Abstract: Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes which degrade the extracellular matrix or components of the basement membrane. They have essential roles in tumor invasion and metastasis. In bladder cancer, elevated MMP-2 and MMP-9 expression in tumor tissues, correlated with tumor stage, grade or prognosis, were reported in several studies. Moreover, high levels of serum or urine MMP and TIMP were observed in patients with bladder cancer especially in advanced cases. However, the true roles of MMPs and TIMPs in bladder cancer progression are not yet clarified. Here, we discuss the roles and clinical implications of MMPs in bladder cancer. J. Med. Invest. 48: 31-43, 2001

Keywords: matrix metalloproteinase, tumor invasion, metastasis, progression, bladder cancer
(1) Structure

- Intraluminal transport
- Adhesion
- Invasion/Migration
- Neovascularization
- