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A Hypothesis for the Role of RECK in Angiogenesis

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Abstract: Angiogenesis is a key process by which new capillary blood vessels are formed, sustaining the supply of oxygen and other nutrients to the body allowing its growth and wound healing, among others. However, angiogenesis also associates with pathological processes, such us tumor growth. Vascular endothelial cells produce different matrix remodeling enzymes such as matrix metalloproteinases and a-disintegrin and metalloproteinases, which have both positive and negative effects on angiogenesis, regulating the cell environment and signaling. However, little is known about the regulation of the activity of these proteases during vascular development. Reversion-inducing cysteine-rich protein with Kazal motifs (RECK) is a membrane-anchored inhibitor of different matrix metalloproteinases and a-disintegrin and metalloproteinases, being a critical regulator of extracellular matrix remodeling and signaling pathway, particularly Notch, which is critical for the maturation of the growing vessels. *Reck* knockout mice die in utero showing vascular developmental defects and massive hemorrhages. These defects were not observed in knockout mice for secreted-soluble matrix metalloproteinase inhibitors pointing to an exclusive role of RECK in vascular development and maturation since its location at the plasma membrane. Despite the above, the exact role of RECK in this process has not been clarified. This review is focused to summarize the available information on the role of RECK as membrane anchored matrix metalloproteinases and a-disintegrin and metalloproteinases inhibitor, proposing a hypothesis by which RECK play key roles in the physiology and pathophysiology of the angiogenesis processes.

Keywords: RECK, angiogenesis, matrix metalloproteinases, a-disintegrin and metalloproteinase, endothelium.

INTRODUCTION

Angiogenesis is the process by which new capillary blood vessels growth leading to, for example, vascularization of the placenta during implantation [1], embryonic development, organs growth and wound healing [2-4]. However, angiogenesis also associates with pathological processes including tumor angiogenesis, pregnancy diseases, cardiovascular disease and age-related blindness [5-10]. Angiogenesis regards with generation of a new vessel from an existing one, while vasculogenesis is *the novo* formation of a vessel from mesoderm derived endothelial precursor cells [11, 12]. Thus, angiogenesis expand and remodel an existing vascular network promoting its maturation and tissue irrigation [11, 12]. This remodeling process comprises two different mechanisms, *i.e.*, sprouting [13] and intussusceptive angiogenesis [14]. The sprouting angiogenesis is based on activation of quiescent or resting vascular endothelial cells. The endothelial cells migrate from the vessels, proliferate and form the tube-like structure leading to formation of a new vessel in response to proangiogenic signals. This phenomenon is involved in almost every vascularization process occurring in normal or disease tissues [13, 15]. Intussusceptive angiogenesis involves less cell proliferation and corresponds to a division of existing vessels leading to extension of the vessel wall into the lumen to split a single vessel into two new ones. This phenomenon is mainly associated to the formation of hierarchically branched structure in rapidly forming organs, leading to reorganization of existing cells and allowing a rapid increase of the capillary number without demanding new endothelial cells [14]. Both in sprouting and intussuseptive angiogenesis a final remodeling and adjust-

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ment step is required. This comprises a regression or pruning to eliminate excess of vessels and recruitment of pericytes and smooth muscle cells [2]. The latter allows the formation of a new basal membrane surrounding the newly generated vessel [13, 14]. In addition, recruitment of these cell types leads to the generation of survival signals maintaining the homeostasis and quiescence of endothelial cells [13, 14, 16].

Reversion-inducing cysteine-rich protein with Kazal motifs (RECK) is a membrane-anchored inhibitor of different matrix metalloproteinase (MMPs) and is conceived as a critical regulator of the extracellular matrix (ECM) remodeling process [17, 18]. *Reck* knockout mice exhibit vascular developmental defects and massive hemorrhages [18, 19]. These vascular defects are not seen in knockout mice for secreted-soluble MMP inhibitors (TIMPs) [18, 20-22], pointing out to a critical, and perhaps exclusive role of RECK in vascular development and maturation. Vascular endothelial cells synthesize different MMPs with pro- and anti-angiogenesis effects [15, 23-25]. However, little is known about the regulation of the activity of these proteases during vascular development.

In this review we focused on the role of RECK as a potential membrane anchored MMP inhibitor in the physiological and pathological angiogenesis processes. We propose RECK as a key regulator of the endothelial cell behavior in angiogenesis, highlighting the possibility that RECK could be a potential target for therapeutic angiogenesis.

