Histol Histopathol (2008) 23: 1003-1010

http://www.hh.um.es

Histology and Histopathology

Cellular and Molecular Biology

Review

RECK, a novel matrix metalloproteinase regulator

N. Meng[1], Y. Li[1], H. Zhang[2] and X-F Sun[3]

[1]Department of Surgery, The Forth Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China

[2]Division of Biomedicine, School of Life Science, University of Skövde, Skövde, Sweden and

[3]Department of Oncology, Institute of Clinical and Experimental Medicine, University of Linköping, Linköping, Sweden

Summary. Extracellular matrix (ECM) macromolecules are important for creating the cellular environments required during development and morphogenesis of tissues. Matrix metalloproteinases (MMPs) are a family of Zn-dependent endopeptidases that collectively are capable of cleaving virtually all ECM substrates, and play an important role in some physiological and pathological processes. MMP activity can be inhibited by some natural and artificial inhibitors. A newly found membrane-anchored regulator of MMPs, the reversion-inducing-cysteine-rich protein with kazal motifs (RECK), is downregulated when the cells undergo a process of malignant transformation, and is currently the subject of considerable research activity because of its specific structure and function. In this review, we have chosen to concentrate our efforts on the structure, function, regulation, and future prospect of RECK in order to provide a new target for prevention and treatment of tumours.

Key words: RECK, MMPs, TIMPs

Introduction

Invasion and metastasis are the characteristics of malignant tumours and the remodelling of basement membrane (BM) and degradation of extracellular matrix (ECM) is one of the critical steps in tumour development. BM is the first and the most important barrier that carcinoma must break through in order to accomplish the process of invasion and progression. Disruption of BM is the supreme factor during the process of transformation from intraepithelial carcinoma or carcinoma in situ to invasion carcinoma. Adhesion to BM and ECM is another way to finish the process of carcinoma cell local infiltration. Many factors have been reported thus far as being potentially involved in the metastasis/dissemination process of cancer cells. Among them, matrix metalloproteinases (MMPs) are a key family of proteolytic enzymes (Egeblad and Werb, 2002). Several studies show that MMPs have an influence on the adhesion and motility of carcinoma cells, as well as taking part in the degradation of ECM and angiogenesis, therefore they have a significant effect during the process of invasion and metastasis (McCawley and Matrisian, 2001; Rhee and Coussens, 2002). In recent years, lots of research has been focused on the MMPs and their inhibitors. However, recent clinical studies have failed to show a clear benefit from MMP inhibitors compared to conventional therapies (Zucker et al., 2000; Coussens et al., 2002; Egeblad and Werb, 2002). The reversion-inducing-cysteine-rich protein with kazal motifs (RECK) is newly found as a transformation-suppressor gene, which can inhibit the process of tumour invasion and metastasis though regulating the expression of several MMPs. In addition, RECK is also a key regulator of angiogenesis in tumour development.

Offprint requests to: Prof. Xiao-Feng Sun, M.D., Ph.D., Department of Oncology, Institute of Clinical and Experimental Medicine, Linköping University, S-58185 Linköping, Sweden. e-mail: xiasu@ibk.liu.se

RECK gene and protein

The RECK gene is isolated by using an expression cloning strategy, which is designed to isolate human cDNA inducing flat reversion in a v-Ki-ras –transformed NIH3T3 cell line (Kitayama et al., 1989; Noda et al., 1989; Takahashi et al., 1996). The gene has been mapped on human chromosome 9p13–p12, with a length of 87kb (transcription of 4.6kb) and consists of 21 exons. So far, 13 single-nucleotide polymorphisms have been identified, four of them are in the coding region of exons 1, 9, 13 and 15, and the remaining 9 are in introns 5, 8, 10, 12, 15 and 17. The coding region of the gene

Abbreviations: BM, basement membrane; ECM, extracellular matrix; ECs, endothelial cells; HDAC, histone deacetylase; MMPs, matrix metalloproteinases; MVD, microvessel density; RECK, reversion-inducing-cysteine-rich protein with Kazal motifs; TIMPs, tissue inhibitor of matrix metalloproteinases; TGF-ß, transforming growth factor-ß; VEGF, vascular endothelial growth factor.

starts at the 110th basyl of the exon 1 and ends at the 221st basyl of the exon 21. The upstream 52-base region contains a promoter activity. This region contains two Sp1-binding motifs, one cEBPb-binding motif, and one CAAT box (Takahashi et al., 1998; Sasahara et al., 1999; Eisenberg et al., 2002).

Sequence analyses have revealed that RECK cDNAs encode an 110kDa membrane-anchored glycoprotein of 971 amino acid residues, which is rich in cysteine (9.2%) and contains hydrophobic regions at both the NH_2- and COOH-terminal ends. Some studies show that the NH_2-terminal hydrophobic region (26 residues) serves as a signal peptide. The COOH-terminal hydrophobic region (ca. 29 residues) appears to serve as a signal for glycosylphosphatidylinositol anchoring. The middle portion of the protein contains three serine protease inhibitor-like domains, one of which matches the consensus sequence of so-called 'Kazal motif'. In addition, two regions of weak homology to the epidermal growth factor-like repeats have been detected (Takahashi et al., 1998).

