Journal of Inflammation Research

Dovepress
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REVIEW

RECK as a Potential Crucial Molecule for the Targeted Treatment of Sepsis

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Abstract: Reversion inducing cysteine rich protein with kazal motifs (RECK), a Kazal motif-containing protein, regulates pro-inflammatory cytokines production, migration of inflammatory cells, vascular endothelial growth factor (VEGF) and Wnt pathways and plays critical roles in septic inflammatory storms and vascular endothelial dysfunction. Recently, RECK has been defined as the negative regulator of adisintegrin and metalloproteinases (ADAMs) and matrix metalloproteinases (MMPs), which are both membrane "molecular scissors" and aggravate the poor prognosis of sepsis. To better understand the roles of RECK and the related mechanisms, we make here a systematic and in-depth review of RECK. We first summarize the findings on structural characteristics of RECK protein and the regulation at the transcription, post-transcription, or protein level of RECK. Then, we discuss the roles of RECK in inflammation, infection, and vascular injury by focusing on the RECK function on ADAMs and MMPs, as well as the pathways of VEGF, WNT, angiopoietin, and notch signaling. In conclusion, RECK participation as a guardian in the development of sepsis provides insight into the strategies of precisely intervening in RECK dysregulationfor the treatment of sepsis.

Keywords: RECK, sepsis, vascular endothelial function regulation, inflammation

Introduction

Sepsis is a severe condition characterized by organ malfunction, posing a life-threatening risk to the patient. It occurs when the body's immune system responds abnormally to an infection, disrupting normal bodily functions. The primary pathophysiological process involves a cytokine storm and vascular endothelial leakage triggered by an exaggerated inflammatory response.[1] Invasion of the body by pathogen-associated injury molecules (PAMPs) and exogenous injury-related molecules (DAMPs) activates innate and adaptive immune systems, leading to a significant inflammatory response.[2] These mechanisms help moderate the exaggerated inflammatory response, commonly called "cytokine storm".[3]

Meanwhile, it must be acknowledged that vascular dysfunction as a result of endothelial cell activation and vascular injury is critical to triggering Multiple Organ Dysfunction Syndrome (MODS) during sepsis. Endothelial cells release many cytokines, including Tumor Necrosis Factor-α (TNF-α), TNF receptor1/2(TNFR1/2), IL-6 receptor (IL-6R), C-X3-C Motif Chemokine Ligand 1(CX3CL1), C-X-C Motif Chemokine Ligand 16(CXCL16), VE-cadherin/CDH5, and Vascular Cell Adhesion Molecule 1(VCAM1), among others.[4] The over-activation of these cytokines has been shown to contribute to the endothelium's heightened permeability, resulting in systemic endothelial dysfunction and ultimately aggravating sepsis to

Received: 21 October 2024
Accepted: 19 January 2025
Published: 6 February 2025

MODS.[2] ADAM family consists of molecules that regulate the release of cytokines. Furthermore, the cytokines mentioned above have recently been shown to be negatively regulated by RECK.[5–7] However, the relative importance of RECK in developing sepsis is largely unexplored.

RECK is a multifunctional glycoprotein,[8,9] and its gene and protein expression levels are reduced in pathological conditions involving infection and related tissue injury; thus, RECK is of great significance in maintaining the normal structure and function of tissues and organs. One of the crucial functions of RECK is to inhibit the activation of matrix metalloproteinase (MMP), whose increase is attributable to the initiation or exacerbation of septic inflammation.[10] This function enables RECK to exert biological effects such as ameliorating extracellular matrix (ECM) degradation, leukocyte exudation and epithelial cell destruction, and airway remodeling. Thus, low expression of RECK may disrupt the ECM's steady state. At the same time, MMP inhibitors have been proven to combat cytokines generation and reduce pulmonary vascular permeability, mortality, and other adverse reactions during sepsis.[11,12] In addition, RECK also interacts with various inflammatory factors that affect their expression and activity, such as interleukin 6(IL-6) signaling pathways. RECK regulates the expression of IL-6 levels, and it can interact with IL-6R and Glycoprotein 130(gp130), thereby weakening IL-6-mediated downstream biological effects.[13–15] As is well known, IL-6 and other cytokines participate in the immune response, cell proliferation, and inflammatory reaction process. The cytokine storm is a critical pathophysiological mechanism of organ damage in sepsis. The regulatory effect of RECK on cytokines is suggestive of its role in the inflammatory response of sepsis. In addition, the RECK in endothelial function regulation is also involved in angiogenesis and vascular permeability, among others.[16] RECK plays a vital role in maintaining vascular endothelial cell function and anti-aging. Moreover, RECK serves to maintain vascular permeability. RECK can affect blood-brain barrier formation and angiogenesis in the nervous system by activating the endothelial WNT/β-catenin signaling pathway.[17–19] RECK also blocks the production and function of vascular endothelial growth factor (VEGF) in other systems. Inhibition of VEGF can reduce vascular permeability, which is beneficial to reducing acute lung and kidney damage caused by lipopolysaccharide (LPS).[20–23] However, a direct study of RECK in sepsis is lacking.

Given the sensitive impact of RECK on inflammation and vascular permeability, it is highly possible that RECK may play a critical role in the development of sepsis. This review summarizes the most recent advances of RECK and its impact on inflammation and vascular permeability, and we propose that RECK may have considerable potential as a therapeutic target against sepsis.

Methods

This review was conducted by searching the literature in PubMed, Google Scholar, and Web of Science databases using the keywords "RECK", "sepsis", "inflammation", and "endothelial injury". The search time range was from 1998, when RECK protein was discovered, to 2024. Most of the included articles were peer-reviewed clinical research and basic research articles; a small part were review articles, and conference abstracts were excluded.

The Structural Characteristics of RECK Protein

RECK protein was found in 1998 by Takahashi et al. It is a protein with 971 amino acid residues.[8] Evidence shows a cowbell-shaped RECK unique dimer form (Figure 1A and B).[24] Among them, the NH2 terminal hydrophobic water (1–22) acts as a signal peptide, and the COOH terminal hydrophobic regions (943–971) as glycosyl phosphatidyl inositol anchor is associated with RECK membrane positioning.[8,24] RECK functions as a GPI-anchored protein located in the lipid raft microdomain of the cell membrane. It is worth noting that this unique cell surface topology GPI anchored feature allows RECK concentration in the plasma membrane domain to increase the accessibility of the substrate, which could make the RECK finer to adjust the function of membrane proteins.[25,26] Most GPI-anchored proteins degrade typical membrane proteins in the cell by endocytosis uptake and subsequent recircle.[27] RECK is proven to have the same features that can adjust its substrate membrane type 1 matrix metalloproteinases(MT1-MMP) endocytosis pathway, similar to the clathrin and dynamin-independent endocytic pathway (CLIC-GEEC, CG pathway).[28] However, it has yet to be explored whether there are more similarities to the substrates.

RECK has three important function structure domains, including sequences rich in cysteine (37–338), sequences similar to the structure of the epidermal growth factor (EGF) domain (49–523, 67–709), a domain resembling serine