MATRIX METALLOPROTEINASES AND ITS REGULATION

MMPs are zinc/calcium-dependent endopeptidases associated with different processes requiring modification of the extracellular matrix in different biological processes, including angiogenesis, tissue remodeling, embryonic development, cell migration and morphogenesis [26, 27]. MMPs are either secreted to the extracellular medium as soluble MMPs (MMPs 1 to 13 and MMPs 18 to 20) or integrated into the plasma membrane by a transmembrane domain (MMPs 14 to 17). All MMPs catalyze the proteolytic degradation of specific elements of the extracellular matrix [28-30]. The MMPs-dependent extracellular matrix degradation is controlled at different levels, including (1) transcriptional level, where several external stimuli, including cytokines, growth factors and changes in cell-cell and cell-extracellular matrix interactions, regulate the expression and secretion of a variety of MMPs [31, 32], (2) the proteolytic activation of the zymogen, that is, the process by which the inactive MMPs, produced as zymogens are extracellularly activated by other proteinases by removing pro-peptides, leaving them in a full active state [21, 33, 34], and (3) inhibition of the active enzyme, where the catalytic activity of MMPs is under the control of specific MMPs inhibitors, known as tissue inhibitor of metalloproteinases (or TIMPs) and RECK [18]. Lack of the regulation of the expression, secretion or activation of MMPs associates with several pathological processes such as inflammation, cell invasion, renal disease, tumoral progression, metastasis, and cell death [35-37]. Consequently, a better understanding on how MMPs function is regulated is a critical step for a better characterization of the genesis of several pathological processes including abnormal angiogenesis.

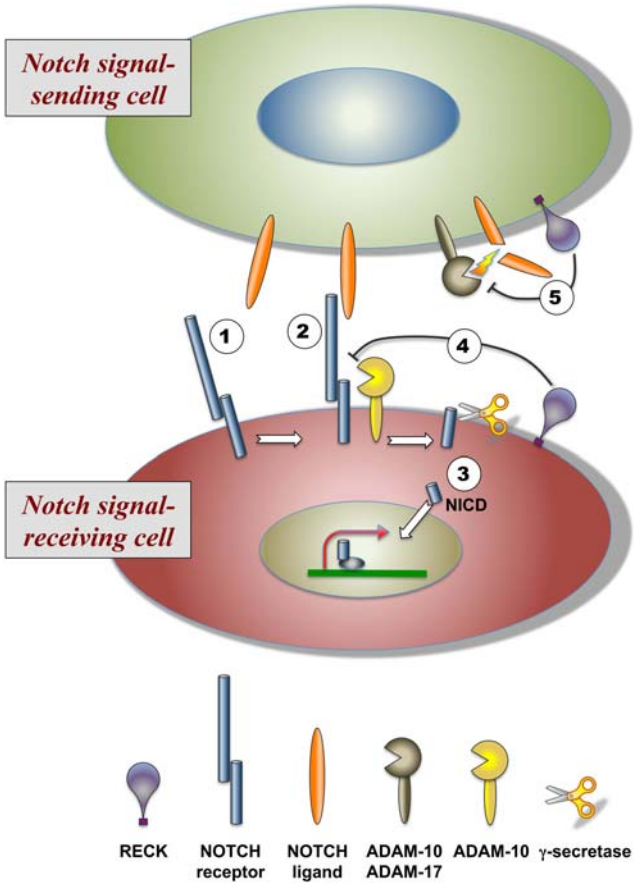

Fig. (1). RECK as modulator of Notch signaling through ADAM-10 and ADAM-17.
The Notch signal-sending cell express Notch ligand, which is available for the Notch receptor at the Notch signal-receiving cell (see step 1). Notch ligand binds to Notch receptor, which then suffers a conformational change leading to the exposure of a region of the extracellular domain that is prone to be cleavaged by ADAM-10 protease (see step 2). This initial cleavage of Notch-bound Notch receptor is followed by subsequent proteolytic cleavages of this protein within the plasma membrane-spanning region by a γ-secretase (see step 3). This phenomenon triggers the Notch signaling through the release of the Notch intracellular domain (NICD), which translocates to the nucleus to regulate the expression of target genes. RECK could negatively regulates the activity of ADAM-10 and ADAM-17 in the Notch signal-receiving cell by inhibiting the first Notch cleavage by ADAM-10 (step 2) leading to subsequent reduced Notch-dependent signaling (see step 4). By the contrary, RECK expressed in the Notch signal-sending cell protects Notch ligands from ADAM-10 and ADAM-17 protease activity, thus potentiating Notch signaling (see step 5). From data in [38, 39, 79, 80].

