibition of Rac1 activity by FilGAP or Arhgap22 controls endothelial integrin and cadherin adhesions. This could be involved in mechanotransduction pathways that are relevant during age-related cardiovascular disease when stiffening of the vascular ECM increases tension on integrins, and during inflammation when permeability factors or leukocytes regulate tension on VE-cadherin-based adhesions.[22,23,49-51]

Arhgap29

Arhgap29 is a Rho GAP that is highly expressed in HUVECs (**Table 1**), and was previously described to be strongly expressed in the vasculature of zebrafish.[52] Arhgap29 is a binding partner of Rasip1, an endothelial restricted effector protein of the

small GTPase Rap1.[53,54] Rasip1-null mutant mice have severely hampered early vascular development; they show edema formation and their vascular lumens do not form properly. This is a consequence of a failure of angioblasts to adhere to ECM and to maintain cell–cell adhesions.[54] Depletion of Arhgap29 from human endothelial cells by siRNAs increased RhoA-ROCK-mediated actomyosin activity and lowered Cdc42 and Rac1 activities. As a consequence, the organization of the actin cytoskeleton and integrin-based adhesions, particularly those based on β1 integrins,[54] as well as adherens junctions, were strongly perturbed.[53] However, loss of Arhgap29 did not induce an increase in biochemically detectable RhoA activity in cell lysates, which might suggest that Arhgap29 is important for local or temporal inhibition of RhoA. In summary, the strong expression of Arhgap29 in endothelial cells is thus important to locally inhibit RhoA-dependent signaling to maintain integrin- and cadherin-based adhesions during vascular development.

Arhgap18

The highly expressed Arhgap18 (21-fold higher than in other tissues) is a RhoA-specific GAP that was recently found to be expressed in HUVECs.[55,56] Arhgap18 suppresses RhoA-dependent actin remodeling induced by integrin-mediated adhesion.[55] This RhoGAP was described to protect endothelial monolayer integrity during inflammatory responses. Moreover, overexpression of Arhgap18 perturbed HUVEC tube formation on matrigel, presumably by inhibiting RhoA activity.[56] To date no other relevant information on Arhgap18 in the context of vascular adhesion is published.

ARAP3

We find ARAP3 highly expressed in human endothelium, over 16-fold compared with other tissue. ARAP3 was recently also reported to be strongly endothelial enriched in mouse vascular development.[57] ARAP3 is an effector of PI3K and has GAP activity for both RhoA and Arf6 GTPases.[58] The GAP function of ARAP3 is important for actin cytoskeleton organization and focal adhesion distribution, and siRNA-mediated loss of expression showed that ARAP3 is required for platelet-derived growth factor (PDGF)-induced membrane ruffling.[59] ARAP3 is also expressed in other cell types, including leukocytes, regulating integrin-dependent adhesion through inhibiting RhoA activity.[60-62] Most importantly, mouse studies based on deficiency of ARAP3 or transgenic expression of mutated ARAP3 showed that its expression in endothelial cells is crucial for angiogenesis during development, and depends on phosphoinositide 3-kinase (PI3K)-mediated recruitment to the plasma membrane.[63] ARAP3 was recently identified as a strongly downregulated gene in mouse and zebrafish models for lymphatic vascular disorders, and shown to be crucial for lymphangiogenesis by mediating the response of lymphatic endothelial cells to VEGF-C.[64] For future research, it would be of interest to study to what extent these defects in angiogenesis are depending on the regulation of either Rho or Arf6 GTPases downstream of ARAP3.

RacGAP1 and the Rho GEF ECT2

The expression of RacGAP1, also known as CYK4 and MgcRacGAP, is 10-fold higher in HUVECs compared with other cells, and is best known for its Rac-suppressive function as part of the centralspindlin complex that stimulates actomyosin-driven contraction at the cleavage furrow during the final steps of cytokinesis. This occurs in conjunction with recruitment of the RhoA GEF ECT2,[65-68] the expression of which is also high in HUVECs (see **Table 2**). Besides their role in cytokinesis, these Rho GTPase regulators have important extra-mitotic functions. The centralspindlin complex interacts with α-catenin at adherens junctions, thereby recruiting ECT2, to support local RhoA-driven myosin activation and cell–cell junction stabilization in highly polarized epithelial cells.[69] Moreover, the inhibition of Rac1 activity by RacGAP1 is important to control cell adhesion and spreading,[70] and recruitment of RacGAP1 by the fibronectin-binding integrin α5β1 at protruding membranes greatly enhances the directionality of migration and invasion of tumor cells.[71,72] Thus far, not much evidence for endothelial RacGAP1 and ECT2 in vascular biology has been published.