Function of RECK

MMPs: basic information

MMPs are a multigene family of Zn-dependent endopeptidases with a highly homologous structure. To date, 26 members of the MMP family have been identified in vertebrates, and 23 of them have been found in humans (Visse and Nagase, 2003). Based on substrate specificities and sequence characteristics, the MMPs can be divided into at least 5 subgroups: collagenases, gelatinases, stromelysins, matrilysins, and membrane-type MMPs (MT-MMPs) (Nagase et al., 2006; Raffetto and Khalil, 2008). They can collectively degrade most ECM components and connective tissue proteins. In addition, some MMPs digest other extracellular molecules such as cytokines (e.g. transforming growth factor-ß, TGF-ß), transmembrane proteins (e.g. integrins, CD44), etc. MMPs play a major role in physiological and pathological processes, such as embryonic development, differentiation, immune surveillance, apoptosis, wound healing, tumour angiogenesis, invasion and metastasis (Lukashev and Werb, 1998). Furthermore, MMPs also have an important effect on the endothelial invasion occurring during neovascularization (Sun and Zhang, 2006), which may be important in the early stages of vascular remodelling in order to maintain blood flow to various organs. Studies show the cDNA transfection of MMP-2, MMP-9, and MT1-MMP can enhance the ability of metastasis of several types of tumours. A high level of MMPs expression has been detected in cancer in the thyroid, breast, ovarian, prostate, colon, lung, head and neck as well as in the plasma of patients with solid tumour (lizasa et al., 1999; Cox and O'Byrne, 2001).

MMPs are synthesized as pre-proenzymes, secreted from cells as proMMPs, and activated on demand by detaching of the hemopexin domain (Nagase et al., 2006; Raffetto and Khalil, 2008). Enzymes involved in such proteolytic processing are also MMP family members in some cases, forming proteolytic activation cascades (Noda et al., 2003). The activity of MMPs can be regulated at different levels: gene expression, proenzyme processing, and inhibition of enzymatic activity (Hidalgo and Eckhardt, 2001). Recently, the study of MMP inhibitors has become a hot spot. Until now, four of the endogenous tissue inhibitors of matrix metalloproteinases (TIMPs), TIMP-1, -2, -3, and -4, have been cloned. The ability of TIMPs to block the autocatalytic activation of latent MMPs and to limit the proteolytic functions of activated MMPs is a function of their ability to bind both latent and active MMPs with a 1:1 stoichiometric ratio (Bode and Maskos, 2001). TIMPs can inhibit all MMPs tested so far, but TIMP-1 is a poor inhibitor for MT1-MMP, MT3-MMP, MT5-MMP and MMP-19. While TIMP-1-null mice and TIMP-2-null mice do not exhibit obvious abnormalities, TIMP-3 ablation in mice causes lung emphysema-like alveolar damage (Leco et al., 2001) and faster apoptosis of mammary epithelial cells after weaning (Fata et al., 2001), indicating that TIMP-3 is a major regulator of metalloproteinase activities in vivo. Studies show that upregulation of TIMPs can inhibit tumour invasion and metastasis. Human α2-macroglobulin is also a key endogenous inhibitor found circulating in the plasma, which can form a complex via binding MMPs, which is eliminated by scavenger receptor-mediated endocytosis. Besides, several other proteins have been demonstrated to inhibit selected members of MMPs: A C-terminal fragment of procollagen C-proteinase enhancer protein and the secreted form of ß-amyloid precursor protein can inhibit MMP-2; the NC1 domain of collagen IV decreases the activity of MMP-2, MMP-3 etc.. Tissue factor pathway inhibitor-2, a serine proteinase inhibitor, is reported to inhibit MMP-1 and MMP-2, but this effect is controversial. In addition, some synthetic MMP inhibitors have reached clinical trials, such as BAY 12-9566 (Bayer) (Molina et al., 2005), BMS-275291 (Rizvi et al., 2004), etc.

RECK inhibits MMPs activity

Many studies suggest that RECK can inhibit MMPs activity through several mechanisms, including direct inhibition of protease activity, regulation of their release from the cell and possibly through sequestration of MMPs at the cell surface (Welm et al., 2002). RECK inhibits the activity of at least three MMP members, including MMP-2, MMP-9, and MT1-MMP (Takahashi et al., 1998; Oh et al., 2001; Sternlicht and Werb, 2001; Sasahara et al., 2002; Liu et al., 2003b) (Fig. 1).

One particular group of MMPs, the gelatinase A and B, also known as MMP-2 and MMP-9, have the capacity to degrade native collagen type IV, a major component of BM. Furthermore, both of them are also involved in the processes of cell differentiation, apoptosis, angiogenesis,

immune response, and growth of tumour cells (Mook et al., 2004), playing an important role in tumour development and progression. MT1-MMP plays a dual role in pathophysiological digestion of several ECM components (including collagen I) through direct cleavage of the substrates in vivo and activation of MMP-2 (Sato et al., 1994; Murphy et al., 1999). During the process of activation of MMP-2, the effect of TIMP-2 is very important. TIMP-2 bridges MT1-MMP with pro-MMP-2 and another MT1-MMP molecule cleaves a portion of the prodomain on pro-MMP-2 to form an intermediate MMP-2 protein, which is then converted into a fully activated enzyme by an autoproteolytic mechanism (Will et al., 1996). In addition, MT1-MMP/MMP-2 axis and TIMPs also play a key role in mediating pro-MMP-9 activation (Toth et al., 2003). Reduction of active MMP-2 is probably due to direct inhibition of its two processing enzymes, MT1-MMP and MMP-2, by RECK, and it has been reported that restored expression of RECK in the HT1080 fibrosarcoma cell line results in reduced amounts of the secreted intermediate form of MMP-2 and of active MMP-2 (Oh et al., 2001). Besides, RECK negatively regulates MMP-9 in two ways: suppression of pro-MMP-9 secretion from the cells and direct inhibition of its enzymatic activity, which inhibit tumour cells invasion and metastasis (Takahashi et al., 1998). MMP-9 can transform the ECM bound or latent growth factor to free or mature growth factor (Fig. 1). RECK directly regulates MMP activity and can indirectly modulate membrane localized growth factor availability. At present, the mechanism of MMP-9 releasing from the cell is still unclear (Welm et al., 2002). Studies have indicated that a significant inverse correlation between the level of RECK expression and extent of MMP-2 activation, but not of MMP-9 activation. Although MMP-9 expression is lower in RECK-high tumours than in RECK-low ones, these differences are not significant (Masui et al., 2003; van der Jagt et al., 2006; Cho et al., 2007). A study shows that collagen fibers around the neural tube, whose peripheral region expresses MMP-2 and MT1-MMP, are dramatically reduced in RECK-deficient mouse embryos (Oh et al., 2001). Thus, MMPs can degradate collagen fibers solely or cooperatively, both of which can be inhibited by RECK.