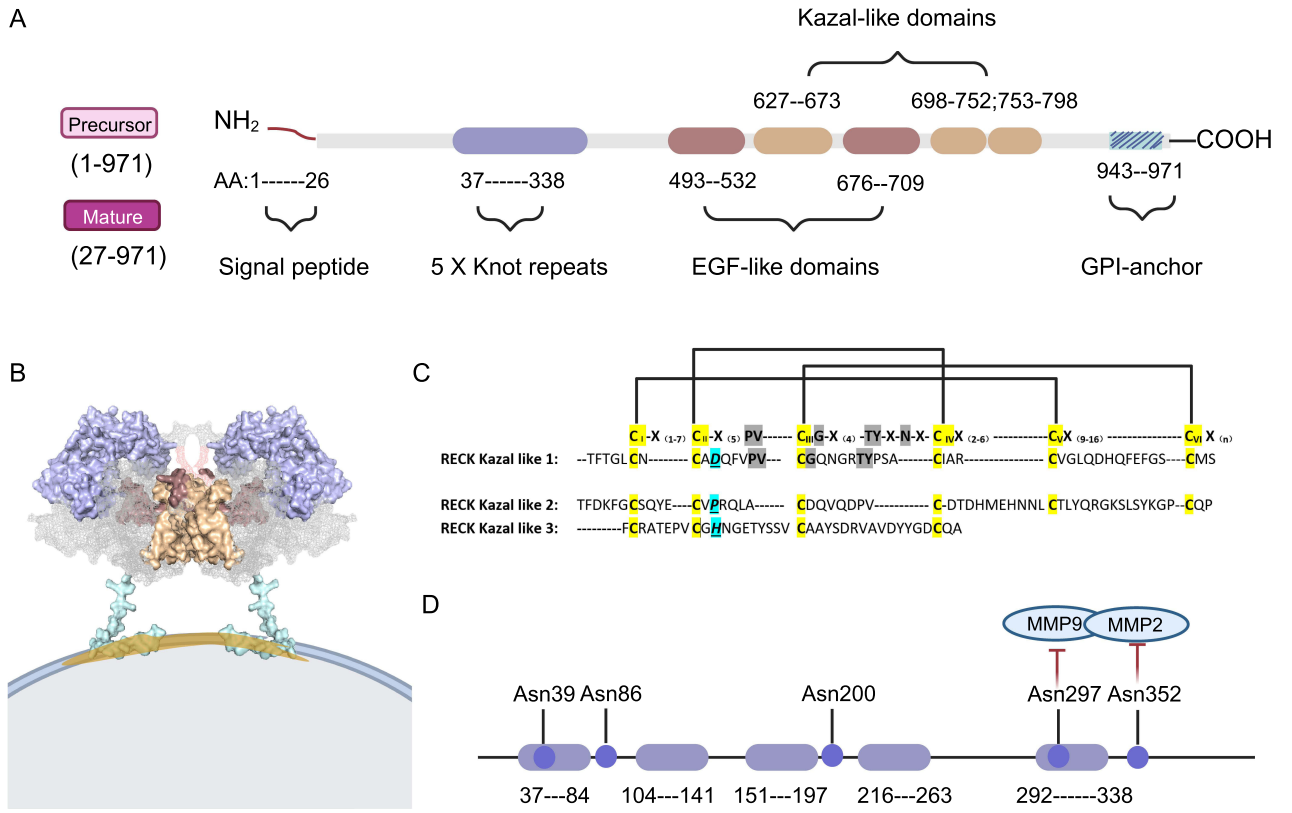

Figure 1 Structural characteristics of RECK: (**A**) RECK has three important domains in between and functions as a negative regulator of several membrane proteins. Cysteine-rich sequences (37–338), domains resembling the epidermal growth factor (EGF)(49–523; 67–709), and three domains resembling the serine protease inhibitor (SPI) are shown from left to right. The ends of NH2 and COOH are both abundant in cysteine (9%).[8] (**B**) RECK contains a distinctive dimer in the shape of a cowbell.[24] (**C**) In contrast to the second and third domains of RECK, which are atypical Kazal motifs, the first domain of RECK (residues 635–654) precisely matches the standard Kazal motif. Researchers have constructed recombinant proteins containing 3 Kazal motifs (named K123), 676–799(named K23), and full-length RECK with 2 Kazal motifs to investigate the function of this domain.[8] The Kazal motifs are typically composed of 50–60 amino acids, with three pairs of disulfide bonds created by six cysteine residues (Cys I–Cys V, Cys II–Cys IV, and Cys III–Cys VI) to preserve the domain's molecular shape.[29] At a region of P1 activity, which is crucial for establishing the specificity of protease inhibitors, there is an additional amino acid residue following the second cysteine.[30] There are no hydrogen bonds, but only two sets of disulfide bonds that connect CysIII and Cys VI are present in the unusual Kazal domain (K23). (**D**) Five glycosylation sites were discovered among the aforementioned five cysteine node patterns (Asn86, Asn200, Asn297, Asn352, Asn39), and some research has indicated that the extent of glycosylation affects its protein localization.[31,32] Created in BioRender. Qin, Y (2024) https://BioRender.com/i21f361.

protease inhibitor (SPI) (Figure 1A). Among them, a similar SPI domain structure seems essential for RECK to act as a negative regulatory factor of various membrane proteins. Serine protease inhibitors are one of the more conservative families, generally repeated by one or more conservative Kazal structural domains.[33] Specifically, the SPI region of RECK can be subdivided into three domains. The first domain of RECK (K1, residues 635 to 654) matches the canonical Kazal domain compared to the second and third domains (Figure 1A). The canonical Kazal motif usually consists of 50 to 60 amino acids with six cysteine residues (Cys I-Cys V, Cys II-Cys IV, and Cys III-Cys VI) forming three pairs of disulfide bonds to maintain the molecular shape of the domain.[29] In the nonclassic Kazal structure domain, there are only two groups of disulfide bonds and no hydrogen bonds (Figure 1C). Cys II and the connection between the Cys VI, the second and third structure domains (K23) are more inclined to match the classic Kazal domain structure. Whether the difference between the two domains is an evolutionary advantage phenomenon is still unclear.[25,34] Chan et al constructed different lengths of the Kazal base sequence, including three Kazal motifs region (named K123), two Kazal motifs region located 676–799(named K23), and the total length of RECK recombinant protein, to study the function of the structure of the domain. However, only full-length RECK and K23 inhibited MMP9 secretion and activity.[35] Curiously, the K123 recombinant protein containing the three Kazal motifs did not exert an inhibitory effect.

Nevertheless, the inhibitory effect of RECK on MMP9 secretion is controlled by the Asn297 glycosylation in its cysteine-rich domain.[31] Glycosylation is crucial for protein modification after translation and is closely related to protein

signaling function and protein fold correctly. Combining the above, whether or not a recombinant protein conformation change affects its functionor are there are unknown crosstalk effects that lead to loss of inhibition function in the K123 classic Kazal motif with the classic Kazal motif and the nonclassical Kazal motif remains to be answered.

The domain structure rich in cysteine (37–338) has five repeated assumptions of cysteine knot motif (cysteine - knot domain, CK)(37–84, 104–141, 151–197, 216–263 and 292–338). This structure is required for RECK to participate in the WNT7a/7b signaling pathway to promote angiogenesis, where the first cysteine knot motif (CK1) interacts with the adhesion G protein-coupled receptor A2(Gpr124). Mutation of ^{68}QRAP^{70}/^{91} VFKK ^{93}amino acid to alanine (A) could eliminate their binding on the cell surface.[36] The fourth and fifth cysteine knot motif, CK (CK4-5), interact with WNT7a/WNT7b.[37] In addition, the above five cysteines were also found to be in the junction between the base sequence glycosylation sites (Asn86, Asn200, Asn297, Asn352, Asn39). Part of the study shows that protein glycosylation and positioning are related. However, glycosylation does not seem to be required for RECK's cell surface location and is more associated with RECK's enzyme activity function (Figure 1D).[31]

So far, each domain of RECK has been reported to have its unique function, except for its epidermal growth factor (EGF) -like domain (EGFD) (Figure 1A). RECK was detected to have two domains (residues 493–523 and 676–709) with weak homology to epidermal growth factor-like repeats.[8] Epidermal growth factor-like domains are a common feature of many extracellular proteins with a wide range of functions.[38] It is worth noting that EGFD is also one of the cleavage sequences of the ADAM family,[39] which includes seven members that regulate immune responses during sepsis.[40] For instance, the EGF protein structures, such as Notch and EGFR ligands, are important substrates of the ADAM family. So far, RECK is a negative regulator of ADAM10/17, but their relationship may be far beyond this.[7] Similarly, RECK, also a negative regulator of MMP2 and MMP7, can be shedded by MMP2 and MMP9.[11,24,41] However, whether ADAM10/17 shed RECK or if there are further crosstalks in between them still needs to be discovered.

Regulatory Mechanisms of RECK Expression and Activity

It has been proven that increasing the expression of RECK through genetic engineering can attenuate the progression of various disease models where RECK gene expression levels are decreased.[13,42–44] Therefore, an in-depth exploration of the molecular mechanism regulating RECK gene expression is of great significance for developing specific drugs that can specifically regulate RECK.

Regulation at the Transcriptional Level of RECK

In humans, the RECK gene is in the short arm of chromosome 9 region 1, band 3, subband 3(9p13.3), with a total length of 87543 bp and a coding region of 2916 bp, which contains 29 exons. RECK genes are now known to determine seven transcripts (https://www.ncbi.nlm.nih.gov/nuccore) (Table 1). Research has shown that transcriptional functions have remarkable differences (Table 1).[45,46] The full-length transcript encodes a protein with 971 amino acid residues.[8] The full-length transcript (NM_021111.3) is the subtype mainly discussed in this paper.

Acting on the RECK Promoter

According to Kyung Ju Lee's report in 2010, the RECK promoter region of the complete sequence has 4168 bases with five predicted promoter binding sites. They include two reverse hypoxia response elements (reverse hypoxia-responsive element, rHRE2), a reverse Spl site (rSP1), and two forward Sp1 sites.[54] Combined with the current studies on the regulation of RECK, two critical sites (SP1, rHREs) in RECK have been revealed (Figure 2A). These sites interact with different promoters, interfering with RECK gene expression (Table 2). Among them, rHRE2 (−2345, −2333), which negatively regulates RECK transcription, was recruited to the rHRE2 region of the RECK promoter under hypoxia, thereby repressing the RECK promoter (Figure 2A).[54] The SP1 site (82–71) is a significant and widespread influence. When tumors, inflammation, or other diseases occur in vivo, the RAS gene and Reactive Oxygen Species (ROS) abundance increase in vivo, leading to phosphorylation of its downstream key molecule ERK. The p-ERK activates the transcription factor SP1.[55] In the study of Chang and others, Sp1 and Sp3 were dose-dependent, instimulating the RECK promoter rather than a reverse activator, as predicted previously (Figure 2B).[56] ERK has been found to inhibit

Table 1 Transcripts/Regions of RECK and Their Function

Transcripts/Regions	Function		Ref.
RECKVar1/RECK-A (NM_021111.3)	Negative tumor regulatory factors The longest isoform 1 is encoded by this variation 1, which has a total of 21 exons and 20 introns.		[47]
RECKVar2(NM_001316345.2)	Compared to variant 1, variant 2 has two alternate exons at the 5′ end. In contrast to isoform 1, the resulting isoform 2 has a shorter and more recognizable N-terminus.		[46]
RECKVar3/RECK-B (NM_001316346.2)	Tumor-stimulating gene: can be used to predict melanoma/glioblastoma, which is substantially connected with tumor aggressiveness and adversely correlated with the survival rate of melanoma patients TIMP3 mRNA levels were reduced, although MMP9 and MMP14 mRNA levels were elevated		[45, 46]
RECKVar4/RECK-I (NM_001316347.2)	Positively linked with mRNA levels of MMP2, MMP14, TIMP1, and TIMP2		[46]
RECKVar5(NM_001316348.2)	It was controlled both during and following the therapy with transforming growth factor-1(TGF-1). Competitive inhibition of MMP9 through binding to the full-length RECK protein's kazal-like domain. It promotes glioma growth and improves fibroblasts' capacity for invasion. Control of tubulin's post-translational alterations.		[48, 49]
Common denominators	The transcription start site and the first eight exons are shared by these three variants (3–5), of which Var3 and Var4 share the first 213 amino acids. Compared to variant 1, these variants (3–5) substitute an alternative 3′-most exon for the final 13 exons.		
NH2 terminal hydrophobic zone (aa:1–22)	Acts as a signal peptide		
CK domain (aa:33–338)	Glycosylation sites:	Asn39,Asn86, Asn200, Asn297, Asn352	[31,32,36,37]
	Asn86/297/352:	Related to tumor cell invasion and MMP active	
	Asn35/200:	Unknown	
	Interaction:	CK-1 interacts with Gpr124 CK-4 and CK-5 interact with WNT7a/7b	
EGF-like domain (aa:493–523, 676-709)	Calcium-binding and hydroxylation? Claevage by ADAM10/17?		[40, 50]
SPI-domain (aa: K1=635-654,K23=676-799)	Interacting with Var5 and MMP9 K23 inhibits the secretion and activity of MMP9		[35, 48, 49]

RECK expression in other studies, including auxiliary HDAC1 participation and methylation process factors such as joint action.[57–59] ERK activation promotes HDAC1 phosphorylation and accumulation in the nucleus. Activation of the ERK pathway and increased histone deacetylases prevent the interaction of SP1 with the Sp1-binding region of the RECK promoter, resulting in the inhibition of RECK expression (Figure 2B). The expression of RECK was restored by ERK/HDAC inhibitor (PD98059/Tricastatin A) or the dominant adverse ERK pathway.[60] Many non-steroidal anti-inflammatory drugs, such as aspirin and celecoxib, NS398, and others, have also been shown to affect RECK expression through the SP1/ERK pathway.[61]