DLC1

The RhoGAP DLC1 (deleted in liver cancer-1; 7.5-fold upregulated in HUVECs) is crucial for embryonic development.[73] DLC1 is described as a tumor suppressor gene, since it is lost in a variety of human cancers. The DLC1 protein shows GAP activity toward RhoA, B, C, and Cdc42 GTPases.[74] This GAP activity is required for its regulation of integrin-dependent adhesion and migration, as well as cytoskeletal organization in epithelial cell types. Recruitment of DLC1 to integrin-based adhesion depends on its interaction with tensin proteins[75,76] or through interactions with talin and focal adhesion kinase (FAK).[77] In addition, an interaction through α-catenin recruits DLC1 to adherens junctions, which stabilizes the cadherin complex in a GAP-dependent manner.[78] Interestingly, we find that the closely related DLC2 isoform (also known as STARD13) is clearly expressed in HUVECs (~2.5-fold higher expressed; see **Table S1**) and mouse studies have previously shown that the expression of DLC2 suppresses experimentally induced angiogenesis.[79] The authors further showed that siRNA-mediated loss of DLC2 in HUVECs perturbed adhesion and migration on fibronectin or matrigel in a RhoA-dependent manner. Although there is no experimental evidence for a function of DLC1 in endothelial cells, the fact that the DLC2 isoform does regulate endothelial adhesion, and the finding that DLC1 is highly expressed in HUVECs, suggests that DLC isoforms are important for endothelial cell adhesion.

Arhgap17 and the RhoA GEF Syx

Arhgap17 is also known as Rich1 or Nadrin and is ~7 times upregulated in HUVECs. This GAP regulates Cdc42 and Rac1[80] and contains an N-Bar domain that targets the protein to convex-curved membranes during lamellipodial protrusion-retraction cycles.[81] Arhgap17 associates with the scaffolding protein angiomotin (Amot) at tight junctional complexes to control cell polarity and junction integrity in a GAP-dependent manner.[82,83] The regulation of Rho GTPases by Arhgap17 at cell–cell junctions is potentially important during angiogenesis, since Amot and its isoform AmotL1 regulate the migration of tip cells and stability of cell–cell junctions in stalk cells during embryonic sprouting angiogenesis.[84,85] Interestingly, Amot family proteins also locally activate RhoA at endothelial cell protrusions during sprouting

angiogenesis, through recruitment of the RhoA GEF Plekhg5 (better known as Syx),[86,87] which is also expressed in HUVECs (**Table S1**). Vascular growth factor-induced signaling determines the localization and function of Syx; VEGF promotes the removal of Syx from cell–cell junctions, thereby inducing junction disassembly and endothelial permeability. By contrast, signaling induced by the vascular stabilizer angiopoietin-1 maintains Syx at cell–cell junctions to promote monolayer integrity via the RhoA effector Dia.[88] These endothelial functions of Syx appear to be important for sprouting angiogenesis, because Syx-deficient zebrafish and mice display defects in their vascular networks and integrity.[87,88]

Arhgap31

Arhgap31, also known as CdGAP, is a GAP for Cdc42 and Rac1.[89] CdGAP localizes at focal adhesions and its activity, which is dependent on integrin-mediated adhesion, controls directional membrane protrusions, cell migration, and invasion.[90,91] In epithelial cells, the activity of CdGAP is inhibited by ERK-mediated phosphorylation, which increases Cdc42 activity at tight junctions and induces their disassembly.[92] Although there is no experimental data on a role for CdGAP in endothelial cells, the Arhgap31 gene shows a genetic association with increased risk for coronary artery disease.[93]

Ralbp1

Ralbp1 is an effector of R-Ras and Ral GTPases that contains a GAP-like domain, which inhibits activity of Cdc42 and Rac1.[94-96] The GAP domain is required for its interaction with R-Ras, for Ras-mediated Rac1 activation, and cell spreading.[97] However, this occurs independently of Ralbp1 enzymatic GAP activity, but depends on recruitment and signaling via R-Ras. Although it is unclear if the GAP function of Ralbp1 controls cell adhesion, the expression of this multifunctional protein in endothelial cells is involved in tumor-associated angiogenesis in vivo.[98] Moreover, auto-antibodies directed against Ralbp1 were detected in sera of patients that suffer from immune-mediated endothelial dysfunction, suggesting that Ralbp1 is associated with cardiovascular disease.[99] To understand the role of Ralbp1 in endothelial cells, it would be interesting to investigate which specific adhesion events are regulated by Ralbp1 during angiogenesis.