RECK inhibits angiogenesis

Angiogenesis is the process of forming new blood vessels from existing ones, and requires degradation of the vascular basement membrane and remodelling of the ECM in order to allow endothelial cells (ECs) to migrate into the surrounding tissue (Folkman, 2006), which is an indispensable step in malignant tumour development and progression (Folkman et al., 1989). The ECM can actively regulate cellular proliferation, migration, adhesion and invasion, which influence embryonic development, tissue morphogenesis, angiogenesis, tumour transformation and metastasis (Sun and Zhang, 2006). The balance between ECM breakdown and deposition is critical for EC homeostasis and contributes to vasculogenesis and angiogenesis. MMPs are a family of ECM degrading proteinases, whose activation is the earliest and the most important event during

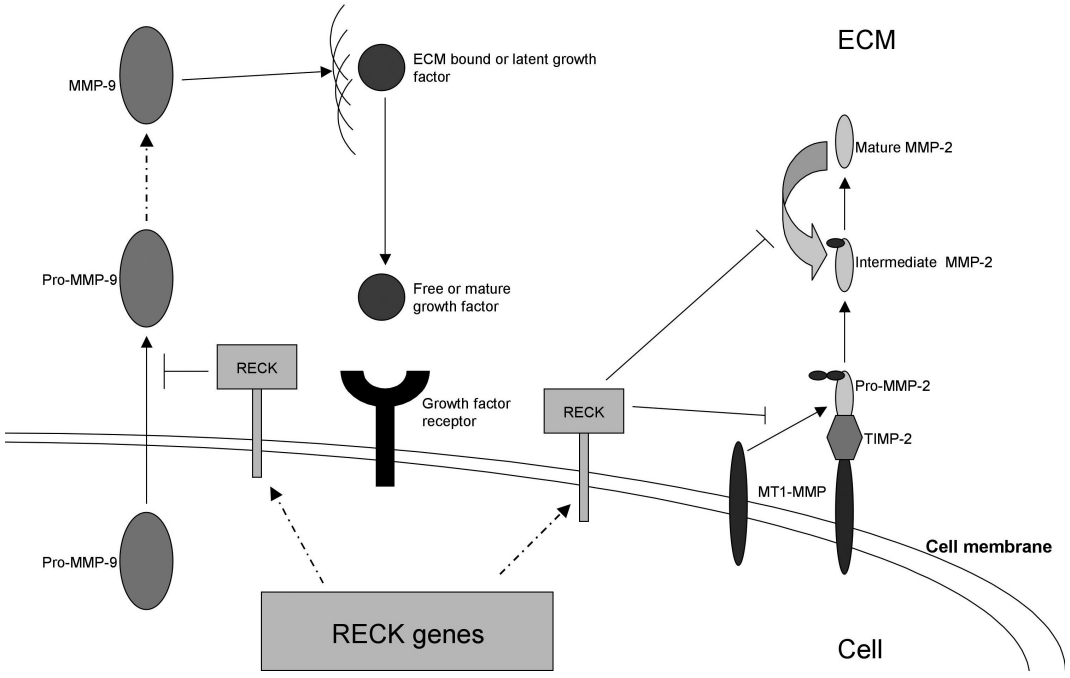

Fig. 1. Reversion-inducing-cysteine-rich protein with kazal motifs (RECK) regulates three matrix metalloproteinases (MMPs). ECM, extracellular matrix; TIMPs, tissue inhibitor of matrix metalloproteinases.

angiogenesis (Heissig et al., 2003). In the presence of high RECK expression, MMP activity is reduced to the point where ECM remodelling is compromised and the ability of preexisting blood vessels to send out capillary sprouts and produce new vessels is inhibited. Thus, the magnitude and spatial pattern of RECK and MMP activity are crucial for normal angiogenesis (Oh et al., 2001). Thus, RECK can also be regarded as a regulator of ECM remodelling by suppressing related MMPs activity, and seems to be essential for proper angiogenesis (Noda et al., 2003).

Application of a blocking peptide that prevents the interaction of MMP-2 with its substrates has been shown to reduce angiogenesis. When tumour cells are introduced into MMP-2 knockout mice, the tumours that develop are less vascularized and exhibit reduced growth compared to the tumours in wild-type animals (Egeblad and Werb, 2002). More recently, a study showed that inhibition of MMP-9 and urokinase plasminogen activator receptor by using siRNA insulted in a decreased angiogenesis in both in vitro and in vivo models of gliomas (Lakka et al., 2005). Adenoviral-mediated MMP-9 downregulation in EC is found to inhibit migration and tube formation, two determinants of angiogenesis (Jadhav et al., 2004). In general, inhibition of MMPs activity plays an important role in suppression of neovascularization (Moses et al., 1990).