Regarding the regulation of RECK promoter activity, Makoto Noda's team constructed a promoter fragment. They screened a chemical library containing 65,000 small molecules and found two compounds (#638 and #639) that could increase RECK protein levels by more than two times.[64] Among them, DSK638, which is similar to histone deacetylases

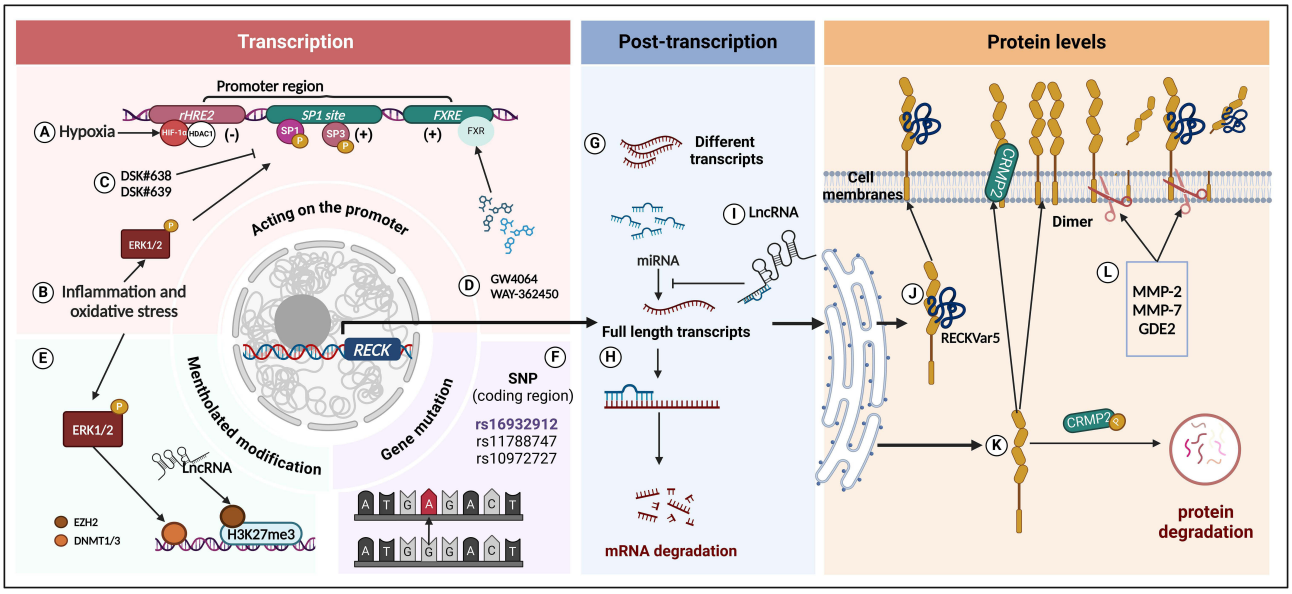

Figure 2 Multiple levels regulate the RECK expression mechanism: (**A**–**E**) Regulation of RECK at the transcriptional level: (**A**) Under hypoxic conditions, HIF-1 nuclear translocation is active, which activates the hypoxic element rHRE2 and suppresses RECK promoter activity. HDAC1 collaborates with other enzymes (e.g HIF-1a, SP1) in this process. (**B**) The inflammatory process activates Ras genes and causes the release of ROS to promote the nuclear translocation of the SP1 transcription factor. These above-mentioned reactions would subsequently facilitate SP1's binding to the SP1 site in the promoter region, inhibiting RECK promoter activation. (**C**) DSK#638 and DSK#639 inhibit the binding of SP1 to and RECK promoters. (**D**) The FXR agonists WAY-362450 and GW4064 can facilitate FXR to bind to the FXR element in RECK intron one and hence stimulate RECK transcription. (**E**) The methylation of the RECK promoter results in the downregulation of RECK expression at the gene level when the activation of the ras gene and its downstream ERK1/2 signaling pathway occurs in an environment induced by ROS or under certain illness conditions. Some lncRNAs serve the same purpose (details in Table 2). (**F**) Three SNPs (rs16932912, rs11788747, rs10972727) in the RECK gene have been found in exons 9, 13, and 15, respectively. One SNP rs10814325 was found in the promoter region. Among the above SNPS, only rs16932912(G/A) was reported to be closely related to RECK protein expression.[12,51–53] (**G**–**I**) Regulation of RECK at the post-transcriptional level: (**G**) different transcripts (**H**) A vast number of miRNAs (detail in Table 2) have been discovered to serve important regulatory roles in RECK post-transcriptionally. (**I**) lncRNA GAS5 /miR-21 forms a related competitive endogenous RNA (ceRNA) network. (**J**–**L**) Regulation of RECK at the protein level: (**J**) RECK Var5 can compete with RECK for binding to MMP9, reducing RECK's inhibitory effect on MMP9 activity. (**K**) CRMP2 protein protects RECK protein against degradation, which is inhibited when CRMP2 is phosphorylated. (**L**) MMP2/7 reduces the 110kD RECK to 55kD; GDE2 was discovered to cleave RECK's GPI anchor, allowing RECK to be released from the cell membrane. Created in BioRender. Qin, Y (2024) https://BioRender.com/j35u075.

(HDACs) inhibitors, enhances RECK promoter activity mainly by relieving the inhibition of SP1/KLFs family protein KLF2 targeting SP1 site (Figure 2C). Alternatively, an FXRE element is located in the first intronic region.FXR agonists reverse RECK downregulation by binding to FXRE in mice fed a methionine-choline deficient (MCD) diet (Figure 2D).[90] This result makes it possible to realize the therapeutic application of RECK in diseases.

Menthylated Modification

Ras gene and ROS also trigger the methylation process, producing more DNA methyltransferases.[99,100] RECK has two methylation regions: the first intron region and a promoter/exon-1 region (Figure 2E).[101] Shi et al[101] defined the Methylation process of the two regions as "RIM" (RECK Intron-1 Methylation) and "RPM" (RECK Promoter/exon-1 methylation), respectively. The RPM silent RECK gene is more than RIM.[101] It has been found that methyltransferases such as DNMT1 and DNMT3b can bind to the RECK promoter and effectively silence the RECK gene.[58,59] In breast cancer cells (MCF7/T470), there is 27HC (27-hydroxycholesterol) -induced increase in DNMT1, which down-regulates RECK expression.[58] When HA-RASVal12 cancer genes are inserted into NIH3T3 cells (2–12 cells), RAS activation increases the production of DNMT3b and also leads to a decline in RECK expression.[59] In this case, using SAM (S -S-adenosyl methine) to increase the supply of methyl groups can prevent RECK gene silencing. The suppression measures intervention will slow down the RECK methylation process and improve the tumor cells, Such as si-RNA and methyltransferase inhibitors (AZA, 5-Aza-2′-deoxycytidine).[102,103] In addition to RECK DNA methylation, EZH2, a histone methyltransferase enhancer, was found to epigenetically repress RECK expression by catalyzing H3K27 trimethylation (H3K27me3). LINC01419 could stabilize EZH2 mRNA and enhance the above process.[91]

Table 2 List of Factors With Relevance to RECK Expression

Mechanism	Initiation Factor	Related Processes	Cells/Tissue	Related Molecules	Ref
Repression of the RECK promoter by the Sp1 binding site located in the RECK gene. (Sp1 binding site, the −82/-71 region of the translation start site)	Ras	Ras may activate ERKs to phosphorylate HDACs and induce the binding of HDACs to Sp1 protein, thereby inhibiting the expression of RECK.	2–12 cells, NIH-3T3 cells	Casticin, curcumin, and PTEN can inhibit the DNA binding activity of SP1 and upregulate the expression of RECK	[42,56,60,62–69,83,84]
	ERK	ERKs may enhance the DNA binding and transcriptional activity of the Sp1 protein by phosphorylating its Thr453 and Thr739.	B104-1, NIH3T3, HACAT	Both HER-2/neu kinase inhibitor AG825 and MEK1 inhibitor PD98059 effectively inhibited ERK activity and counteracted the inhibitory effect of RECK promoter.	
	HDAC1	HDAC1 acts as an accessory protein and binds to Sp1 protein to inhibit RECK expression.	CF migration, B104-1, NIH3T3, HACATSL2, C2C12 cells,293T cells	The histone deacetylase inhibitors trichostatin A(TSA) and Mocetinostat(MGCD) effectively activated RECK promoter activity.	
	ROS	ERK/STAT3	SGC7901, MGC803, MCF7, T47D		
	KLF2/6	Kruppel-like factors (KLFs) recruit transcriptional regulatory proteins, including coactivators and corepressors, to promoters.	RM72 cells		
	Her-2(neu)	HER-2(neu) activates HDAC1 in the Sp protein that binds to the RECK promoter, thereby inhibiting RECK expression.	B104-1, NIH3T3, HACAT		
	RbAp46	RbAp46 can bind to histone deacetylase (HDAC1) and Sp1, and then bind to Sp1 site in RECK promoter.	MCF-7-ras, NIH3T3		
	Ang-2	Ang-2 inhibits RECK expression in adult mouse cardiac fibroblasts (CF) through AT1/ NOX4-dependent ERK/Sp1 signaling.	CF migration		
	IL-18	Induction of Sp1-mediated RECK inhibition by IL-18 requires NOX4-dependent H2O2 production.	CF migration	Acetylsalicylic acid (ASA) could inhibit IL-18-induced H2O2 production and RECK inhibition.	
	STAT3/ SKP2/P21	STAT3 can activate SP1 by promoting SKP2, and P27 itself dephosphorylates Sp1.	SGC7901 MGC803		
	P27	P27 can be degraded in a Skp-dependent manner activated by STAT3, and P27 itself has the function of phosphorylating Sp1.	SGC7901, MGC803	–	
	Mycoplasma pneumonia	Induced Sp1 phosphorylation	Bronchial epithelial cells	–	
	LMP1	EB virus latent membrane protein 1 (LMP1) can effectively stimulate the activity of extracellular signal-regulated kinase (ERK) and phosphorylate Sp1 to enhance its DNA binding ability.	TW04 cells	–	

(*Continued*)

https://doi.org/10.2147/JIR.S501856

Table 2 (Continued).