Other highly expressed Rho GAPs

Myo9b is a GAP for RhoA that is recruited to regions of actin polymerization at membrane protrusions, depending on the activity of its own myosin motor domain. In addition, Myo9b is required for directional migration.[100,101] Myo9b is crucial for tight junction formation and intestinal epithelial barrier formation,[102] but no role in endothelial cells has been reported to date. Arhgap19 was recently identified as one of the repressed targets of miR-24,[103] a microRNA enriched in cardiac endothelial cells after ischemia that inhibits angiogenesis in mouse models of myocardial infarction.[104] Suppressing Arhgap19 expression enhanced keratinocyte differentiation and reorganizes the actin cytoskeleton, cell–matrix adhesions, and cell–cell junctions.[103] Nothing is known about its putative role in endothelial cells. In addition, we find several other endothelial-enriched Rho GAPs, like DEPDC1, DEPDC1b, Arhgap11a, and Arhgap28, of which we know very little in the context of cell adhesion and vascular biology.

Non-enriched Rho GAPs with endothelial functions

Because GAPs and GEFs are not only regulated by transcription, we summarized the function of important non-enriched (in HUVECs) Rho regulators in **Table 3** based on literature, and we overview the results from a Gene Ontology-based functional annotation search of all Rho regulators in **Table S2**. The Rho GAP expression profile of HUVECs shows for instance that p190RhoGAP (Arhgap35), an inhibitor of RhoA, is not differently expressed in endothelial cells compared with other cell types (**Table S1**). However, the expression of p190RhoGAP in endothelial cells is crucial for angiopoietin-1-induced cell–cell adhesion and endothelial barrier function, as it mediates angiopoietin-1-induced antagonistic signaling of active Rac1 toward RhoA.[40,105] Also many cytokine-dependent signaling pathways that temporary perturb the endothelial barrier function require p190RhoGAP to suppress RhoA activity at later phases, and to recover endothelial monolayer integrity.[106-108] In addition, p190RhoGAP activity toward RhoA was shown to be required for semaphorin-induced chemorepulsion of HUVECs.[109] Expression of p190RhoGAP is also needed to control balancing of transcription factors that govern retinal neovascularization.[110] Thus, it is clear that p190RhoGAP and six other GAPs (see **Table 3**) regulate endothelial functions. This emphasizes that the importance of endothelial Rho GAPs or GEFs is not only determined by their level of expression, but also strongly relies on local growth factor- or cytokine-induced changes in enzymatic activity.

The Roles of Rho GTPase GEFs in Endothelium

Highly expressed GEFs

NME1

Based on our analysis, NME1, also known as nucleoside diphosphate kinase 1 or NM23-H1, is the most abundantly expression-enriched "GEF" in HUVECs (21-fold higher, **Table 2**). In epithelial cell types, NME1 is shown to control integrin-mediated adhesion and migration/invasion,[111] and regulation of its expression is associated with many tumor types. In solid cancer, NME1 usually functions as a tumor suppressor,[112] but in the pediatric solid cancer, neuroblastoma high levels of NME1 correlate with a poor prognosis.[113] There is no direct proof that NME1 can exchange guanine nucleotides on GTPases, but it has been described that NME1 regulates other GEFs, such as Dbl, that in turn activate Cdc42.[114,115] Moreover, in epithelial cells, NME1 regulates ARF6-mediated endocytosis of cadherin-based cell–cell junctions, via inhibition of Rac1.[116] In neuronal cells, NME1 interacts with α-catenin and suppresses Rac1-GTP at cell–cell junctions by inactivating the GEF Tiam1.[117] Thus, NME1 is an important Rho GTPase regulator, as a GEF or as a scaffolding protein, but whether NME1 is involved in endothelial adhesion remains to be determined.