Studies show that metastasis formation is a complex multi-step process, which includes the invasion of tumour cells into the stroma, migration through the stroma, probably coupled with protease activity, association with angiogenesis, penetration of the circulation, and settling in the 'newworld', or the metastatic site (Song et al., 2006). Several clinical studies have shown that microvessel density (MVD) acts as a measurement indicator in tumour angiogenesis during the process of tumour invasion and metastasis. The transitional mucosa adjacent to the carcinoma displays intermediate levels of MVD between normal mucosa and the carcinoma. The highest level of MVD is found at the invasive margin of carcinomas, a site of active tumour invasion. Thus, MVD closely correlates with tumour progression and prognosis in a variety of malignant tumours (Hlatky et al., 2002). Takenaka et al. (2004) have demonstrated that RECK expression is negatively associated with MVD, and plays an important role in angiogenesis in non-small cell lung cancer. Furthermore, angiogenic growth factors such as TGF-ß, vascular endothelial growth factor (VEGF), and angiogenin etc., act as autocrine or paracrine growth factors to induce angiogenesis (Folkman, 2006). The ligands of the VEGF family include VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E (Sun and Zhang, 2006). VEGF is a potent angiogenic factor, and bioactive as freely diffusible proteins in the extracellular space, where it acts on EC by stimulating cell proliferation, migration, and tubular organization and increases vascular permeability. Many studies have shown that expression of VEGF is positively related to MVD in several types of malignant tumours (Kern et al., 2002; Niedergethmann et al., 2002; Wendum et al., 2003). Interestingly, the effects of RECK are determined to be most robust in the tumours which expressed VEGF at higher levels, raising the possibility that RECK may suppress the tumour angiogenesis induced by VEGF (Song et al., 2006). Overexpression of MT1-MMP in breast cancer cells results in increased VEGF expression, correlating with rapid development of highly vascularized tumours (Sounni et al., 2002). However, studies do not uncover any significant correlations between RECK and VEGF at present, although they are increased in tumour compared with normal tissue (Song et al., 2006).

Vascular development is a key process that must occur for embryonic development to proceed. Mice lacking functional RECK allele die around embryonic day 10.5 (E10.5) with a defect in vascular maturation, while about one-third of the mice lacking RECK and MMP-2 are still alive around day 11 (E11.0), but none of them can survive beyond day 11.5 (E11.5), which suggests that abrogating MMP-2 activity partially rescues the phenotype (Oh et al., 2001). However, it is unclear exactly why vascular development stops when RECK is absent. Vu and Werb (2000) have demonstrated that RECK might regulate the amount or fate of certain extracellular signalling molecules, such as TGF-ß, VEGF, thrombospondin, etc., which in turn regulate collagen production or other aspects of angiogenesis. However, Oh et al. (2001) have reported that accelerated degradation of ECM components, such as collagen I, is likely to be the primary consequence of RECK-deficiency. Thus, RECK is crucial for angiogenesis and plays an important role in the process of mice embryonic development.

Regulation of RECK

RECK expression can be detected in a number of normal human tissues or cultured cells derived from them, while its expression is low or undetectable in many tumour-derived cell lines; also, RECK expression can be downregulated by several oncogenes including ras (Takahashi et al., 1998; Sasahara et al., 1999). ras genes, consisting of three functional genes, H-ras, K-ras, and N-ras, are frequently found to harbour a mutation in human tumours. ras is known to affect cell-ECM interaction in several ways: activated ras downregulates several ECM proteins, such as fibronectin and collagen I, as well as ECM-receptors (integrins), while it upregulates several MMPs. A recent study showed that ras can suppress RECK expression via inhibition of transcription (Sasahara et al., 1999). Sp3, a member of the Sp transcription factors family, sharing with Sp1 the same consensus binding sequence, is reported to be a dual-function regulator that can either induce or inhibit transcription, depending upon both the promoter and the cellular context (Majello et al., 1997). Several studies have demonstrated that a high ratio of Sp1 to Sp3 may

activate gene expression, whereas a high ratio of Sp3 to Sp1 represses gene expression (Chadjichristos et al., 2002; Wong et al., 2003; Pang et al., 2004). Chang et al. (2004) have found that transcription factors Sp1 and Sp3 can activate the full-length RECK promoter, as well as its deletion mutant containing the proximal 52 bp region in a dose-dependent manner in SL2 cells. These data indicate that Sp1 and Sp3 are transactivators, rather than repressors, for the RECK gene. A study has shown that ras might induce histone deacetylases (HDACs) phosphorylation in vitro and in cells, and increase nuclear accumulation of HDACs (Zhou et al., 2000). Whether the process can induce the binding of HDACs to Sp1 protein to suppress RECK expression or not are still to be tested. HER-2/neu oncogene also inhibits the expression of the MMP inhibitor RECK to promote cell invasion. Hsu et al. (2006) have reported that HER-2/neu transcriptionally represses RECK expression through inducing extracellular signal-regulated kinases activation, which in turn phosphorylates Sp1 to enhance its DNA binding activity. After phosphorylation, the interaction between Sp1 and HDAC1 may be modulated. Specific HDAC inhibitor trichostatin A, HER-2/neu kinase inhibitor AG825 can effectively reverse the inhibitory effect of ras on RECK promoter activity. Whether hypermethylation of the RECK promoter region is also involved in ras-mediated downregulation of the RECK gene is still the subject of experiment (Sasahara et al., 2002). Tgat, originally identified in a cDNA library derived from fresh ATL cells (Yoshizuka et al., 2004), may block the function of RECK by physical association via the C-terminal unique sequence, resulting in activation of MMPs and enhancing cell invasion (Mori et al., 2007). In addition, the RECK expression is significantly downregulated in these cell lines transfected by other oncogenes such as v-fos, c-myc, v-src, v-fms, v-fes, v-mos, ect. (Takahashi et al., 1998). To this end, RECK is the negative co-target for many oncogenes. However, the detailed mechanism inducing downregulation of RECK is not yet clear.