Mechanism	Initiation Factor	Related Processes	Cells/Tissue	Related Molecules	Ref
The activation of the RECK promoter is done by the Sp1 binding site located in the RECK gene	SPRY1	Forced expression of SPRY1 in wild mice reversed Ang-2-induced ERK activation and RECK inhibition.	CF migration	–	[56,65,68,69,85–89]
	SP1/SP3	Sp1 and Sp3 stimulated RECK promoter activity in SL2 cells in a dose-dependent manner.	SL2 cells	–	
	Rap1	Rap1, a small Ras-like GTPase, can compete with Ras for Raf1, antagonize Ras activity, and reduce Ras-mediated ERK activation.	hMVECs	–	
	TIMP2	Crk-C3G-Rap-1	hMVECs	–	
Binding to the rHRE2 site inhibits RECK promoter activity; The second reverse HRE (rHRE2, −2345 to −2333)	HIF-1α	HIF-1α and HDAC1 are recruited to the rHRE2 region of the RECK promoter under hypoxic conditions.	HEK293, TCMK-1	Hypoxia significantly down-regulated RECK mRNA and protein expression, and this inhibitory effect was reversed by HDAC inhibitor trichostatin A(TSA) and HIF-1 inhibitor YC-1.	[54]
	HDAC1				
Binding to the potential IR-1 element: FXRE (AGGTCACTGACCC, nucleotide +2797/2809) in mouse in the first intron.	FXR	FXR directly regulates RECK transcription by binding to IR-1 elements within intron 1 of the RECK gene	LIVER tissue, Primary mouse liver cells	The FXR agonist way362450/ GW4064 induced an increase in RECK mRNA levels in WT mice	[90]
Epigenetically attenuated RECK expression by catalyzing RECK promoter methylation.	ERK1/2	ERK1/2 activation increases H3K27me3 levels in HUVECs, and subsequently, RECK is transcriptionally silenced in a time-dependent manner.	HUVECs	Treatment with U0126, a small molecule inhibitor of the ERK1/2 signaling pathway, effectively inhibited ERK1/2, resulting in the reduction of H3K27me3, accompanied by the activation of RECK transcription.	[91]
	Ras/ DNMT3b	RAS induces DNMT3b expression through the extracellular signal-regulated kinase signaling pathway. Thus, the binding of DNMT3b to the RECK gene promoter was increased, and promoter methylation was induced.	NIH3T3 cells, 2–12 cells	DNA methyltransferase (DNMT) inhibitors 5′-azacytidine and curcumin can inhibit RECK methylation. Casticin could down-regulate the expression of DNMT1 mRNA and protein and then down-regulate the methylation of RECK.	[59]
	Ros/DNMT1	ROS induces DNA methylation, which down-regulates RECK expression in breast cancer cells.	MCF7, T47D	27HC (27-hydroxycholesterol)	[58]
	EZH2	The histone methyltransferase enhancer of zeste homolog 2 (EZH2) can epigenetically suppress RECK expression by catalyzing H3K27 trimethylation (H3K27me3) within the promoter region of RECK.	HUVECs, Hs-578T, MDA-MB-231 breast cancer cells	–	[70]
	LINC01419/ EZH2	The interaction of LINC01419 with FUS stabilizes EZH2 mRNA, thereby enhancing EZH2 expression and leading to histone methylation of the RECK promoter.	HCC cells	–	[91]

Targeting RECK mRNA resulted in post-transcriptional regulation of RECK expression and decreased RECK protein levels.	miR-4-21p, miR-7, miR-21/miR-21-5p, miR-25,miR-92a/-92b,miRNA-96, miR-130a, miR-135b, miR-145, miR-181a-5, miR-182-5p,miR-183, miR-210, miR-221,miR-222, miR-374b-5p, miR-590-5p, miR-1080				[16,71–82]
SNP	rs16932912 (V275I)	In ameloblastoma patients, RECK protein levels were decreased relative to healthy volunteers, and the decrease was more significant in samples positive for SNPs (V275I).	Ameloblastoma tissue and healthy gingival tissue		[51]
Regulatory protein expression	CRMP2	CRMP2 interacts with RECK to prevent RECK degradation.	MDA-231, HEK293T,		[92]
	Gpr124	Gpr124 upregulates RECK cell surface expression.	HEK293		[93]
Regulatory protein activity	RECK var5	RECKVar5 can competitively bind RECK kazal-like domains to prevent RECK from binding to MMP9.	293T cells		[48]
Cleavage of protein	GDE2	GDE2 is a GPI-anchor cleaving enzyme that can cleave RECK, causing it to lose its membrane anchoring function.	DIV14 cortical neuronal, HEK293T cells		[94,95]
–	TGF-β	After TGF-β1 treatment, MDA-MB-231 cells showed a significant increase in RECK mRNA expression level but a decrease in RECK protein expression. The reduction in protein expression appeared to be dependent on ERK1/2.	MDA-MB-231 cells	PD98059, an inhibitor of ERK1/2, blocked TGF-β1-induced RECK protein down-regulation.	
		TGF-β1 signaling may propagate through the Smad3 pathway and protect RECK from proteolytic degradation.	Pancreatic stellate cells (PSC)		
		TGF-β1 stimulation of OA chondrocytes had no significant effect on RECK gene expression.	OA chondrocytes		
	IGF-2	Stimulates gene expression of RECK	OA chondrocytes		[98]
	TNF-α, IL-1, IL-6	Down-regulate gene expression of RECK	OA chondrocytes		[98]

https://doi.org/10.2147/JIR.S501856

Related Signaling Pathways of RECK

The regulating methods mentioned above may involve multiple signaling pathways, including but not limited to the RAS/ERK pathway and signal transducer and activator of the transcription 3(STAT3) pathway. Rap1, another small GTPase homolog of Ras, was found to participate in the regulation of RECK. M Noda and WG Stetler-Stevenson found that the regulation pathway Crk-C3G-Rap1 participates in RECK signaling.[89] By enhancing the Src-Csk interaction, TIMP2 can enhance the phosphorylation of Tyr-527, a negative regulatory site of Src, which reduces Src kinase activity and leads to the disassembly of the paxillin-Crk-DOCK180 molecular complex, ultimately leading to the inactivation of Rac1 and conversion to Rap1. Forced expression of Rap1 reversed the inhibitory effect of TIMP2 on RECK, whereas TIMP2 did not affect the upregulation of RECK in response to forced expression of Rap1.[69,89] Rap1 plays a more critical role in RECK control. Some recent studies have shown that it can compete Raf1 with Ras to inhibit Ras activity and reduce the ERK activation mediated by Ras.[85–87] Coincidentally, in the inflammatory disease we focus on, Rap1 is decreasing expression in acute lung injury induced by LPS.[88,104] Could the loss of Rap1 contribute to the decline in RECK? Given the importance of Ras/ERK in RECK regulation, the competitive interaction between Rap1 and Ras is a crucial target for regulating RECK upregulation, which will surely benefit the treatment of many diseases.

Gene Mutation

In addition to interacting with the promoter region, mutations in RECK itself can also impact its expression. ThirteenSingle-nucleotide polymorphisms (SNPs) in the RECK gene have been found, including 3 SNPs (rs16932912, rs11788747, rs10972727) in exon 9, 13, and 15, respectively.[12,51–53] One SNP rs10814325 was found in the promoter region. Among the above SNPS, only rs16932912(G/A) was reported to be closely related to RECK protein expression (Figure 2F). When base G was mutated to base A, RECK protein was down-regulated. Future research may find more mutations associated with the regulation of RECK expression. These mutations may alter RECK gene transcriptional activity, mRNA stability, or protein translation efficiency, resulting in altered RECK expression levels.

Different Transcripts

The National Library of Medicine (NLM) included seven transcripts of RECK and corresponding coding protein 7(two to predict variation) (Table 1) (Figure 2G). The currently available studies found them to be part of the function differences. Compared with the total length of the transcript, transcription 2 has two alternate exons in the 5 end. Thus, two peer isoforms can be generated, and the resulting isoform 2 has a shorter and more recognizable N-terminus than isoform 1, and its function has yet to be reported. In addition, transcripts 3-5 shared the transcription start site and the first eight exons, with Var3 and Var4 sharing the first 213 amino acids. These variants replaced the last 13 exons with an alternative 3-UTR compared to the full-length transcript. Transcript three is defined as a tumor-stimulating gene: it can be used to predict melanoma/glioblastoma, which is closely related to tumor invasiveness. Transcript three negatively correlated with the survival rate of melanoma patients and can regulate the reduction of tissue inhibitor of metalloproteinases 3 (TIMP3) mRNA levels and the increase of Matrix Metallopeptidase 9(MMP9) and MMP14 mRNA levels.[45,46] Transcript 4 was also positively correlated with MMP2, MMP14, TIMP1, and TIMP2 mRNA levels.[46] However, studies on transcript five have focused more on its protein level. The transcript was increased by transforming growth factor-1 (TGF-1) stimulation. The last exon encodes its 13 amino acids, and the 3′-UTR is not present in the mRNA encoding RECK. Transcript 5(molecular weight = 25kda) shares 212 amino acids with the long RECK isoform (molecular weight = 110kda) and contains a 13-amino acid long sequence at its C-terminus that is specific for the short RECK isoform but does not contain a GPI-anchored structure. Transcript 5(Translated as Var5) can bind the full-length RECK to play a crucial inhibitory role, reducing RECK's inhibitory effect on MMP9 activity[48,49] (Figurere 2J). Variants of RECK always repress the full-length isoform of RECK.

The regulation of RECK gene expression is a complex and interesting area of investigation. Further studies on the RECK expression regulation mechanismshould help usto better understand its in-cell biology and its effect on disease development, providing new ideas and methods for treating related diseases.