FGD5 and FGD6

Two other highly upregulated GEFs in HUVECs are FGD5, 16-fold, and FGD6, 7-fold (**Table 2**). Interestingly, FGD5, among other proteins, is transcriptionally regulated during vascular development in zebrafish by the ETS-family transcription factor Etv2, suggesting that FGD5 is involved in vascular development.[52] Moreover, FGD5 is specifically expressed in

endothelial cells, and siRNA-mediated knockdown of FGD5 in HUVECs showed that this GEF is required for VEGF-induced Cdc42 activation, endothelial cell migration, and monolayer integrity.[118] Very recently, it was demonstrated that Rap1 activates FGD5 at endothelial cell–cell junctions, increasing local Cdc42 activity that signals to myotonic dystrophy kinase-related Cdc42-binding kinase (MRCK), which stabilizes the actin network at tightening junctions.[119] The local regulation of endothelial cell–matrix and cell–cell adhesion by FGD5 appears important during angiogenesis, as evidenced by the finding that FGD5 inhibits neo-vascularization in mice in a Cdc42-dependent manner.[120] This GEF may be important for other endothelial processes that depend on Cdc42-mediated adhesion signaling, such as polarization and lumen formation during tubulogenesis. To date, the function of its family member FGD6, which is highly expressed in HUVECs, is unknown.

DNMBP/Tuba

The upregulated GEF DNMBP, also known as Tuba, specifically exchanges GTP on Cdc42, but not on Rac1 or RhoA, and recruits the GTPase effectors N-WASP and Ena/VASP to remodel the actin cytoskeleton.[121] Tuba itself is recruited to cell–cell adhesions by ZO-1, and its actin remodeling function is important to organize the association of the F-actin cytoskeleton to adherens junctions at the apical part of epithelial monolayers that are under high mechanical tension.[122] The GEF activity of Tuba at cell–cell junctions is crucial for polarization during epithelial 3D cyst formation,[123-125] a process that closely relates to lumen formation during angiogenesis and vasculogenesis. Whether Tuba regulates cell adhesion in endothelial cells is still unknown.

Rgnef/p190RhoGEF

Rgnef, also known as p190RhoGEF, is a GEF that interacts with Rho, but not with Rac or Cdc42,[126] and controls adhesion-induced RhoA activation by fibronectin-binding integrins.[127] Part of this adhesion-induced GTPase signaling depends on a scaffolding function of Rgnef that promotes FAK activation, whereas the GEF activity of Rgnef toward Rho is especially important to activate another focal adhesion protein, paxillin, downstream of fibronectin–integrin binding.[128] Interestingly, Rgnef recruitment to the leading edge of migrating tumor cells corresponds with local activation of RhoC, which sustains directionality of protrusion activity by remodeling of the actin cytoskeleton.[129] Because Rgnef is also highly expressed in HUVECs, we speculate that this GEF might control endothelial cell adhesion to the vascular ECM.

DOCK family

Members of the DOCK family, DOCK4, 6, and 9, are found to be highly expressed in HUVECs. However, no literature on the role of these DOCKs in endothelial cells is available. DOCK4 can activate Rac1 and is involved in neurite differentiation and extension.[130] DOCK6 has dual specificity for Rac1 and Cdc42, whereas DOCK9 can only activate Cdc42, both GEFs are involved in neuronal development.[131-133] Future research will have to reveal the possible functions of these GEFs in the vasculature.

Arhgef15

Interestingly, two recent studies indicate that the novel GEF Arhgef15 (also known as Ephexin5 or Vsm-RhoGEF) is an endothelial-enriched gene during mouse vascular development. By studying Arhgef15-null mutant mice, both investigations demonstrate that this GEF is required for vessel stabilization during retinal vascularization as it mediates signaling from VEGF towards Cdc42.[57,134]

Arhgef7/β-Pix/COOL-1

According to our analysis, Arhgef7 is highly expressed in HUVECs. Arhgef7, better known as β-p21-activated kinase (PAK)-interacting exchange factor (β-Pix) or COOL-1, regulates Cdc42 and Rac1 GTPases at membrane protrusions.[135] The abundance of β-Pix at focal adhesions decreases when myosin-dependent tension rises, and β-Pix was shown to negatively affect actomyosin contractility-mediated adhesion maturation, whereas it is important for Rac1 activation at nascent adhesions at the front of membrane protrusions that are associated with low myosin activity.[136] In addition to its GEF function, β-Pix serves to target Rac1 to these membrane ruffles.[137] Interestingly, β-pix localizes at endothelial cell–cell junctions, and the interaction of β-Pix with the GTPase effector PAK is needed for VEGF-induced permeability.[138] Many other reports imply a role for β-Pix in adhesion and membrane dynamics in the context of cell migration (reviewed in ref. 139), suggesting that activation of Cdc42 and Rac1 by β-Pix might also be relevant for migratory behavior of endothelial cells for instance during angiogenesis.