RECK AS MODULATOR OF MMPs

RECK is a glycosyl-phosphatidylinositol (GPI)-anchored glycoprotein of 971 amino acids acting as a membrane-anchored inhibitor of MMP-14 (also addressed as MT1-MMP), MMP-2, and MMP-9 expression and activation [18]. RECK is also involved in the regulation of Notch signaling through the modulation of the activity of the a-disintegrin and metalloproteinase-10 (ADAM-10) and -17 (ADAM-17) [38, 39]. Fig. (**1**) shows a summary of the role of RECK as regula-

tor of Notch signaling through modulation of ADAM-10 and ADAM-17. RECK was initially identified as a transformation suppressor protein [17, 40, 41]. *RECK* gene is highly conserved with 93% identity for both human and mouse at cDNA level [42]. Structurally, the protein is cysteine-rich (9%) and includes hydrophobic regions in the NH_2- and COOH-terminal domains. The NH_2-terminal operates as a signal peptide, while the COOH-terminal acts as a signal for GPI anchoring. RECK contains three serine protease inhibitor-like (SPI) domains with the first one corresponding to the Kazal motif [42]. These SPI domains are reported to inhibit the protease activity and probably play crucial roles in the inhibition of MMPs [43]. RECK also contains two epidermal growth factor-like repeats, which are essentials for a proper interaction between RECK and MMP9 or MMP2 [43].

RECK is expressed in normal tissues in humans [44]. RECK expression is under regulation by oncogenes, miRNAs, farnesoid X receptor (FXR), myogenic regulatory factors (MyoD and MRF4), interleukin-6 (IL-6), angiotensin II (AngII), transforming growth factor β (TGFβ) and Notch pathway (Table **1**). MMPs activity can induce or enhance

Table 1. Regulation of RECK expression.

Regulator	Cell or tissue	Mechanism	Ref
RAS, v-FOS, c-MYC, v-SRC, v-FMS, v-FES, v-MOS	Mouse fibroblast cell line (NIH 3T3)	Suppression of RECK promoter	[42, 119]
miR-15a	Human neuroblastoma cell lines (GI-LA-N, SK-N-SH, IMR-32 and CLB-P)	mRNA destabilization	[120]
miR-15b	Human fibroblasts (MRC-5), lung adenocarcinoma (A549), mammary adenocarcinoma (MCF-7, MDA-MB-231 and MDA-MB-468), colon adenocarcinoma (SW480 and SW620), fibrosarcoma (HT1080), malignant melanoma (A375) and pancreatic carcinoma (Panc-1) cell lines	mRNA destabilization	[86]
miR-21	Human fibroblasts (MRC-5), human lung adenocarcinoma (A549), human mammary adenocarcinoma (MCF-7, MDA-MB-231 and MDA-MB-468), human colon adenocarcinoma (SW480 and SW620), fibrosarcoma (HT1080), malignant melanoma (A375) and pancreatic carcinoma (Panc-1) cell lines; human glioblastoma tissue; human gastric cancer tissue and cell lines (AGS, SGC7901, MKN45 and MKN28); human osteosarcoma tissue	mRNA destabilization	[86, 121-123]
miR-25	Human gastric cancer tissue and cell lines (SGC7901, MKN28 and MKN45)	mRNA destabilization	[124]
miR-92a	Human non-small cell lung cancer cell lines (H460, H1299 and H358)	mRNA destabilization	[125]
miR-92b	Human non-small cell lung cancer tissue and cell lines (A549, SPC-A1, H1299 and H1650)	mRNA destabilization	[126]
miR-96	Human non-small cell lung cancer tissue (A549, SK-MES-1 and H1299)	mRNA destabilization	[127]
miR-135b	Human hepatocellular carcinoma tissue	mRNA destabilization	[128]
miR-182-5p	Human prostate cancer tissues and cell lines (LNCaP, PC-3 and DU145); human bladder cancer tissue	mRNA destabilization	[129, 130]
miR-182-5p	Human breast tumor tissues and cell lines (MCF-7, MDA-MB-231 and SKBR3)	mRNA destabilization	[131]
miR-221	Human colorectal cancer cell lines (SW620 and LoVo)	mRNA destabilization	[132]
miR-372, miR-373	Colon adenocarcinoma cell lines (SW480 and SW620)	mRNA destabilization	[86]
miR-374b-5p	Human gastric cancer cell line (MGC-803)	mRNA destabilization	[133]
Notch pathway	*Drosophila melanogaster* adult muscle progenitors (AMPs) cells	Upregulated gene expression	[134]
TGF-β	Human non-tumorigenic epithelial cell line (MCF10A)	Upregulated gene expression	[135]
Angiotensin II	Mouse cardiac fibroblasts (primary culture)	Downregulated gene expression	[136]
FXR	Mouse liver tissue	Upregulated gene expression	[137]
Interleukin-6	Human gastric cancer cell lines (SGC7901 and MGC803)	Downregulated gene expression	[138]
MRF4	Mouse embryo fibroblasts (primary culture)	Upregulated gene expression	[139]
MyoD	Mouse embryo fibroblasts (primary culture)	Downregulated gene expression	[139]