Regulation at the Post-Transcriptional Level of RECK

Regarding the post-transcriptional regulation of RECK, existing studies have mainly focused on binding microRNAs (miRNA) to their mRNA. MicroRNAs in the body will cause most mRNA degradation by combining mRNA.[105] In the currently published studies, most of the known regulating RECK microRNAs are targeted to the RECK 3′UTR region, making the RECK protein levels drop (Figure 2H). The regulation of RECK by miR-21 has been demonstrated in a variety of diseases. Such as miR-21/miR-21-5p,miR-25, miR-92a/-92b,miRNA-96, and miR-130a have also been shown to be involved in the post-transcriptional regulation of RECK (Table 2).[16,71–82] In particular, β-catenin can restore RECK expression by binding to the miR-182 promoter and reducing the targeting of miR182 to the 3′-UTR region of RECK mRNA.[106]

In addition, Long non-coding RNA (lncRNA) also affects RECK protein expression by competing with microRNAs in the post-transcriptional stage. For example, lncRNA GAS5/miR-21 forms a related competitive endogenous RNA (ceRNA) network, and lncRNA GAS5/miR-21 forms a ceRNA network (Figure 2I). The increase of lncGAS5 in esophageal squamous cell carcinoma (ESCC) upregulates the expression of RECK by down-regulating miR-21, thereby increasing the apoptosis of ESCC cells after radiotherapy and enhancing the radiosensitivity of cells[107] (Table 2).

Regulation at the Protein Levels of RECK

Protein Stability and Membrane Localization

Collapsin response mediator protein 2(CRMP2), a cytosolic phosphoprotein, protects RECK from destruction.[92] CRMP2 interacts with RECK and stops the RECK degradation, thus blocking the NF-kappa B and WNT signaling pathways. However, the primary physiological function of CRMP2 depends on the phosphorylation status. When phosphorylation occurs on the CRMP2 T514 and S522 sites, the protection of RECK from degradation by CRMP2 has been inhibiting[92] (Figure 2K). Research shows that the interaction existing between CRMP2 and AMPA receptors is similar to that between RECK and CRMP, except that it maintains stability and promotes cell surface delivery. CRMP2, known for its affinity for tubulin heterodimers and its function in regulating microtubule networks, is vital in transporting voltage and ligand-gated ion channels.[108] In addition, the expression of adhesion Vallon found such as G protein-coupled receptor (GPCR) Gpr124 raised RECK expression of the cell surface through its leucine-rich repeat domain (LRR) interaction with RECK's N-terminal domain.[93] These two domains form a WNT7a/WNT7b specific signaling complex, which may also indirectly enhance RECK transport to the cell surface.[93,109]

Processing and Cleavage of Proteins

Maintenance of membrane localization is also required for RECK protein activity. Structurally, RECK is a GPI-anchored protein whose cell membrane localization relies on GPI-anchor. GDE2 is a kind of GPI-anchored lyase that can cut the GPI structure of RECK and cause the loss of its membrane anchoring function. It also inhibits RECK's negative effect on ADAM10 activity[94,95] (Figure 2L). Regrettably, the study did not use the RECK recombinant proteins lacking GPI structure to interact with ADAM10 in vitro.[94,95] Whether the alteration of the RECK function by the GPI anchor domain is due to its altered localization, making it unable to contact ADAM10, or its conformational change disrupts the RECK function itself is yet to be explored. RECK downstream substrates MMP7 and MMP2 can cleave the RECK (110 kd) into 55 kd, which is interesting because the RECK can also inhibit shedding activity[24] (Figure 2L). Does the 55 kD RECK lose the function of the inhibitory activity? There may be a negative feedback mechanism.

Activity of Protein

As mentioned above, RECK has five kinds of transcripts (Table 1), including RECK var5(NM_001316348. 2) shorter encoding protein (25 kDa). It can be competitive with a long RECK SPI domain, which leads to the combination between RECK and MMP9, thereby enhancing the function of MMP9. It can also inhibit RECK's resistant migration function (Figure 2I).[48] The interaction between short and long RECK is initiated in the endoplasmic reticulum (ER), and the complex containing both protein isoforms follows a protein secretion pathway through the Golgi apparatus for final localization to the cell surface. Even if PI-PLC cutting long RECK's GPI anchor makes its release, a combination of both effects remains.

Controversial Regulatory Mechanism and Application Prospects

However, it seems complicated to agree on the involvement of TGF-β1 in the regulation of RECK.[96–98] Following TGF-β1 treatment in MDA-MB-231 cells, there was a notable rise in the expression of RECK mRNA, although the expression of RECK protein showed a considerable drop. Gomeset al showed that the decrease in protein expression might rely on ERK1/2.[97] TGF-β1 signaling may protect RECK from protein degradation through the Smad3 pathway in Pancreatic stellate cells (PSC).[96] However, TGF-β1 stimulation of OA chondrocytes did not significantly affect RECK gene expression.[98] This difference in regulation may be caused by cell specificity or may be due to the cross-linking of multiple factors in different pathological processes.

Currently, several existing medications can regulate RECK. Liu et al employed reporter gene detection to screen 34 compounds from 880 bioactive chemicals that can trigger RECK expression.[110] Doxorubicin, minocycline, aspirin, and several natural items are among the 12 anti-cancer medications. Furthermore, investigations have revealed that RECK expression can be increased by adenovirus. Given the various properties of RECK, such as homocysteine concentration, its biological function necessitates carbohydrate modification and sensitivity to proteolysis, making large quantities of full-length RECK protein challenging to manufacture in the laboratory.[24] Thus, recombinant proteins containing different RECK domains are functional. Given the increasing application of artificial peptides,[111] the question remains: Could RECK be more widely used by precisely designing peptides based on the corresponding substrate domain for different diseases?

Regulatory Role of RECK in Inflammation

Inflammatory Cytokine and Related Signaling Pathway

During infection and tissue injury, blood flow motility stimulates acute phase responses, hematopoiesis, and immune responses following IL-6 synthesis locally in the lesion to aid host defense.[112] The existence of the blood-soluble IL-6 is a crucial symbol of sepsis.[113] The increase of IL-6 inhibits the expression of RECK dependent on STAT3.[13] Kimura et al also found that IL-1 beta and the expression of TNF alpha decrease RECK expression.[98] They show that RECK may be in a state of lower expression when inflammation occurs. Notably, RECK is involved in regulating IL-6 levels. After RECK siRNA was given, the mRNA and protein levels of IL-6 increased in the hippocampus of rats.[13]

In contrast, after miRNA-200-3c inhibitor was given to relieve its sponge inhibitory effect on RECK mRNA, the expression of RECK in the hippocampus of rats increased, while the expression of IL-6 decreased.[98] Meanwhile, Russell et al found that adenovirus-mediated forced expression of RECK inhibited IL-6-induced SMC proliferation.[13] In addition, RECK plays an important regulatory role by reversing the process of cell migration and oxidative stress mediated by inflammatory factors such as IL-17 and IL-18.[42,114] In both cases, RECK expression was reduced by pro-inflammatory cytokines. Although the exact mechanism is unclear, many studies have shown that RECK expression influences the release of cytokines[42,114,115] (Table 3). Cytokine storm is one of the main pathophysiological mechanisms of sepsis. What and how RECK works on cytokines is expected to make it a new target for the treatment of sepsis.

Monocytes and macrophages are the two cell types most frequently producing IL-6.[133] IL-6 is known to bind to two different receptors (gp130 and membrane-bound IL-6R (mIL-6R) or cyclosoluble IL-6R (sIL-6R)) to initiate its signaling pathway.[14] In breast cancer cells, immunity precipitation and Western blotting prove RECK can interact with IL-6R and gp130 and can increase the expression of RECK to less IL-6 mediated downstream effect (Figure 3C).[13] So, the RECK, IL-6R, and gp130 seem to be interacting competitively.[15] As can be seen, the reason why RECK cut IL-6 fundamental action mechanisms downstream is that RECK not only reduces the production of IL-6 but can also affect the accessibility of its receptor (Table 3).

Notably, IL-6R is only expressed in a few cell types, such as lymphocytes, monocytes/macrophages, and hepatocytes, while gp130 is ubiquitous.[134–136] So, it had to be mentioned that the trans-signaling pathways (one method of IL-6 mediated pathways downstream) combined with circulating protein sIL-6R and gp130 assembly.[137] sIL-6R is predominantly produced by ADAM10 and ADAM17.[116,117] Given the importance of sIL-6R in broadly activating the downstream effects of IL-6, RECK as ADAM10 and ADAM17 negative regulatory factors can reduce it by cutting substrates and lowering protease activity.[7] Pretreatment of cells with GW280264X, a specific ADAM10/ADAM17 inhibitor,

Table 3 The Major Role of RECK Involved in Inflammation and Vascular Barrier Disruption

Role	Related Biological Processes	DIRET Target Molecules	Final Effect	Ref.
Inhibition of proinflammation cytokine signaling pathways	Suppression of cytokine production at the gene level	–	IL-17/IL-18/IL-6/IL-8/IL-10 mRNA ↓	[13, 15, 42, 98, 114]
	Protein levels inhibit cytokines released	ADAMs	TNFA↓	[7,94,116–120]
	Inhibition of soluble receptor release		sIL-6R↓: inhibition of IL-6 Trans signaling pathway	
	Competitive combined with inflammatory factor receptor	IL-6R/ gp130	Competitively binding IL-6R/ gp130 to inhibit of IL-6 signaling pathway	[13,121]
	RECK with cell surface receptors to form new compounds	B1-integrin, Galectin-1, IL-6RA, gp130, UPAR	p-STAT3↓: RECK binds to various cell surface receptors and regulates cytokine and STAT3 signaling	[15]
Adjust the extracellular environment	Limiting extracellular matrix (ECM) breakdown	MMPs	–	
	Cell chemotaxis and migration	MMP2, MMP9, MMP14	It can inhibit the migration and invasion of tumor cells. These include colorectal, breast, pancreatic, gastric, hepatocellular, prostate, and non-small cell lung cancers.	[44,122–128]
		MMP14	RECK is involved in regulating the motility, adhesion, homing, and mobilization of human hematopoietic progenitor cells.	[129]
		MMP13	RECK can block IL-17A-induced TRAF3IP2-dependent SMC migration and proliferation to ameliorate neointimal thickening in proliferative vascular diseases.	[114]
		ADAMs	The release of ICAM1 and VCAM1 factors on immune cells affects migration to endothelial cells	[130]
Protect the endothelial function	Inhibiting vascular leakage /improving vascular permeability)	WNT7A/B, Gpr124	In the presence of Gpr124, RECK potentiates WNT7/β-catenin signaling by raising WNT7A/B to Fz5/Lrp5/6 complexes.	
		ADAMs	Nocth1 pathway: It can affect the release of the active form of the Nocth1 receptor in the Notch pathway and the expression of Notch ligands on the membrane.	[7,131]
			ADAM10/17 by shear endothelial cell surface protein broken endothelial connection tightness	[5]
	Promoting angiogenesis	VEGF	The expression and function of VEGF are often somewhat inhibited when RECK is overexpressed.	[15,132]
		Ang	Forced expression of RECK reduces Ang-2-induced cardiac fibroblast migration.	[63]
Regulate cell differentiation and function		EGFR	RECK can inhibit the phosphorylation of EGFR, which affects the response of macrophages to LPS and its subsequent polarization.	[133]