Future prospect

Accumulating evidence has suggested that the altered expression of RECK plays a role in various human malignancies. Studies have shown that the expression of the RECK protein in tumour is inconsistent with the fact that RECK gene expression is suppressed in several tumour-derived cell lines and ras-transformed fibroblasts (Sasahara et al., 2002). Pancreatic cancer cell lines do not exhibit RECK expression, according to the results of Western blot analysis, although a high level of RECK protein expression is demonstrated in 52% of pancreatic cancers (Masui et al., 2003). Similar results have been seen in gastric (Song et al., 2006) and colorectal cancers (Takeuchi et al., 2004). Furumoto et al. (2001) have reported that high RECK expression correlates with less invasive tumours and a better prognosis in patients with hepatocellular carcinoma. Tumours which retained RECK expression are less prone to recur, probably due to reduced angiogenesis and inhibited ECM remodelling. On the other hand, downregulated RECK expression could induce tumour angiogenesis and promote tumour progression (Takahashi et al., 1998; Oh et al., 2001; Weaver, 2002). Li et al. (2005) have shown that in hilar cholangiocarcinomas, the expression of RECK is significantly lower than in normal bile duct tissue, and a similar result has been seen in breast cancer versus the corresponding normal tissue (Span et al., 2003). Song et al. (2006) have demonstrated that the significant correlation between RECK expression and the growth pattern of gastric cancer. Reduced RECK expression is more commonly found in cancers with macroscopically infiltrative growth than those with expansile growth. Taken together, these results support the view that RECK is an important tumour suppressor gene.

Some studies have shown that RECK is a promising molecule with regard to the prediction of tumour invasion and metastasis, via the dual mechanisms of MMP pathways (Oh et al., 2001, 2004; Rhee and Coussens, 2002; Liu et al., 2003a; Span et al., 2003; Takenaka et al., 2004; Takeuchi et al., 2004; van Lent et al., 2005) and angiogenesis (Takahashi et al., 1998; Oh et al., 2001; Takenaka et al., 2004; Takeuchi et al., 2004), which can act as a prognostic indicator in patients with hepatocellular (Furumoto et al., 2001), pancreatic (Masui et al., 2003), gastric (Song et al., 2006), breast (Span et al., 2003) and lung cancer (Takenaka et al., 2004). Furthermore, the transmembrane part of the RECK gene is involved in signal transduction, which makes it play a more important role than what we have found during tumour growth and metastasis. Non-steroidal anti-inflammatory drugs are known to have anti-angiogenic and anti-metastatic activities both in vivo and in vitro. Liu et al. (2002) have considered that an induction of RECK expression may be one of the mechanisms by which non-steroidal anti-inflammatory drugs suppress MMP activity to block angiogenesis and metastasis. Application of the RECK gene or protein, its pharmaceutical mimetic, or drugs which activate endogenous RECK expression, should be assessed for their efficacy as possible therapeutic or preventive agents for various human cancers, which may provide a new strategy for cancer therapy.

Conclusions

The newly found MMPs inhibitor, RECK, which contains a unique glycosylphosphatidylinositol domain and a number of cysteine residues, does not show robust similarities to TIMPs in amino acid sequence, which makes it a novel membrane-targeted MMP inhibitor. RECK can inhibit at least three members of the MMP family: MMP-2, MMP-9, and MT1-MMP, and plays an important role in the process of degradation of BM and ECM, as well as angiogenesis, which are crucial for tumour invasion and metastasis. Several studies have

shown that RECK can be suppressed by ras at the transcription level, although, the detailed mechanism is yet unclear. Accumulating evidence has suggested that the altered expression of RECK plays a role in various human malignancies. Studies on the RECK gene and protein may contribute to development of new strategies for cancer prevention and therapeutic intervention.

References

Bode W. and Maskos K. (2001). Structural studies on MMPs and TIMPs. Methods Mol. Biol. 151, 45-77.

Chadjichristos C., Ghayor C., Herrouin J.F., Ala-Kokko L., Suske G., Pujol J.P. and Galera P. (2002). Down-regulation of human type II collagen gene expression by transforming growth factor-beta 1 (TGF-beta 1) in articular chondrocytes involves SP3/SP1 ratio. J. Biol. Chem. 277, 43903-43917.

Chang H.C., Liu L.T. and Hung W.C. (2004). Involvement of histone deacetylation in ras-induced down-regulation of the metastasis supressor RECK. Cell Signal. 16, 675-679.

Cho Y.B., Lee W.Y., Song S.Y., Shin H.J., Yun S.H. and Chun H.K. (2007). Matrix metalloproteinase-9 activity is associated with poor prognosis in T3-T4 node-negative colorectal cancer. Hum. Pathol. 38, 1603-1610.

Coussens L.M., Fingleton B. and Matrisian L.M. (2002). Matrix metalloproteinase inhibitors and cancer: trials and tribulations. Science 295, 2387-2392.

Cox G. and O'Byrne K.J. (2001). Matrix metalloproteinases and cancer. Anticancer Res. 21, 4207-4219.

Egeblad M. and Werb Z. (2002). New functions for the matrix metalloproteinases in cancer progression. Nat. Rev. Cancer. 2, 161-174.