RAS, Rat Sarcoma; v-FOS, Viral Feline Osteosarcoma Oncogene; cMYC, Myelocytomatosis Oncogene; v-SRC, Rous Sarcoma Oncogene; c-FMS, McDonough Feline Sarcoma Oncogene; v-FES, Feline Sarcoma Oncogene; v-MOS, Viral Murine Osteosarcoma Oncogene; RECK, Reversion-Inducing-Cysteine-Rich Protein with Kazal Motifs; TGF-β, Tumor Growth Factor β; FXR, Farnesoid X Receptor; MRF4, Myogenic Factor 6; MyoD, Myogenic Differentiation Factor.

tumor survival, invasion and metastasis, through mechanisms involving proteolytic breakdown of tissue barriers to facilitate cellular invasion. The main RECK targets, MMP2, MMP9 and MMP14 exhibit important roles in this process [35] and low expression of RECK associates with different types of cancer [43-48]. In this regard, it has been reported that restoration of RECK expression results in diminishing the mobilization and metastasis of tumor cells [46-48]. *Reck* knock out mice show smaller body size and massive hemorrhage compared with wild type mice. Since *Reck* knock out mutant embryos show unstructured mesenchymal tissues with almost absent collagen arrays and abnormal organogenesis, a role for Reck as a regulator of MMPs-dependent extracellular matrix remodeling in mammalian development is likely [18, 49].

RECK AND ANGIOGENESIS

The role of RECK in angiogenesis was first suggested by studies performing histological examination of $Reck^{-/-}$ mouse embryos, which exhibit several embryonic vascular defects [18]. *RECK* is expressed in human umbilical vein endothelial cells (HUVECs) and a defective expression of RECK causes altered vascular tube formation and cell senescence in this cell type [50]. RECK is also expressed in vascular associated cells, such as vascular smooth muscle cells (vSMC), pericytes and surrounding stromal cells [18, 19, 50], but the role of RECK in these cells has not been addressed [19, 51]. *RECK* expression is found to be reduced in several tumor types resulting in increased tumor growth, enhanced tumor vascularization and metastasis [43, 44, 48, 52, 53]. On the contrary, *RECK* overexpression reduces branching of tumor vessels and increases vessel size leading to insufficient blood supply to tumor cells [18, 42, 54, 55]. These results suggest that RECK is required for physiological angiogenesis in the embryo development; however, *RECK* overexpression represses tumor vascularization. *RECK* expression is induced in HUVECs co-cultured with hypervascular tumor-derived cells [50]. Thus, *RECK* expression seems to be required in endothelial cells, but not in tumor or stromal cells, to promote tumor angiogenesis. The latter is supported by studies showing that *RECK* deletion in tumor-associated endothelial cells causes reduction of tumor growth due to poor vascularization [50, 56, 57].

RECK promotes the formation of the vascular network during human placenta development [19, 51]. Downregulation of *Reck* expression in the implantation chamber results in defects in the formation and organization of new blood vessels in the developing mice placenta [19]. These alterations were similar to those in the vasculature of $Reck^{-/-}$ mice embryos [18, 19]. The vascular network formation was found arrested at the stage of primary capillary plexus, indicating that angiogenesis rather than vasculogenesis is altered [18, 19]. Some studies have shown that RECK is required at later stages of development, where sprouting angiogenesis is prominent [19, 58]. As a working hypothesis we speculate on the likely cell and molecular events associated with sprouting angiogenesis (Fig. **2**), highlighting the potential processes that may involve RECK in this phenomenon.