Note: ↑/↓: The expression level of target molecules increased/decreased.

prevented IL-6R proteolysis induced by inflammatory stimuli.[7,13,94,118,119] RECK may reduce the synthesis of sIL-6R to curb circulating IL-6 trans widespread activation of signaling pathways. Visible RECK control in every link of IL-6 signaling pathways, it can not help but ponder that a decrease in the level of RECK may serve to balance the mechanism of active defense, or due to excessive inflammation, the passive decrease of RECK cause the loss of the ability to regulate

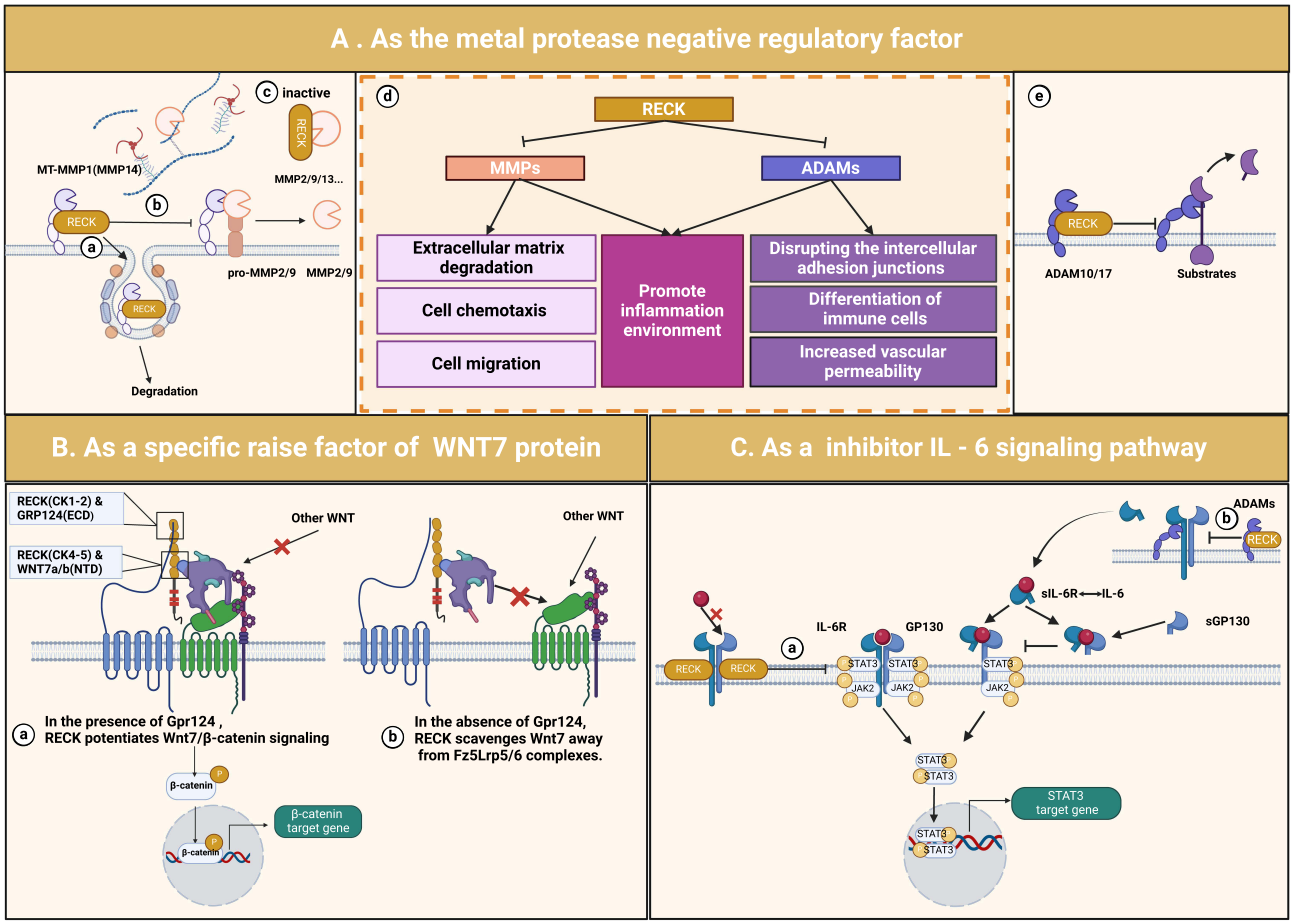

Figure 3 The major function of RECK: (**A**) RECK is a metal protease negative regulatory factor: (**a**) RECK binds to MT1-MMP and binds it to the GEEC-CLIC endocytic pathway for degradation. (**b and c**) MT1-MMP1 can cleave matrix metalloproteinases such as MMP2 and MMP9 and release its mature form. RECK can negatively regulate the release of MMP2 and MMP9 by inhibiting MT1-MMP and can make MMP2 and MMP9 inactive by directly binding to them. (**d**) RECK negatively regulates its downstream effects by inhibiting the activity or expression of MMPs and ADAMs. (**e**) RECK can negatively regulate the release of MMP2 and MMP9 by inhibiting MT1-MMP and can make MMP2 and MMP9 inactive by directly binding to them. (**B**) RECK is a specific raise factor of WNT7 protein: (**a**) In the presence of Gpr124, RECK potentiates WNT7/β-catenin signaling. (**b**) In the absence of Gpr124, RECK scavenges WNT7 away from Fz5/Lrp5/6 complexes. (**C**) RECK is involved in both the IL-6 signaling pathway and the Trans signaling pathway: (**a**) RECK can competitively bind the IL-6 receptor and gp130, forming the IL-6 receptor complex, and can block the IL-6 signaling pathway. (**b**) RECK can inhibit ADAM10 cleavage and release soluble IL-6R so that harmful IL-6 trans signal path. Created in BioRender. Qin, Y (2024) https://BioRender.com/p82z625.

and balance inflammation factors? (Figure 3C) Therefore, the follow-up study of RECK in inflammatory disease may encounter challenges.

Negative Regulation in the ADAMs Mediated Inflammatory Process

ADAMs are a kind of proteins across the membrane that influence cell adhesion, migration, protein hydrolysis, and signal transduction to control the cell phenotype.[138] As surface-expressed proteases, they mediate the cleavage of vascular surface molecules at extracellular sites close to the membrane. This process, known as shedding, results in the release of extracellular domains of soluble substrates, thereby critically regulating the biological function of the substrate. ADAMs metalloproteinase activity enables immune cells and endothelial cells to release approximately 40 substrates, including inflammatory chemicals (e.g, TNF-α, IFN-γ, TGF-β, IL-4, IL-10, IL-13, IL-6, FKN), as well as cell surface adhesion molecules (e.g, VCAM-1, ICAM-1) and chemokines (e.g, CX3CL1, CXCL16). If these factors are overexpressed, they will cause a cytokine storm and cause damage to the body.[5,6] In the early days of the study, we found that ADAM10 and ADAM17 in sepsis endothelial injury played an important role. ADAM10 and ADAM17 are highly elevated and associated with the development and progression of sepsis.[139–142] RECK has been reported to interact with ADAM10/17 in the ADAM family (Figure 3A-**e**). It has been shown that RECK physiologically inhibits ADAM10. The

regulation of this adverse effect is limited to its enzyme activity, and its mRNA or protein expression level has not been affected.[7] However, it has been shown that endocytosis occurs when ADAM10 is inactivated.[143] Does the negative regulation of ADAM10 by RECK proteins involve a more complex regulatory mechanism? It needs further research.

RECK Inhibits ADAM10/17 Proteolytic Activity to Control Its Downstream Inflammation Factor Release

Muraguchi et al showed that RECK directly inhibited the proteolytic activity of ADAM10, protected Notch ligands from being shaded of extracellular domains, stabilized the expression of Notch ligands on the cell membrane, and enhanced Notch signaling.[7] In Alzheimer's disease, RECK inhibits ADAM10 cutting APP, GDE2 by cutting RECK to reverse this.[94,95] In other words, RECK has been shown to inhibit Notch signaling in neural tissue and during angiogenesis.[16] These findings suggest that RECK may change due to the ADAM10/17 downstream substrate effect, which can significantly affect the microenvironment. Notch signaling is associated with several pro-inflammatory conditions, such as rheumatoid arthritis and uveitis.[144,145] ADAM10 also sheds the Notch extracellular domain at the cell membrane to generate the soluble DLL1 ligand.[7] In the intensive care unit (ICU) for the first 24 hours, sDLL1 was found to distinguish sepsis and biomarkers of systemic inflammation induced by surgery.[146] DLL1 has been identified as potential T-cell fate rules Notch1 ligands. It is also involved in immune signaling and plays an important role in the proliferation and homeostasis of immune cells.[146–149] Increasing the activity of Notch2 is known to regulate the fate of monocytes and the inflammatory response's toll-like receptor (TLR) signal.[150] However, ADAMs can cleave cytokines and receptors (erbB4, MET, NGFR, PDGFR, TNFR, etc)., additional ligands (neumodulin), IGF binding proteins, and NOTCH signaling elements.[151–153] In addition to the involvement of ADAM10/17 in the regulation of the IL-6 signaling pathway by releasing soluble IL-6 receptors as mentioned above, ADAM10/17 is also the main protease of TNFR1 and TNFR2 receptors, and soluble TNFRs (sTNFR), and can act as decoy receptors by trapping sTNFα.[154] In particular, ADAM17 cracks mTNF alpha, releasing soluble TNF alpha critical protease ligand (TNF alpha). Soluble TNF alpha can autocrine or paracrine to combine with cell surface TNFRs, which starts the TNF alpha signal pathway.[155]

RECK May Control Inflammatory Diseases by Affecting Immune Cells Through ADAMs

ADAM17 mediated shedding of colony-stimulating factor 1(CSF-1) on the surface of neutrophils and macrophages promotes macrophage proliferation and inhibits macrophage function through CSFR1 in acute and chronic inflammatory states.[156,157]