Eisenberg I., Hochner H., Sadeh M., Argov Z. and Mitrani-Rosenbaum S. (2002). Establishment of the genomic structure and identification of thirteen single-nucleotide polymorphisms in the human RECK gene. Cytogenet. Genome Res. 97, 58-61.

Fata J.E., Leco K.J., Voura E.B., Yu H.Y., Waterhouse P., Murphy G., Moorehead R.A. and Khokha R. (2001). Accelerated apoptosis in the Timp-3-deficient mammary gland. J. Clin. Invest. 108, 831-841.

Folkman J. (2006). Angiogenesis. Annu. Rev. Med. 57, 1-18.

Folkman J., Watson K., Ingber D. and Hanahan D. (1989). Induction of angiogenesis during the transition from hyperplasia to neoplasia. Nature 339, 58-61.

Furumoto K., Arii S., Mori A., Furuyama H., Gorrin Rivas M.J., Nakao T., Isobe N., Murata T., Takahashi C., Noda M. and Imamura M. (2001). RECK gene expression in hepatocellular carcinoma: correlation with invasion-related clinicopathological factors and its clinical significance. Reverse-inducing--cysteine-rich protein with Kazal motifs. Hepatology 33, 189-195.

Heissig B., Hattori K., Friedrich M., Rafii S. and Werb Z. (2003). Angiogenesis: vascular remodeling of the extracellular matrix involves metalloproteinases. Curr. Opin. Hematol. 10, 136-141.

Hidalgo M. and Eckhardt S.G. (2001). Development of matrix metalloproteinase inhibitors in cancer therapy. J. Natl. Cancer. Inst. 93, 178-193.

Hlatky L., Hahnfeldt P. and Folkman J. (2002). Clinical application of antiangiogenic therapy: microvessel density, what it does and doesn't tell us. J. Natl. Cancer Inst. 94, 883-893.

Hsu M.C., Chang H.C. and Hung W.C. (2006). HER-2/neu represses the metastasis suppressor RECK via ERK and Sp transcription factors to promote cell invasion. J. Biol. Chem. 281, 4718-4725.

Iizasa T., Fujisawa T., Suzuki M., Motohashi S., Yasufuku K., Yasukawa T., Baba M. and Shiba M. (1999). Elevated levels of circulating plasma matrix metalloproteinase 9 in non-small cell lung cancer patients. Clin. Cancer Res. 5, 149-153.

Jadhav U., Chigurupati S., Lakka S.S. and Mohanam S. (2004). Inhibition of matrix metalloproteinase-9 reduces in vitro invasion and angiogenesis in human microvascular endothelial cells. Int. J. Oncol. 25, 1407-1414.

Kern A., Taubert H., Scheele J., Rudroff C., Mothes H., Kappler M., Bartel F. and Richter K.K. (2002). Association of p53 mutations, microvessel density and neoangiogenesis in pairs of colorectal cancers and corresponding liver metastases. Int. J. Oncol. 21, 243-249.

Kitayama H., Sugimoto Y., Matsuzaki T., Ikawa Y. and Noda M. (1989). A ras-related gene with transformation suppressor activity. Cell. 56, 77-84.

Lakka S.S., Gondi C.S., Dinh D.H., Olivero W.C., Gujrati M., Rao V.H., Sioka C. and Rao J.S. (2005). Specific interference of urokinase-type plasminogen activator receptor and matrix metalloproteinase-9 gene expression induced by double-stranded RNA results in decreased invasion, tumor growth, and angiogenesis in gliomas. J. Biol. Chem. 280, 21882-21892.

Leco K.J., Waterhouse P., Sanchez O.H., Gowing K.L., Poole A.R., Wakeham A., Mak T.W. and Khokha R. (2001). Spontaneous air space enlargement in the lungs of mice lacking tissue inhibitor of metalloproteinases-3 (TIMP-3). J. Clin. Invest. 108, 817-829.

Li Y., Zhang Y. and Zheng Q. (2005). Expression of RECK gene and MMP-9 in hilar cholangiocarcinoma and its clinical significance. J. Huazhong. Univ. Sci. Technolog. Med. Sci. 25, 552-554.

Liu L.T., Chang H.C., Chiang L.C. and Hung W.C. (2002). Induction of RECK by nonsteroidal anti-inflammatory drugs in lung cancer cells. Oncogene 21, 8347-8350.

Liu L.T., Chang H.C., Chiang L.C. and Hung W.C. (2003a). Histone deacetylase inhibitor up-regulates RECK to inhibit MMP-2 activation and cancer cell invasion. Cancer Res. 63, 3069-3072.

Liu L.T., Peng J.P., Chang H.C. and Hung W.C. (2003b). RECK is a target of Epstein-Barr virus latent membrane protein 1. Oncogene 22, 8263-8270.

Lukashev M.E. and Werb Z. (1998). ECM signalling: orchestrating cell behaviour and misbehaviour. Trends Cell. Biol. 8, 437-441.

Majello B., De Luca P. and Lania L. (1997). Sp3 is a bifunctional transcription regulator with modular independent activation and repression domains. J. Biol. Chem. 272, 4021-4026.

Masui T., Doi R., Koshiba T., Fujimoto K., Tsuji S., Nakajima S., Koizumi M., Toyoda E., Tulachan S., Ito D., Kami K., Mori T., Wada M., Noda M. and Imamura M. (2003). RECK expression in pancreatic cancer: its correlation with lower invasiveness and better prognosis. Clin. Cancer Res. 9, 1779-1784.