Vav family

The Vav family consists of three members, of whom Vav-2 is highly expressed in HUVECs (7-fold upregulated). Vav-1 is strictly expressed in hematopoietic cells, whereas Vav-3 is ubiquitously expressed, including the endothelium. The Vav GEFs can exchange GDP for GTP on several Rho-GTPases, including Rac1, RhoA, RhoG, and Cdc42.[37,140] Seye and colleagues were the first to demonstrate Vav-2 expression in endothelial cells, and they reported that activation of the VEGF receptor 2 (VEGFR-2), downstream of a P2Y2 nucleotide receptor, results in phosphorylation of Vav-2 and corresponding activation of RhoA and Rac1.[141] Other labs subsequently confirmed that VEGFR-2 promotes Src-dependent phosphorylation of Vav-2 and activates Rac1.[142,143] VEGF-induced phosphorylation of Vav-2 directly affects the affinity of Vav-2 for a nucleotide-free mutant of Rac1, which proves that its GEF activity is enhanced.[142,144] Activation of Pak by Rac1-GTP, in turn, results in phosphorylation of residues in the cytoplasmic domain of VE-cadherin, which accounts for its internalization, and thereby, enhances endothelial permeability.[143] Interestingly, mechanosensing of endothelial cells in response to fluid shear flow rapidly enhances Rac1 activation, which depends on phosphorylation of Vav-2.[145] Vav-2 phosphorylation was also increased when endothelial cells were plated on stiff ECM surfaces (21.5 kPa) compared with softer ones (1.72 kPa), which correlated in this study with enhanced activation of RhoA.[146] Moreover, Vav-2 and Vav-3 interact with the EphA2 receptor, and studies using Vav-2/Vav-3-null mutant mice show that these GEFs are crucial mediators of Ephrin-induced Rac1 activation, endothelial cell migration, and angiogenesis,[147] as well as tumor-associated angiogenesis.[148] Thus, the expression of Vav GEFs, Vav-2 in particular, is important to regulate GTPase signaling that controls cell adhesion during angiogenesis.

ITSN (Intersectin)

Both ITSN-1 and ITSN-2 are expressed in HUVECs (**Table 2**; **Table S1**). Intersectins are expressed as long (l) or short (s) isoforms, associate with endocytosis-related components, and act as GEF for Cdc42.[149] Expression of ITSN-1 is an important pro-survival signal for endothelial cells,[150] whereas reducing expression of this protein in vivo perturbs vascular integrity and induces lung injury.[151] Whether these phenomena relate to the GEF function of ITSN-1 is unclear. The GEF function of ITSN-2L was shown to be required for Cdc42 activation and actin remodeling in support of caveolae-induced endocytosis.[152]

Trio

The GEF Trio was originally identified as a binding partner of the transmembrane tyrosine phosphatase LAR.[153] Since it contains three domains with putative enzymatic activity, it was named Trio. Trio is a large, 350 kDa protein that encompasses two DH-PH GEF units with different specificities. The N-terminal DH-PH cassette mediates GDP for GTP exchange on Rac1 and RhoG, whereas the C-terminal DH-PH cassette activates RhoA.[153-155] In addition, Trio contains a serine kinase domain and spectrin repeats that may further contribute to its function.[156] For instance, the kinase domain interacts with FAK, and Trio may thereby regulate focal adhesion dynamics at membrane protrusions.[157] Trio was shown to interact with E-cadherin, and its GEF activity regulates Rac1 activity at epithelial adherens junctions.[158] The interaction of Trio with the actin-binding protein filamin is important to support membrane protrusion activity.[159] In endothelial cells, Trio is recruited to the intercellular adhesion molecule-1 (ICAM-1) upon leukocyte binding. Subsequently, the first GEF domain of Trio becomes activated and induces formation of so-called docking structures around adherent leukocytes, which are crucial for leukocyte transmigration.[160] In a complementary study, we found that expression of Trio is upregulated by the inflammatory cytokine TNFα, and that Trio protein expression in endothelial cells of patients suffering from severe rheumatoid arthritis is higher than in patients with milder arthritis.[161] The increased endothelial Trio-mediated Rac1 activity upregulates vascular cell adhesion molecule-1 (VCAM-1) expression and this further contributes to an inflamed endothelial phenotype. The potential importance of Trio for endothelial cell–matrix and cell–cell adhesion has not been reported in detail yet.

