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Potential Role of Reversion-Inducing Cysteine-Rich Protein with Kazal Motifs (RECK) in Regulation of Matrix Metalloproteinases (MMPs) Expression in Periodontal Diseases

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Periodontal diseases are characterized by pathological destruction of extracellular matrix (ECM) of periodontal tissues. Matrix metalloproteinases (MMPs) are a significant part of the degradation of ECM. However, the regulation of MMPs expression level in periodontal diseases is as yet undetermined.

RECK (reversion-inducing cysteine-rich protein with Kazal motifs), a novel membrane-anchored inhibitor of MMPs, could regulate the expressions of MMP-2, 9 and MT1-MMP as a cell surface-signaling molecule. Thus, we propose that RECK may play an important role in regulating MMPs in the ECM degradation of periodontal diseases. The RECK/MMPs signaling pathway could provide a new approach for prevention and treatment of RECK in periodontal diseases by blocking MMPs.

MeSH Keywords: Matrix Metalloproteinase Inhibitors • Matrix Metalloproteinases • Periodontal Diseases

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Background

RECK and MMPs expression

Periodontal diseases are biofilm-induced chronic inflammatory diseases that lead to irreversible destruction of periodontium – the tooth-supporting structures, such as the gingiva and the underlying alveolar bone [1]. This pathological destructive process, generated through an imbalance between host response and subgingival microbiota, is mainly mediated by complex stimulation of a large group of proteolytic host enzymes. Most important in this respect is matrix metalloproteinases (MMPs), a family of zinc-dependent enzymes that are capable of degrading almost all proteins of extracellular matrix (ECM) and basement membranes (BM) [2].

Because MMP-1, -2, -3, -8, and -9 have been found in human inflammatory periodontal biopsy specimens [3], and collagenase activity in gingival crevicular fluid (GCF) also was reported to be increased and correlated with the severity of periodontal diseases [4,5], accumulating evidence indicates that collagenases, along with other MMPs, play a significant role in periodontal destruction [6,7]. Therefore, suppressing ECM degradation by MMPs inhibitors, such as TIMPs [8] and BB94 [9], is of great interest in periodontal therapy.

The expression of many MMPs is regulated at the level of transcription by a variety of growth factors, cytokines, and chemokines, although post-transcriptional pathways may contribute to this regulation in specific cases [10]. However, the effective regulation of expression of MMPs in periodontal diseases is as yet undetermined.

RECK (reversion-inducing cysteine-rich protein with Kazal motifs), a non-metastatic gene cloned from a v-Ki-ras-transformed NIH3T3 cell line, is a novel MMPs inhibitor and an important regulatory factor of MMPs at the cell surface level. Previous research indicates that RECK mRNA is undetectable in tumor-derived cell lines and oncogenically transformed cells, while being expressed in various human tissues and untransformed cells [11].

As a membrane-targeted MMPs inhibitor, RECK can post-transcriptionally down-regulate the activity of at least 3 members of the MMPs family: MMP-2, MMP-9, and MT1-MMP [12]. MMPs are secreted as latent precursors (proMMPs) and require activation. The regulation of RECK on MMP-2 and MT1-MMP may be through the following mechanisms: RECK binds to MT1-MMP after transcription, forming a membrane-anchored ternary complex on the cell surface, and then inhibits the proteolytic activity of MT1-MMP. Because MT1-MMP is involved in the transition from pro-MMP-2 to active MMP-2, the complex adversely affects the maturation of pro-MMP-2, thus inhibiting the formation of MMP-2 [13]. In addition, RECK negatively regulates MMP-9 in 2 ways: inhibition of MMP-9 mRNA level and suppression of MMP-9 promoter activity [14]. Therefore, RECK can inhibit ECM degradation by down-regulating the proteolytic activity of MMP-2, 9 and MT1-MMP, both solely and cooperatively.

The remodeling of BM and degradation of ECM are critical steps in invasion and metastasis in malignant tumors. Thus, RECK, as a newly-discovered MMPs inhibitor, has attracted considerable attention for its ability to shrink invasive and metastatic tumors. RECK expression level was tested by methods of immunohistochemistry, RT-PCR/qPCR, and Western blot analysis in several tumor types, showing a significant negative correlation between RECK expression and the biological malignancy of skull-base chordomas [15], adenocarcinoma (ADC) of the lung [16], and breast cancer [17], as well as of oral and maxillofacial tumors, such as ameloblastoma [18] and salivary adenoid cystic carcinoma (SACC) [19]. Fibroblasts in the lining become highly invasive and display a tumor-like character in rheumatoid arthritis (RA), and RECK mRNA was also reported to be down-regulated in RA synovial membranes [20]. Expression of RECK simply inhibits tumor growth and RA development by regulating ECM breakdown and inhibiting formation of new blood vessels [20,21].

Hypothesis

RECK and periodontal diseases

The above-mentioned studies lead to an interesting question: Is RECK involved in the degradation of ECM in periodontal diseases? In malignancies, RECK on the cell surface can inhibit the activity of MMP-2, 9, and MT1-MMP, and its expression level is negatively correlated with invasiveness of the tumor cells. Moreover, RECK is involved in the pathological processes of RA, cardiovascular diseases [22], chorioamnionitis [23], and other inflammations. RECK, as a signal molecule in the RECK/MMPs signaling pathway, protects the ECM from degradation to maintain its integrity.

Periodontal diseases are characterized by ECM degradation, which is principally mediated by MMPs; hence, the regulation of MMPs expression appears to have important therapeutic value in this regard. Because ECM degradation is the common pathological process shared by RA, tumors, and periodontal diseases [12,24], we logically propose the hypothesis that RECK may play an important role in regulating MMPs in ECM degradation in periodontal diseases. The RECK/MMPs signal pathway may provide a new approach for the prevention and treatment of periodontal diseases by blocking MMPs via RECK.

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Implication of the hypothesis

Periodontal disease is the second most prevalent oral diseases, and is characterized by pathological ECM degradation of connective tissue and bone, resulting in the loosening and loss of teeth. MMPs are as the principal mediators of ECM destruction, the down-regulation of which is of great importance in the prevention and treatment of periodontal diseases. Our hypothesis suggests that it would provide a new target for inhibiting MMPs by RECK for the prevention and treatment of periodontal diseases.

Our research team has found, for the first time, that the expression of RECK was present in both healthy and diseased periodontal tissues, and the expression level decreased in the later group (in a study supported by a Grant from the National Natural Scientific Foundation of China in 2014, titled *Study on regulation mechanism of novel MMPs inhibitor RECK in degradation of periodontal tissues*). Moreover, we found that low or no RECK expression was correlated with the severity of periodontal inflammation, suggesting that RECK may be involved in the regulation of periodontitis development. RECK may directly inhibit activity of MMP-2, 9 and MT1-MMP as a membrane signaling protein existing in periodontal ligament-derived cells, thus protecting periodontal tissues by suppressing their degradation. However, the precise mechanisms by which RECK regulates MMPs in periodontal tissues require further investigation. If the relation between RECK and MMPs in periodontal diseases were defined, RECK could be a useful prognostic marker and provide a new target for gene therapy in periodontal diseases.

Conclusions

Theoretical considerations suggest that RECK may play a role in suppressing ECM destruction by inhibiting MMP-2, -9 and MT1-MMP in the occurrence and development of periodontal diseases. If our hypothesis is accepted, the RECK/MMPs signaling pathway could provide a new research focus on the expression and regulation of MMPs in periodontal diseases. Regulating MMPs by RECK could be an important new approach to prevention and treatment of periodontal diseases.

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