RECK AS MMPs REGULATOR IN ANGIOGENESIS

The first step in sprouting angiogenesis is the MMP-dependent proteolytic remodeling of the common basement membrane that surrounds the epithelial and mural cells [15, 16], allowing the migration of the selected endothelial cell, the 'tip cell', which lead and direct the formation of the nascent branch, formed by proliferating endothelial cells, known as the 'stalk cells' [13, 15]. MMP activity also associates with the release of several pro-angiogenic growth factors, including vascular endothelial growth factor, hepatocyte growth factor and platelet-derived growth factor from extracellular matrix reservoirs [2, 13, 59]. Under resting conditions endothelial cells express low level of active MMPs, which increases when the angiogenic process is triggered [13]. MT1-MMP, MMP-2 and MMP-9 had been associated with sprouting angiogenesis [13, 60]. The role of other proteases in angiogenesis, both soluble and membrane MMPs, the cell-bound u-PA/plasmin and cathepsins are extensively summarized in excellent already available reviews [61-63]. MMP-2 and MMP-9 have the highest enzymatic activity against type-IV collagen, the main constituent of basement membrane, being essentials in the first step of matrix remodeling [13, 15, 64]. MMP-9 is also generated by macrophages, neutrophils and mast cells [65-67]. It is mainly associated with release of VEGF and other pro-angiogenic factors from the extracellular matrix reservoirs, triggering the angiogenic switch. Inhibition of MMP-9 activity results in blockage of the first step of angiogenesis, suggesting this proteinase as a key component of the angiogenic switch [59]. MMP-2 is constitutively secreted in healthy tissues [68] and associates with endothelial cell migration and angiogenesis [64]. Increased activity of MMP-2 and MT1-MMP associate with sprouting and organization of endothelial cells into chord-like structures [13, 69, 70]. MT1-MMP is involved in pericellular proteolysis [71], being crucial for cell migration and directional matrix degradation in type-I collagen [72]. Its expression is tightly controlled in endothelial cells, induced in response to hepatocyte growth factor, vascular endothelial growth factor and tumor necrosis factor alpha, meanwhile angiopietin-1/Tie-2 reduce its expression [15, 72, 73].

MMPs could also be anti-angiogenic. Proteolytic subproducts derived from extracellular matrix proteolysis by MMPs could act as anti-angiogenic factors, including the release of angiogenic inhibitors such as angiostatin [15]. Thus, localization, expression and activity of specific MMPs must be finely controlled. RECK could play this physiological function, role that becomes evident by the impact on vascular development in the RECK-/- mice [18, 54]. The role of TIMPs in the control of MMPs in the angiogenesis process has been reported [74, 75]. Lack of TIMPs in mice show only mild vascular defects [20-22], compared with those in *Reck* null mice [18, 19]. Since RECK is the only known MMP inhibitor anchored to the plasma membrane, it is likely that this molecule will exert a more precise control than soluble TIMPs at the cell boundary [17, 42, 76]. Considering that RECK acts as inhibitor of the three main angiogenic MMPs [18], the required control over different MMPs by RECK at the endothelial cell surface boundary could be favoring a physiological angiogenesis.