Arhgef12/LARG

Arhgef12, better known as Leukemia-associated Rho GEF (LARG), is a specific GEF for Rho, but not for Rac or Cdc42.[162] LARG is crucial for RhoA signaling downstream of Gαq in mouse fibroblasts.[163] LARG is also particularly important, in conjunction with the GEF-H1, to transmit mechanical force-induced integrin signaling toward RhoA that mediates cytoskeletal reinforcement.[164] Furthermore, LARG interacts with plexin-B1 in endothelial cells, which underlies semaphorin 4D-induced Rho signaling in control of endothelial angiogenic behavior.[165] Signaling downstream of the sphingosine-1-phosphate receptor 2, LARG inhibits sprouting of HUVEC spheroids in 3D collagen matrices; siRNA-mediated loss of LARG reduces RhoC activation.[166] Thus, LARG plays distinct roles in endothelial cells that are relevant in the context of Rho GTPase signaling and adhesion. Moreover, expression of LARG in vascular smooth muscle cells is a crucial element of G-protein-mediated contractile signaling that underlies vascular remodeling and cardiovascular disease.[167,168]

Other highly expressed Rho GEFs

Breakpoint cluster region (Bcr), a protein that contains both GEF and GAP domains, is highly expressed in HUVECs, according to our analysis, and is described as an upstream regulator of RhoA activity, stress fibers, and focal adhesion formation in keratinocytes.[169] In addition, Bcr has GAP activity toward Rac, Cdc42, and RhoA GTPases, which indicates that this Rho regulator is multifunctional.[170] Recent data suggest that the neurological disorder-associated GEF PLEKHG4 activates Rac1, RhoA, and Cdc42, and thereby, organizes the actin cytoskeleton and membrane protrusions.[171] The GEF amyotrophic lateral sclerosis 2 (ALS2), also known as Alsin, is present within neuron growth cones and activates Rac1 to promote neurite outgrowth.[172] In addition, ALS2 is reported to activate the GTPase Rab5 and mutations in this GEF are thought to account for motor neuron diseases.[173] So far, no direct evidence for a role of Bcr, PLEKHG4, or ALS2 in endothelial cells is available. The potential role for vascular biology of three other Rho GEFs that are enriched in HUVECs, Arhgef10, PLEKHG1, and FARP1, is completely unknown.

Non-enriched Rho GEFs with endothelial functions

A summary of the function of all non-enriched (in HUVECs) Rho GEFs that are described to function in endothelial cells can be found in **Table 3**. Here, we briefly discuss the role of a few important Rho GEFs from this list.

Arhgef1/p115-RhoGEF

The GEF p115-RhoGEF, through its phosphorylation by protein kinase C α (PKCα), is responsible for thrombin-induced RhoA activation and downstream signaling toward the actomyosin cytoskeleton promoting endothelial permeability.[174-176] Similarly, p115-RhoGEF mediates lipopolysaccharide (LPS)-induced RhoA activation and permeability in brain endothelial cells.[177] Others recently implicated p115-RhoGEF in crosstalk between endothelial integrin and cadherin adhesions, as conditional deletion of FAK in mouse endothelium enhanced the interaction of p115-RhoGEF with RhoA, reduced junctional integrity, and induced lung injury.[178] In summary, current literature indicates that p115-RhoGEF regulates agonist-induced destabilization of endothelial cell–cell junctions.