McCawley L.J. and Matrisian L.M. (2001). Matrix metalloproteinases: they're not just for matrix anymore! Curr. Opin. Cell Biol. 13, 534-540.

Molina J.R., Reid J.M., Erlichman C., Sloan J.A., Furth A., Safgren S.L., Lathia C.D. and Alberts S.R. (2005). A phase I and pharmacokinetic study of the selective, non-peptidic inhibitor of matrix metalloproteinase BAY 12-9566 in combination with etoposide and carboplatin. Anticancer Drugs. 16, 997-1002.

Mook O.R., Frederiks W.M. and Van Noorden C.J. (2004). The role of

gelatinases in colorectal cancer progression and metastasis. Biochim. Biophys. Acta. 1705, 69-89.

Mori T., Moriuchi R., Okazaki E., Yamada K. and Katamine S. (2007). Tgat oncoprotein functions as a inhibitor of RECK by association of the unique C-terminal region. Biochem. Biophys. Res. Commun. 355, 937-943.

Moses M.A., Sudhalter J. and Langer R. (1990). Identification of an inhibitor of neovascularization from cartilage. Science 248, 1408-1410.

Murphy G., Knauper V., Cowell S., Hembry R., Stanton H., Butler G., Freije J., Pendas A.M. and Lopez-Otin C. (1999). Evaluation of some newer matrix metalloproteinases. Ann. NY Acad. Sci. 878, 25-39.

Nagase H., Visse R. and Murphy G. (2006). Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc. Res. 69, 562-573.

Niedergethmann M., Hildenbrand R., Wostbrock B., Hartel M., Sturm J.W., Richter A. and Post S. (2002). High expression of vascular endothelial growth factor predicts early recurrence and poor prognosis after curative resection for ductal adenocarcinoma of the pancreas. Pancreas 25, 122-129.

Noda M., Kitayama H., Matsuzaki T., Sugimoto Y., Okayama H., Bassin R.H. and Ikawa Y. (1989). Detection of genes with a potential for suppressing the transformed phenotype associated with activated ras genes. Proc. Natl. Acad. Sci. USA 86, 162-166.

Noda M., Oh J., Takahashi R., Kondo S., Kitayama H. and Takahashi C. (2003). RECK: a novel suppressor of malignancy linking oncogenic signaling to extracellular matrix remodeling. Cancer Metastasis Rev. 22, 167-175.

Oh J., Seo D.W., Diaz T., Wei B., Ward Y., Ray J.M., Morioka Y., Shi S., Kitayama H., Takahashi C., Noda M. and Stetler-Stevenson W.G. (2004). Tissue inhibitors of metalloproteinase 2 inhibits endothelial cell migration through increased expression of RECK. Cancer Res. 64, 9062-9069.

Oh J., Takahashi R., Kondo S., Mizoguchi A., Adachi E., Sasahara R.M., Nishimura S., Imamura Y., Kitayama H., Alexander D.B., Ide C., Horan T.P., Arakawa T., Yoshida H., Nishikawa S., Itoh Y., Seiki M., Itohara S., Takahashi C. and Noda M. (2001). The membrane-anchored MMP inhibitor RECK is a key regulator of extracellular matrix integrity and angiogenesis. Cell 107, 789-800.

Pang R.T., Lee L.T., Ng S.S., Yung W.H. and Chow B.K. (2004). CpG methylation and transcription factors Sp1 and Sp3 regulate the expression of the human secretin receptor gene. Mol. Endocrinol. 18, 471-483.

Raffetto J.D. and Khalil R.A. (2008). Matrix metalloproteinases and their inhibitors in vascular remodeling and vascular disease. Biochem. Pharmacol. 75, 346-359.

Rhee J.S. and Coussens L.M. (2002). RECKing MMP function: implications for cancer development. Trends Cell Biol. 12, 209-211.

Rizvi N.A., Humphrey J.S., Ness E.A., Johnson M.D., Gupta E., Williams K., Daly D.J., Sonnichsen D., Conway D., Marshall J. and Hurwitz H. (2004). A phase I study of oral BMS-275291, a novel nonhydroxamate sheddase-sparing matrix metalloproteinase inhibitor, in patients with advanced or metastatic cancer. Clin. Cancer Res. 10, 1963-1970.

Sasahara R.M., Brochado S.M., Takahashi C., Oh J., Maria-Engler S.S., Granjeiro J.M., Noda M. and Sogayar M.C. (2002). Transcriptional control of the RECK metastasis/angiogenesis suppressor gene. Cancer Detect Prev. 26, 435-443.

Sasahara R.M., Takahashi C. and Noda M. (1999). Involvement of the Sp1 site in ras-mediated downregulation of the RECK metastasis suppressor gene. Biochem. Biophys. Res. Commun. 264, 668-675.

Sato H., Takino T., Okada Y., Cao J., Shinagawa A., Yamamoto E. and Seiki M. (1994). A matrix metalloproteinase expressed on the surface of invasive tumour cells. Nature 370, 61-65.

Song S.Y., Son H.J., Nam E., Rhee J.C. and Park C. (2006). Expression of reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) as a prognostic indicator in gastric cancer. Eur. J. Cancer 42, 101-108.

Sounni N.E., Devy L., Hajitou A., Frankenne F., Munaut C., Gilles C., Deroanne C., Thompson E.W., Foidart J.M. and Noel A. (2002). MT1-MMP expression promotes tumor growth and angiogenesis through an up-regulation of vascular endothelial growth factor expression. FASEB J. 16, 555-564.