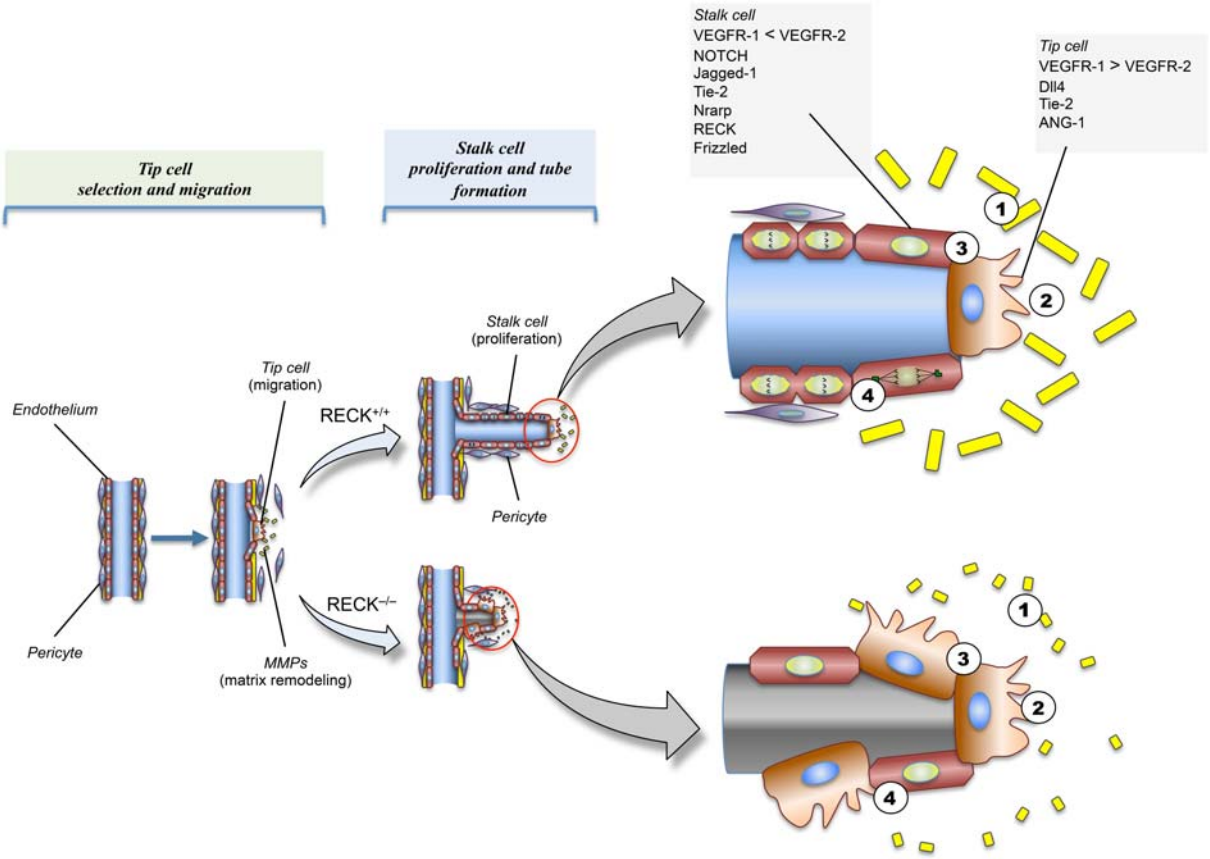

Fig. (2). Working hypothesis for a potential role of RECK in sprouting angiogenesis
Pro-angiogenic growth factors released from tissues requiring neovascularization, stimulate quiescent endothelial cells. One of the endothelial cells of the vascular endothelium is selected as the pioneer cell, *i.e.*, the *Tip cell*, which directs the migration of the endothelial cells and the growing branch. In cells expressing RECK ($RECK^{+/+}$), to leave and migrate away, the tip cell requires the surrounding basal lamina (yellow blocks) be remodeled by matrix-metaloproteases (*MMPs*) and other proteases generated by pericytes (*Pericyte*) and endothelial cells (*Endothelium*) (see step 1). The endothelial cells following the migrating tip cell (at step 2), *i.e.*, the *Stalk cells*, will be the structural cells of the nascent tube. *Tip* and *Stalk cells* express different pro-angiogenic and anti-angiogenic factors as wells as their membrane receptors and regulatory proteins, allowing a proper communication between Tip and Stalk cells promoting the correct formation and maturation of the new vascular branch (see step 3). Subsequently, endothelial cell junctions are stabilized and pericytes are recluted by mature *Stalk cells* (see step 4) leading to formation of the new basal lamina. This process finishes with the fusion of this growing branch with a branch from another vessel. In cells not expressing RECK ($RECK^{-/-}$), the angiogenesis process is impaired showing a retarded maturation of the early vascular network and a phenotype characterized by the generation of several short nascent branches. From data in [2, 13, 15, 18, 19, 50, 53, 110].

As indicated, MT1-MMP is involved in the extracellular matrix degradation required for tip cells migration and vessel extension [15, 71, 77]. However, it is also essential for migrating cells, to count with a substrate to generate the pulling forces required to move forward [78]. Thus transient blockage of MT1-MMP activity until the migrating cell has moved could be feasible. These findings highlights the potential involvement of RECK as inhibitor of MMPs, particularly MT1-MMP, playing a key role in angiogenesis. In addition, this protein also controls the activity of other proteases of the ADAMs family, particularly ADAM-10 and ADAM-17 [38, 39, 79]. These two proteases are involved in ectodomain shedding and activation of specific receptors associated to neovascularization, such as Notch [80]. Reck has been shown to associates with ADAM-10 and ADAM-17 at the cell surface [38, 79] suggesting a role of RECK in the control of Notch pathway (Fig. **1**).