Arhgef17/ TEM4

Recently, the function of the actin-binding GEF TEM4, also known as Arhgef17, was characterized in biochemical experiments that show its activity toward RhoA, B, and C.[179] In endothelial cells, TEM4 appears critical for organization of the actin cytoskeleton and integrin-based adhesions at membrane protrusions of migrating cells.[180] This work was followed up by Ngok and co-workers, who showed that TEM4 associates with the cadherin complex at endothelial cell–cell junctions in confluent monolayers, independent of F-actin binding, whereas TEM4 remains associated with the F-actin cytoskeleton in cells cultured at low density.[181] The authors conclude that TEM4

expression in HUVECs is needed for efficient adherens junction formation, tube formation on matrigel, and endothelial barrier function.[181]

GEF-H1 (Arhgef2)

GEF-H1 is a RhoA-specific exchange factor that is regulated by microtubule binding, and couples microtubule dynamics to Rho-GTPase signaling in a variety of cellular events.[182] In endothelial cells, GEF-H1 is described to regulate agonist-induced endothelial cell permeability.[183] Moreover, the presence of GEF-H1 is crucial for the mechanotransductory response of pulmonary arterial cells to cyclic stretching.[184] The importance of GEF-H1 in endothelial menchanotransduction can be explained by the finding that GEF-H1, together with the GEF LARG, is required for cytoskeletal reinforcement induced by mechanical tension on fibronectin-binding integrins.[164] Increased stiffening of the vascular ECM occurs during aging, suggesting that integrin-dependent regulation of GEF-H1 activity may underlie the increased permeability and inflammatory phenotype of endothelial monolayers in stiffening vessels during atherosclerosis development.

Arhgef26/ SGEF

Arhgef26, or SH3-GEF (SGEF), is widely expressed and specifically activates RhoG, but not Rac1 or RhoA.[185] SGEF is strongly implicated in the induction of endothelial docking structures that are required for transendothelial migration of leukocytes.[186] SGEF-null mutant mice appear healthy and fertile, and its deficiency in combination with a lack of ApoE results in much smaller, Western diet-induced atherosclerotic lesions.[187] This result could be attributed to a reduced capacity of aortic endothelial cells to form docking structures leading to a reduced number of leukocytes accumulating at early atherosclerotic lesions. These findings suggest that SGEF plays an important role in the heterotypic interaction between endothelial cells and leukocytes during vascular inflammation.

ELMO/DOCK180

In endothelial cells, DOCK180 (also known as DOCK1), together with its adaptor protein Engulfment-and-celL-MOtility (ELMO) is required for endothelial cells to adapt to changes in shear flow and Rac1-dependent polarized membrane protrusions.[188] This function of the atypical Rac1 GEF complex ELMO/DOCK180 appears important for endothelial cell migration during development, as indicated by in vivo knockout studies that show cardiovascular defects upon functional deletion of DOCK180 or ELMO.[189,190]

P-Rex family

Both phosphatidylinositol (3,4,5)-trisphosphate-dependent Rac exchanger (P-Rex)1 and P-Rex2 are expressed in HUVECs. Moreover, expression of the P-Rex1 and P-Rex2b isoforms in endothelial cells mediate stromal cell-derived factor 1 (SDF-1)-induced Rac1 signaling that controls cell adhesion and migration.[191,192] P-Rex1 was recently shown to act downstream of TNFα-induced Rac1 signaling controlling cell–cell junctions, as P-Rex-null mutant mice display enhanced lung permeability defects when challenged with TNFα or LPS.[193] P-Rex1 expression is also required for Rac1-dependent secretion of Weibel-Palade bodies, endothelial storage vesicles that contain von Willebrand factor.[194]

Tiam1

The role of Tiam1 is extensively studied in epithelial cells, where it controls cell–matrix and cell–cell adhesion through its GEF and/or scaffolding function for Rac1.[195] Mice deficient for Tiam1 are healthy and develop a normal vasculature.[196] Expression of Tiam1 or its close homolog Tiam2 in HUVECs was not clearly detectable on mRNA level (**Table S1**). However, studies in VE-cadherin-null mutant endothelial cells show that the presence of VE-cadherin does control junctional localization of Tiam1, concomitant with persistent Rac1 activation.[197] Also, in pulmonary endothelial cells, OxPAPC (a barrier protective agent) induced the translocation of Tiam1 to cell–cell junctions, where it supports OxPAPC-induced barrier enhancement.[198] Most likely, the stabilizing effect of Tiam1 on cell–cell junctions depends on cortical F-actin rearrangements.[199] In microvascular endothelial cells, it was recently shown that the localization of Tiam1 at cell–cell junctions, as well as its barrier protective function, depends on the production of nitric oxide, an important intermediate for vascular permeability factors.[200] In contrast, during TNFα-induced permeability of HUVEC monolayers, the PI3K p110α subunit was shown to promote the association of Tiam1 with the VE-cadherin complex, which in this case is thought to destabilize cell–cell junctions.[201] Lastly, Tiam1 was recently described to be part of a polarity complex that locally recruits and activates Rac1 in response to fluid shear flow.[145] Taken together, these studies demonstrate that, despite its low mRNA expression in HUVECs, Tiam1 does regulate endothelial cell–cell adhesion.