Many studies have shown that epidermal growth factor receptor (EGFR) can be a potential therapeutic target for inflammatory diseases. The activation of EGFR may be involved in the occurrence of inflammatory diseases. Excessive expression of epidermal growth factor receptors may be associated with a variety of skin diseases, such as psoriasis, atopic dermatitis, etc. In addition to these diseases occurring spontaneously, it has been reported that TLR4 mediates macrophage activation to initiate EGFR phosphorylation.[158] While inhibiting EGFR signaling can inhibit or prevent phosphorylation of its downstream, AKT, ERK1/2, and IκB predominate also can reduce the renin-angiotensin system (RAAS) activity.[159] Some studies have shown that RECK can reduce the tyrosine phosphorylation of EGFR, but there is no evidence of direct interaction between the two.[28] EGFR belongs to the HER family, and seven known official ligands mainly activate its phosphorylation. These include EGF (classical ligand), transforming growth factor-α (TGFA), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin (AREG), β-cellulose (BTC), epidermal regulatory protein (EPR), and epidermal growth factor (EPGN) associated. The above ligands are anchored across a membrane protein on the surface of the cell membrane and need to be released by proteases cut through the action on the membrane of the EGFR secretion pathway, further opening the ring form dimers of EGFR via the phosphorylated tyrosine loci and activate the downstream pathway.[153] ADAMs are reported to be involved in almost all known ligand EGF samples from the release of the cell membrane. ADAM10 and ADAM17 can cut several ErbB ligands in different experimental conditions, especially ADAM17.[160] In ADAM17 knockout mice and cells, the interaction between EGFR and its ligands was absent. In Kasina's prediction, inhibition of metalloproteinase activity is vital for blocking EGFR signaling when ADAMs are highly expressed.[152] Therefore, the inhibitory effect of RECK on EGFR phosphorylation is most likely mediated by its function in negative regulation of metalloproteinase activity. So far, the visible RECK itself has certain

reduced inflammation factors; it not only can block the inflammatory pathways but also participates in regulating macrophage activation.

From the above, it can be seen that the substrates of ADAMs are extensive, which also endows it with diversity in microenvironmental regulation. Researchers familiar with ADAMs have learned that the chaperone proteins of ADAMs, such as TSPAN and RHIOM, play a key role in substrate selection. This raises an important question: Does RECK have differential affinity for the complexes formed by ADAMs with different chaperones? This question is directly related to whether RECK can specifically regulate the ability of ADAMs to cleave specific substrates. Therefore, the development of strategies that can obtain or induce RECK expression may provide new potential avenues for the treatment of inflammatory diseases. Therefore, maintaining or inducing the RECK expression strategy has therapeutic potential in inflammatory diseases.

RECK Negatively Regulates MMPs-Related Inflammatory Process

RECK is an established MMP inhibitor (Figure 3A(**a-c**)) (Table 3). Inhibition of the Extracellular MMPs has been used in the treatment of inflammatory diseases, acute respiratory distress syndrome(ARDS), and endotoxin injection reaction of cytokines and chemokines, the increased impact on the inflammatory response.[161–163] Studies have shown that MMP inhibitors can protect mice against cytokines generated, pulmonary vascular permeability, mortality, and other adverse reactions.[11] Currently, the substrates of RECK have been identified as MMP2, 7, 9, 14, and 17.[11,24,41]

A large number of studies have shown that MMP7/17 plays a role in a state of inflammation. For example, MMP17 regulates the production of interleukin-1(IL-1) and extracellular matrix aggregated sugars in articular cartilage in an inflammatory environment.[164,165] MMP7 attenuates animal intestinal permeability induced by LPS and reduces mortality because LPS triggers the excessive expression and activation of small intestine MMP7.[166] It has recently been found that RECK can promote MMP14 to endocytosis in clathrin-independent pathways.[13,122] By blocking MMP14(MT1-MMP), RECK can limit the production of active MMP2 while controlling the enzyme activity that breaks down MMP2. The inhibition of MMP2 and MMP9 and RECK-mediated activity has been shown in multiple tissues and regulates inflammation in different models.[35,103,122] MMP2 and MMP9 are widely studied markers of sepsis and are the leading indicators of sepsis.[167] Elevated levels of MMP2 and MMP9 are associated with sepsis's occurrence, prediction, and progression.

Reducing its levels is a therapeutic goal in diseases such as sepsis, lung injury, and refractory vasoconstrictor/coagulopathy.[168–173] In experimental asthma, acute pyelonephritis model, and joint inflammation, the levels of MMP2 and MMP9 are directly related to the severity of inflammation.[174–176] In the experimental autoimmune encephalomyelitis (EAE) model, the $CD4^{+}$T cells invade and need local MMP2 and MMP9, which mediates the essence of the basement membrane damage.[177] Ries such as those found in cultured human mesenchymal stem cells, inflammatory cytokines increase MMP2 and MMP9 and, in turn, allow chemotactic migration through the reconstruction of the basement membrane.[178] MMP9 has proven to be involved in ischemia after actively raising $CD11b^{+}$ white blood cells in the liver and neutrophil migration.[179] RECK expression in Chronic Obstructive Pulmonary Disease (COPD) patients is low and negatively correlated with inflammation.[180] Tip the inflammatory cytokine, MMP activity, and through the basement membrane of the complex interacts between immune cells infiltration. RECK can also negatively control MMP9 and prevent pro-MMP9 from escaping the cell membrane.[122] The k23 motif of RECK can physically bind to MMP9 in lung cancer cells, preventing the functional competition of MMP9 and tumor angiogenesis and dissemination.[35] RECK may inhibit inflammation and the migration of neutrophils by down-regulating MMP9. RECK may also control leukocyte extravasation into other organizations at the core of the adjustment factor.

Regulatory Role of RECK in Vascular Endothelial Function

Endothelial function refers to the endothelial cells regulating vascular smooth muscle cells, including vasomotor, anticoagulant, anti-inflammatory, and other functions (Table 3). The regulation role of RECK in endothelial function is crucial to its mechanism diagram, which shows the complexity of this process in detail and accuracy.

RECK and VEGF

VEGF is a mitogen and angiogenic agent that increases vascular permeability and mediates endothelial proliferation, migration, and survival.[181–183] Patients with sepsis have high VEGF levels, and in a meta-analysis, high VEGF was linked to patients' poor clinical outcomes.[184,185] Oncology is currently the most active field of RECK and VEGF research. The main conclusions about RECK and VEGF are that overexpression of RECK can hinder the production and function of VEGR.[15,132,184,186–188] However, the precise mechanism remains unclear. RECK, as previously established, inhibits MMP9's function.[122] Contrarily, tissues that need neovascularization produce VEGF, which is mostly released by MMP9 activity in the extracellular matrix library.[189,190]

Furthermore, several studies have shown that inhibiting the availability of VEGF leads to a decrease in the permeability of blood vessels and a reduction in the progression of acute lung and kidney damage generated by LPS.[20–23] Inhibiting STAT3 shields the endothelium barrier from VEGF-mediated vascular permeability, and this route is linked to JAK2/STAT3 signaling.[191] RECK has the effect of inhibiting STAT signaling, as was previously mentioned.[15] We propose that the detrimental consequences of VEGF signaling pathway activation in sepsis are considerably exacerbated by RECK downregulation.

RECK and WNT

The WNT signaling system is involved in several physiological, pathological, and developmental pathways. The WNT/catenin axis seems to have a pro-inflammatory role, and the activation of the WNT/catenin axis is closely related to organ function damage in sepsis, and many studies have shown that inhibition of this axis can treat sepsis.[192,193] RECK has been shown to interact with WNT7a, WNT7b, and Gpr124 and trigger canonical WNT signaling (β-catenin signaling) in vascular endothelial cells (ECs).[109,194,195] The Gpr124/RECK complex is the only known WNT ligand-specific receptor complex, which is a key therapeutic target for vascular function.[196] That implies that RECK performs a crucial role in vascular maturation and growth, indicating that RECK might be a potential therapeutic target for vascular injury (Figure 3B).[197,198] However, the WNT7a/7b-RECK pathway in sepsis, on the other hand, is unknown.

RECK and Notch Signaling

Notch signaling is essential for angiogenesis and consists of five homologous ligands (Delta-like ligands (DLL) −1, −3, −4, Jagged-1, −2) and four receptors (Notch-1, −2).[199] DLL1 is cleaved by ADAM10 to create sDLL1, and stimulation of sDLL1 has been demonstrated to induce activation, as well as loss of the tight endothelial structure and barrier function.[200] DLL4 is only present in the endothelial cells of arteries, and its lack or suppression can result in excessive and ineffective formation of hyperbranched blood vessels. VEGF/VEGFR2 can activate DLL4. Another crucial role of DLL4 is to increase the expression of VEGFR1 and decrease the expression of VEGFR2, the cell's sensitivity to VEGF, and inhibit the formation of new blood vessels in a proangiogenic environment. VEGF seems to facilitate the development of sprouts in this stage, while DLL4 signaling seems to impede the production of sprouts. VEGF upregulates DLL4 expression, suggesting that this signaling pathway may function as a negative feedback mechanism for endothelial budding. RECK has the ability to inhibit ADAM10 activity, hence regulating the Notch signaling pathway.[201] Simultaneously, ADAM10 has been shown to enhance the production of endothelial cell membrane DLL4, which is dependent on Notch pathway activation. DLL4-induced Notch signaling upregulates DLL4 expression, forming a feedback loop with the Notch signaling pathway.[199] Therefore, RECK is likely to play a negative regulatory role for DLL4. Jagged-1, another Notch pathway ligand, is cleaved by ADAM17, which has proangiogenic action and inhibits DLL4-dependent signaling. At the same time, it can promote cell cycle progression and endothelial cell proliferation via the evolutionarily conserved route WNT signaling. We hypothesize that RECK may work to oppose DLL4 and stabilize DLL1 and Jagged-1 in cell membranes, ensuring that angiogenesis occurs correctly. As a result, the Notch pathway is also an important connection in RECK's regulation of angiogenesis.