RECK AND ANGIOGENESIS SIGNALING PATHWAYS

Hypoxia

The main physiological and pathological inducer of angiogenesis is hypoxia [81, 82]. When in a given tissue the required oxygen levels fall, the hypoxia response system promotes the activation of the conserved transcription factors hypoxia-inducible factors (HIFs), which control the expression of a variety of angiogenic, metabolic, and cell cycle genes [81]. Accumulation of HIF1α is the primary cellular response to low oxygen (O_2) supply, leading the formation and growth of new blood vessels ensuring supply of O_2 and other nutrients to hypoxic tissues [83, 84]. Since the fast growth in tumor tissue, a hypoxic environment is produced in the tumor womb [85]. In this regard, RECK expression is diminished by the HIF1α/Twist-related protein 1 pathway in

several tumor cell lines [86]. This phenomenon occurs *via* a mechanism involving expression of miRNAs, such as miR-372/373, which act on the 3′ untranslated region (UTR) of RECK mRNA in tumor cells [86]. Moreover, since *RECK* expression in HUVECs is induced by co-culture with hypervascular tumor-derived cells [50] and because hypoxic conditions did not induce *RECK* expression in this cell type in the absence of tumor cells, a tumor cell released factor or a direct contact with tumor cells induce *RECK* transcription in these human fetoplacental endothelial cells [50].

VEGF

VEGF is the main family of growth factors controlling the angiogenic process [87]. VEGF-A or simply VEGF, stimulates angiogenesis through the activation of the transmembrane VEGF receptor 2 (VEGFR-2), which is critical for the selection of tip cells, promoting the branching and extension of new vessels [88]. The VEGFR-1 is found as trans-membrane (VEGFR-1) and soluble (sVEGFR-1) forms. Both VEGFR-1 forms, act as traps or decoys for VEGF, maintaining the ligand in the plasma membrane or in the extracellular matrix, away from VEFGR-2 [89, 90]. Thus, the VEGFR-1 angiogenic role falls mainly in its anti-VEGF activity. This is particularly important for guidance of the growing branch, avoiding the formation of new sprouts from stalk cells which express more VEGFR-1 than VEGFR-2 [2]. VEGF is produced by tissues requiring neovascularization [82, 87], but is also released from the extracellular matrix reservoirs, mainly by MMP-9 activity, which is a key step for triggering the angiogenic process [59]. Elevated expression of VEGF correlates with high MMP-9 expression in a canine lymphoma [53, 91] and tumor mast cells [53, 92]. Thus, it seems plausible that expression of RECK and VEGF could also correlate. RECK expression is downregulated in glioma tumor cells, however many CD34+ endothelial cells inside the tumor tissue co-localize with RECK [56]. Interestingly, *RECK* expression in endothelial cells was shown positively correlated with the malignancy degree in these tumors. Although VEGF expression is associated to both tumor and endothelial cells also showing positive correlation with malignancy degree [56], not significant positive correlation between *VEGF* and *RECK* expression was found [56]. Thus, it is unlikely that VEGF is directly involved with increased *RECK* expression in tumor-associated endothelial cells [56]. The latter was complemented by studies *in vitro* where VEGF failed to induce RECK expression in HUVECs [50]. Thus, VEGF seems no to be involved in RECK positive association with endothelial cells, at least, in tumor angiogenesis.

Angiopoietins

Angiopoietins (ANG) is a family of vascular growth factors playing roles in embryonic and postnatal angiogenesis [93]. In humans, ANG-1 y ANG-2 are relevant pro-angiogenic factors [94]. These molecules signal in a competitive manner trough angiopoietin receptors and tyrosine kinase with immunoglobulin-like and EGF-like domains-2 (TIE-2). ANG-1 is expressed and released by mural cells, maintaining the quiescence of endothelial cells trough activation of TIE-2 [94, 95]. Upon pro-angiogenic stimuli, including VEGF, expression and release of ANG-2 is induced in endothelial cells at the sprouting site, which compete with ANG-1 for TIE-2, promoting the activation of the tip cell and also pericyte detachment, at the sprouting site [2, 96]. As the sprout growths, ANG-1 released by pericytes cause an initial induction of stalk cell proliferation, followed by stabilization of the vessels, potentiation of cell-cell adhesion, increased anti-permeability effect, and promotion of cell survival [94, 97]. RECK expression is induced by ANG-1 in HUVECs [50]. Since RECK expression is required for endothelial cell proliferation and tube formation [50], we speculate on the possibility that RECK expression dependent on ANG-1 is associated with stalk cell proliferation and with formation and stabilization of the new formed vessels.