Span P.N., Sweep C.G., Manders P., Beex L.V., Leppert D. and Lindberg R.L. (2003). Matrix metalloproteinase inhibitor reversion-inducing cysteine-rich protein with Kazal motifs: a prognostic marker for good clinical outcome in human breast carcinoma. Cancer 97, 2710-2715.

Sternlicht M.D. and Werb Z. (2001). How matrix metalloproteinases regulate cell behavior. Annu. Rev. Cell Dev. Biol. 17, 463-516.

Sun X.F. and Zhang H. (2006). Clinicopathological significance of stromal variables: angiogenesis, lymphangiogenesis, inflammatory infiltration, MMP and PINCH in colorectal carcinomas. Mol. Cancer. 5, 43.

Takahashi C., Akiyama N., Matsuzaki T., Takai S., Kitayama H. and Noda M. (1996). Characterization of a human MSX-2 cDNA and its fragment isolated as a transformation suppressor gene against v-Ki-ras oncogene. Oncogene 12, 2137-2146.

Takahashi C., Sheng Z., Horan T.P., Kitayama H., Maki M., Hitomi K., Kitaura Y., Takai S., Sasahara R.M., Horimoto A., Ikawa Y., Ratzkin B.J., Arakawa T. and Noda M. (1998). Regulation of matrix metalloproteinase-9 and inhibition of tumor invasion by the membrane-anchored glycoprotein RECK. Proc. Natl. Acad. Sci USA 95, 13221-13226.

Takenaka K., Ishikawa S., Kawano Y., Yanagihara K., Miyahara R., Otake Y., Morioka Y., Takahashi C., Noda M., Wada H. and Tanaka F. (2004). Expression of a novel matrix metalloproteinase regulator, RECK, and its clinical significance in resected non-small cell lung cancer. Eur. J. Cancer. 40, 1617-1623.

Takeuchi T., Hisanaga M., Nagao M., Ikeda N., Fujii H., Koyama F., Mukogawa T., Matsumoto H., Kondo S., Takahashi C., Noda M. and Nakajima Y. (2004). The membrane-anchored matrix metalloproteinase (MMP) regulator RECK in combination with MMP-9 serves as an informative prognostic indicator for colorectal cancer. Clin. Cancer Res. 10, 5572-5579.

Toth M., Chvyrkova I., Bernardo M.M., Hernandez-Barrantes S. and Fridman R. (2003). Pro-MMP-9 activation by the MT1-MMP/MMP-2 axis and MMP-3: role of TIMP-2 and plasma membranes. Biochem. Biophys. Res. Commun. 308, 386-395.

van der Jagt, M.F., Sweep F.C., Waas E.T., Hendriks T., Ruers T.J., Merry A.H., Wobbes T. and Span P.N. (2006). Correlation of reversion-inducing cysteine-rich protein with kazal motifs (RECK) and extracellular matrix metalloproteinase inducer (EMMPRIN), with MMP-2, MMP-9, and survival in colorectal cancer. Cancer Lett. 237, 289-297.

van Lent P.L., Span P.N., Sloetjes A.W., Radstake T.R., van Lieshout A.W., Heuvel J.J., Sweep C.G. and van den Berg W.B. (2005).

Expression and localisation of the new metalloproteinase inhibitor RECK (reversion inducing cysteine-rich protein with Kazal motifs) in inflamed synovial membranes of patients with rheumatoid arthritis. Ann. Rheum. Dis. 64, 368-374.

Visse R. and Nagase H. (2003). Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res. 92, 827-839.

Vu T.H. and Werb Z. (2000). Matrix metalloproteinases: effectors of development and normal physiology. Genes Dev. 14, 2123-2133.

Weaver V.M. (2002). Membrane-associated MMP regulators: novel cell adhesion tumor suppressor proteins? Dev. Cell. 2, 6-7.

Welm B., Mott J. and Werb Z. (2002). Developmental biology: vasculogenesis is a wreck without RECK. Curr. Biol. 12, R209-211.

Wendum D., Boelle P.Y., Rigau V., Sebbagh N., Olschwang S., Mourra N., Parc R., Trugnan G., Masliah J. and Flejou J.F. (2003). Mucinous colon carcinomas with microsatellite instability have a lower microvessel density and lower vascular endothelial growth factor expression. Virchows Arch. 442, 111-117.

Will H., Atkinson S.J., Butler G.S., Smith B. and Murphy G. (1996). The soluble catalytic domain of membrane type 1 matrix metalloproteinase cleaves the propeptide of progelatinase A and initiates autoproteolytic activation. Regulation by TIMP-2 and TIMP-3. J. Biol. Chem. 271, 17119-17123.

Wong W.K., Chen K. and Shih J.C. (2003). Decreased methylation and transcription repressor Sp3 up-regulated human monoamine oxidase (MAO) B expression during Caco-2 differentiation. J. Biol. Chem. 278, 36227-36235.

Yoshizuka N., Moriuchi R., Mori T., Yamada K., Hasegawa S., Maeda T., Shimada T., Yamada Y., Kamihira S., Tomonaga M. and Katamine S. (2004). An alternative transcript derived from the trio locus encodes a guanosine nucleotide exchange factor with mouse cell-transforming potential. J. Biol. Chem. 279, 43998-44004.

Zhou X., Richon V.M., Rifkind R.A. and Marks P.A. (2000). Identification of a transcriptional repressor related to the noncatalytic domain of histone deacetylases 4 and 5. Proc. Natl. Acad. Sci. USA 97, 1056-1061.

Zucker S., Cao J. and Chen W.T. (2000). Critical appraisal of the use of matrix metalloproteinase inhibitors in cancer treatment. Oncogene 19, 6642-6650.

Accepted February 4, 2008