RECK and Angiopoietin (Ang)

Angiopoietin (Ang) is an angiogenic factor linked to neovascularization, and both its Ang-1 and Ang-2 subtypes are major angiogenic factors in humans.[202,203] Ang-1 is a Tie-2 agonist that increases vascular integrity, decreases vascular

leakage, and inhibits the production of inflammatory genes. Ang-2 increases endothelial activation, instability, inflammation, and cell survival in the presence of VEGF.[204–206] Ang-1 and Ang-2 levels in plasma fluctuate during sepsis in the presence of LPS. The fundamental mechanism of organ failure is vascular leakage caused by LPS, specifically decreasing Ang-1 and Tie-2 expression while boosting Ang-2 levels.[207] Increased Ang-2 was associated with decreased RECK expression in vivo.[63,207] During sepsis, the Ang/Tie-2 ligand-receptor system has been shown to play an important role in vascular endothelial cell activation, angiogenesis, and vascular integrity.[206,208] Several clinical studies have also found that sepsis is related to high levels of Ang-2 and low levels of Ang-1, or high levels of Ang-2/Ang-1 and low levels of Ang-1/Tie-2 ratio.[204,209,210] Ang-1 promotes RECK expression in HUVECs, while the expression of both decreases in sepsis.[211] As a result, we postulate that RECK contributes to sepsis by engaging in Ang/Tie axis-mediated vascular stability.

RECK and ADAMs

As mentioned, RECK may regulate inflammation through ADAMs. In the early days of the study, we found that ADAM10 and ADAM17 in sepsis endothelial injury play an important role.[139–141] In the vasculature, ADAM 8, 9, 10, 12, 15, 17, 19, 28, and 33 are expressed on endothelial cells, smooth muscle cells, and leukocytes. Cycle souble cell adhesion molecule (sCAM) interaction with different types of white blood cells, mediating leukocytes in endothelial cells on the surface of the raise, rolling, combination, and then across the endothelial migration, increase endothelial adhesion connection (such as VE-cadherin, E-cadherin) damage, including impact inflammation fade, regeneration and new blood vessels to form, and thus play a unique role in vascular biology.[5,212]

Although the specific mechanism is unclear, many studies have shown that RECK overexpression affects the release of cytokines.[42,114,115] In rat aortic smooth muscle cells (A-10) and human vascular smooth muscle cells (hVSMC), high expression of MIR-195-5p reduced RECK expression and, in turn, increased the release of VCAM1 and ICAM1.[213] VCAM1, and ICAM1 are important members of the adhesion molecule family; they are the key molecules of endothelial cell dysfunction and injury. It is upregulated when endothelial cells are subjected to inflammatory or mechanical stimulation. They aggravate endothelial injury by mediating adhesion and migration of leukocytes and promoting inflammatory cell infiltration.[214–216] These factors are closely related to vascular endothelial injury in sepsis, and their release process depends on the enzymatic activity of ADAMs. ADAM17 mediated VCAM 1 and ICAM1fell off and released.[214,215,217] The change of ADAM17 activity may affect the expression level of L-select, thereby regulating the interaction between leukocytes and endothelial cells and playing an important role in inflammatory response.[218] This process may alter the localization and aggregation of leukocytes at sites of inflammation,[219] further exacerbating vascular endothelial dysfunction. In addition, it has been shown that ADAM17 active particles are able to promote the release of TNF-α, TNF receptor 1(TNFR1) and endothelial protein C receptor (EPCR), thereby regulating the inflammatory balance.[220] Meanwhile, ADAM17-dependent cleavage recruits inflammatory cells to the vessel wall and activates monocytes via CD44.[221]

Thus, the regulation of ADAM17 expression or function by RECK may significantly affect the recruitment of inflammatory cells as well as the activation state of vascular cells. First, RECK has an anti-inflammatory function by inhibiting the inflammatory response and reducing inflammation damage, protecting endothelial cells from inflammation. RECK can inhibit the production and release of inflammatory mediators and reduce the degree of inflammation to maintain the normal function of the vascular endothelium. In addition, RECK can regulate vascular endothelial cell signaling pathways and affect their activity and expression level to realize the precise control of the vascular endothelial function and maintain the stability of the vascular endothelial function and balance.

RECK as a Potential Crucial Molecule for the Targeted Treatment of Sepsis

Sepsis is a potentially fatal organ dysfunction caused by a dysregulated bacterial response to infection. Its pathogenesis is based on cytokine storm and endothelial leakage caused by severe inflammation. The early consensus on sepsis emphasized systemic inflammation induced by infection.[222] When the body is infected, PAMPs and DAMPs derived from necrotic cells bind to pattern recognition receptors, triggering a cascade of events and increasing the production of inflammatory factors.[2] When the body is infected, PAMPs and DAMPs derived from necrotic cells bind to pattern recognition receptors, triggering a cascade of events and increasing the production of inflammatory factors.[1] There are

multiple interactions between cell-cell and cell-cell matrices. Cell-cell interactions include leukocyte-endothelial cell adhesion and lymphocyte-antigen presenting cell interactions.[223] Cell-matrix interactions are required for immune cell migration to areas of inflammation, including endothelial migration and epithelial migration. Remodeling of the ECM through proteolytic degradation is required for these migratory pathways. The circulatory system of different cytokine cascades in the cell-cell and cell-cell matrices also plays a vital role in matrix interaction.[224,225]

RECK may play an important regulating role in sepsis. RECK mRNA expression levels decrease in LPS-stimulated cell models. At the same time, it is essential to note that RECK mRNA level also drops in sepsis patients' peripheral blood (GEO data set: GSE134147), and in the CLP mice organs, the RECK mRNA level drops over time (GEO data set: GSE224127). In bronchial epithelial cells, mycoplasma pneumonia cuts RECK and stimulates the release of matrix metalloproteinases-9. Instead, RECK expression significantly reduces the mycoplasma pneumonia caused by the rise of MMP9 enzyme activity.[62] However, the literature still needs to clarify whether RECK is employed in sepsis. Based on the above discussion, RECK protein has considerable crosstalk with many inflammatory factors and inflammation-related pathways. At the same time, they are involved in activating immune cells and white blood cells, controlling extravasation to other organizations at the core of the adjustment factor. RECK Inhibits a variety of MMPs and integrin and the activity of ADAMs.[13] Many cell surface proteins, ECM, and non-ECM bioactive chemicals (such as growth factors, cytokines, chemokines, etc) are mediated by both MMPs and ADAMs.[226–228] All these provide solid evidence for the regulatory role of RECK in inflammatory diseases. In addition, the RECK endothelial function also shows a strong regulatory role. RECK is expressed in human umbilical vein endothelial cells (HUVECs), and any deviation in RECK expression leads to impaired angiogenesis and cellular senescence in this specific cell type. Vascular endothelium is a key target organ of sepsis. Chemotaxis, adhesion, transendothelial migration of inflammatory cells, and releasing many inflammatory factors are important sources of endothelial injury. The anti-inflammatory function of RECK blocks endothelial cell injury from the source and controls several key molecules conducive to endothelial repair. We expect the RECK to become the key molecule for treating the septic cardiovascular system.

Conclusions and Future Considerations

RECK serves as a crucial target gene in the domains of blood vessels and inflammation, in addition to its role as a beneficial gene in tumor disorders. RECK exerts a potent regulatory function in the microenvironment and is crucial for maintaining the balance of the extracellular matrix and managing inflammatory diseases. Additionally, it acts as a regulator for various signaling pathways, including angiogenesis, enhanced perfusion, oxygen transport, delivery of factors that promote cell survival, and even the mobilization of regenerative stem cells. Simultaneously, RECK plays a crucial role in angiogenesis and tissue healing. The physiological importance of RECK is supported by the findings that mice lacking RECK could not survive beyond embryonic day 10.5(E10.5) due to compromised extracellular matrix integrity and early vascular development.[122] This article provides a concise overview of the substantial impact of RECK in inflammatory disorders and its role in regulating vascular endothelial dysfunction. The fast progression of these two pathological processes results in the resistant nature and elevated fatality rate of sepsis. In the future, we anticipate that RECK might serve as a crucial molecule for the focused treatment of sepsis in the vascular system. However, most studies regarding RECK are still mainly focused on the field of cancer, with only a small number of studies related to inflammation and angiogenesis, and the research in the field of sepsis is still blank, which is the limitation of the current review article. Due to the lack of studies on sepsis, we can only speculate the possible role of RECK in sepsis from closely related septic disease progress, such as inflammation and vascular. We still need a lot of research to understand the actual role of RECK in sepsis. Through an examination of publicly available databases, we discovered a reduction in the expression of RECK in bone marrow-derived macrophages (BMDM) of mice that were stimulated with LPS. This drop was also observed in the heart and liver tissues of a model generated by LPS.[229–231] Understanding the role of RECK in sepsis is critical because RECK regulates several factors closely related to the vascular endothelial barrier and inflammatory storm, and this related process is the main focus of our ongoing investigation. This research examines the regulation of RECK proteins and the impact of modifying these mechanisms on the inflammatory response pathway.

Nevertheless, the production of RECK protein is challenging to modify by human intervention due to its inherent structural features. Fortunately, the technology for using recombinant proteins and peptides is advancing fast. It has been demonstrated that recombinant RECK proteins may effectively mimic the essential activities of RECK. This progress

serves as a solid basis for the future development of RECK applications. The discovery and screening of RECK peptides may result in the creation of peptides that selectively target particular substrates and exert more accurate regulatory functions in the context of diseases. Moreover, besides its function in reducing inflammation in inflammatory illnesses by means of its downstream proteins, RECK also seems to control the process of cell-specific differentiation in particular areas, such as osteoblasts, mesenchymal cells, and neural progenitor cells.[232–234] That also implies that RECK has a promising future in the realm of targeted treatment for sepsis-induced vascular endothelial barrier defects.

Acknowledgment

We would like to thank all members of the Dongguan Key Laboratory of Sepsis Translational Medicine and the Dongguan Key Laboratory of Chronic Inflammatory Diseases for their help and advice. The authors also would like to acknowledge Vanscholar EditorsCo. Ltd, Vancouver, Canada for English editing assistance.All characters are Created in (https://BioRender.com) by Yuting Qin.

Funding

The authors' research was supported by the National Nature Science Foundation of China (82072151), Guangdong Basic and Applied Basic Research Fund (Guangdong-Dongguan Joint Fund)(2023A1515140177), Talent Development Foundation of The First Dongguan Affiliated Hospital of Guangdong Medical University & Foundation of State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia (GCC2023005, SKL-HIDCA-2024-GD4), and Affiliated Hospital of Guangdong Medical University Clinical Research Program (LCYJ2019A002).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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