Notch Signaling

Several lines of evidences indicate that Notch signaling is vital for angiogenesis. [98-102]. Notch signaling maintains tip cells's identity in the growing sprout [2]. Tip cells express the Notch ligand, delta like ligand 4 (Dll4), which is induced by VEGF through VEGFR-2 activation [2, 60, 103]. Dll4 activates the Notch receptor of neighbor stack cells, upregulating VEGFR-1 and downregulating VEGFR-2 [60, 100], which result in reduced stalk cells sensitivity to VEGF avoiding formation of a new vessel branch in an environment enriched in pro-angiogenic signals [104]. Consistent with this, deletion or inhibition of *Dll4* results in excessive, non-productive hyper-branching angiogenesis [105]. As indicated, RECK acts as activator [38, 39] or inhibitor [79] of Notch signaling. Activation of Notch signaling results from RECK inhibition of the ADAM-10–dependent shedding of Notch ligand stabilizing the ligand Dll-1 at ligand expressing cells [38] or *via* a mechanism involving glycerophosphodiester phosphodiesterase 2 (GDE2)–dependent cleavage of the GPI anchor of RECK, thus, releasing it from the plasma membrane and reversing ADAM-10–dependent shedding of the Notch [39]. Thus, pro-angiogenic roles of RECK could be associated with enhanced Dll4-dependent Notch signaling through Dll4 stabilization in tip cells. However, this hypothesis is somehow unlikely, since an ADAM cleavage site has not been reported in Dll4 [106]. Persistent Dll4 signaling is associated with an anti-angiogenic phenotype as well, but contrary to the hyper-branching observed in *Dll4* null mice, is characterized by a non proliferative-quiescent state of endothelial cells [107, 108]. Thus, Notch-Dll4 signaling must be intermittently stopped or reduced, allowing the proliferation of the stalk cell in angiogenesis. This break mechanism seems to be achieved by the Notch ligand, Jagged-1 and Notch-regulated ankyrin repeat protein (Nrarp, an intracellular notch signaling inhibitor [109] expressed by the stalk cells [110, 111]. Jagged1 exerts pro-angiogenic activity, antagonizing Dll4 dependent signaling [111]. Meanwhile, Nrarp, diminish the antiproliferative signal of Dll4 and at the same time potentiates the evolutionarily conserved pathway, Wnt signaling [112], inducing cell cycle progression and endothelial cell proliferation [108]. Thus, both Nrarp and Jagged-1 expression explain why stalk cells readily proliferate although they receive highest levels of Notch activation through Dll4 signaling from the leading tip cells [108, 110, 111].

As mentioned, RECK could act as a negative regulator of NOTCH, inhibiting the ADAM 10 dependent shedding of

NOTCH receptor, which is required for its activation [79]. Since RECK is induced by angiopoietin-1, which is prominently in stalk cells during angiogenesis [96, 97], part of the pro-angiogenic effects of RECK may be directly associated to the stalk cells, inhibiting the activity of ADAM-10 and ADAM-17. ADAM-10 is required for the Dll4-dependent signaling in endothelial cells [113] and Jagged-1 is a substrate of ADAM-17 [111]. Thus, RECK should stabilizes Jagged-1 at the plasma membrane potentiating its antagonizing effect over Dll4 and at the same time by reducing the Dll4–dependent NOTCH activation. The opposite effects of RECK modulating Notch signaling may be explained by the presence of ADAMs in the Notch signal-receiving cell (Notch receptor expressing cell) or in Notch signal-sending cell (ligand expressing cell). Thus, RECK expression could be involved in the fine-tuning of the endothelial Notch signaling ensuring a proper and successful angiogenesis.

CONCLUDING REMARKS

Since the first observations that RECK deficient embryos die *in utero* showing severe vascular defects, much effort has been made to better understand the role of RECK in angiogenesis. However, considering the fact that low expression of RECK is a common feature of many tumors and that its overexpression reduces tumor growth by reducing the tumor neovascularization, the exact angiogenic role of RECK has been puzzling. Studies focused to understand the role of RECK at the single cell level are required to break-down these apparent discrepancies. RECK, as a membrane anchored inhibitor of different MMPs and ADAMs proteases, exert key roles in the extracellular matrix remodeling homeostasis, but also acts as modulator of different signaling pathways involved with the regulation of the cell behavior, particularly Notch. Therapeutic angiogenesis seek the treatment of ischemia, which associates with lower blood supply in different tissues and organs as part of a regenerative process or the disease itself [114-116]. The main target would be to stimulate angiogenesis in the ischemic tissue, improving the perfusion, O_2 supply, deliver of survival factor, or even mobilize regenerative stem cells [88, 117, 118]. RECK act as master regulator of angiogenesis in both physiological and physiopathological vascularization, the control of its expression and/or activity emerges as a key target for therapeutic modulation of angiogenesis.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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