Other potentially relevant endothelial Rho GEFs

Although we do not find Arhgef4 (ASEF) expression in HUVECs, its endothelial expression in mice was shown to regulate cell migration in response to the angiogenic factors bFGF and VEGF, and Arhgef4 is critical for experimental-induced angiogenesis.[202] This illustrates that Rho regulators may be differentially expressed between human and mouse, or reflects differences between endothelial cells derived from distinct vascular beds. Several other GEFs are described to regulate endothelial functions, see **Table 3** for further details and references.

Conclusions and Perspectives

The regulation of Rho GTPase activity by GAPs and GEFs at the plasma membrane enables the coordination of endothelial cell adhesion during vascular development, homeostasis, and disease. In addition to the direct regulation of their activity, Rho GTPases interact with guanine nucleotide dissociation inhibitors (GDIs), regulators that sequester GDP-bound Rho GTPases in the cytoplasm, and thereby, prevent their activation and degradation.[203] Of the Rho GDI family members, only the expression of Arhgdia, known as RhoGDIα, is high in HUVECs (**Table S1**). RhoGDIα is important for many cellular functions: null-mutant mice display multiple organ abnormalities, including increased endothelial permeability and edema in the lungs.[204,205]

Taking together the available evidence on the role of Rho GTPase regulators in endothelial cells, it becomes clear that they all take part in a tightly regulated and highly dynamic signaling network. Depending on the vascular growth factor or on the subcellular localization of GAPs or GEFs, distinct vascular

processes (i.e., barrier function, angiogenesis) are regulated. Context-dependent control of cell–cell adhesion is clearly exemplified by different effects of the angiogenic growth factor VEGF that removes the Rho GEF Syx from cell–cell adhesions, inducing endothelial permeability, whereas the angiostatic factor angiopoietin-1 induces signaling that maintains Syx at cell–cell junctions and stabilizes monolayer integrity. At this moment it is too premature to summarize the specific functions of the many GAPs and GEFs in a coherent model that describes their role in endothelial cell adhesion events, because the available data that deals with local recruitment or upstream regulation of GAPs and GEFs is still limited.

In some occasions, the role of a Rho GTPase in cell adhesion seems even contradictory. For instance, inactivation of Cdc42 by Cdgap at tight junctions in MDCK cells in response to the hepatocyte growth factor (HGF) disassembles cell–cell adhesions,[92] whereas activation of Cdc42 by FGD5 at adherens junctions in HUVECs in response to cyclic adenosine monophosphate (cAMP)-elevating G protein-coupled receptor-induced signaling strengthens cell–cell junctions and enhances monolayer integrity.[119] There are possible explanations for such differences that relate to the cellular architecture; e.g., adherens and tight junction distribution in endothelial cells is different from the polarized junctional build up in epithelial cells. Another explanation might be that parallel-activated signaling pathways are completely different; in this example, HGF-induced changes in cell–cell adhesion are compared with more rapid events induced by cAMP signaling. A similar mechanism may explain why FGD5-induced Cdc42 activation is required for cAMP-induced junction strengthening, but also needed for VEGF-induced permeability.[118] To achieve complete understanding of the specific and non-redundant roles of all Rho GAPs and GEFs in endothelial cell adhesion, we rely on challenging future studies that focus on combining the live imaging of spatiotemporal activation of Rho GTPases with local recruitment and activation of GEFs or GAPs in a physiologically relevant, vascular experimental set up.

We highlighted the role of Rho regulators that are highly expressed in HUVECs to indicate which GAPs or GEFs may be important for endothelial cell adhesion. We wish to emphasize that regulation of GAPs and GEFs occurs not only at the level of their expression, but also strongly depends on their localization, upstream regulators, and on protein modifications such as phosphorylation. Another interesting avenue to pursue would be to investigate if the level of expression of certain Rho GAPs or GEFs occurs in arterial or venous endothelial cells specifically, possibly explaining their different permeability properties.[206]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Supplemental Material

Supplemental material may be found here:
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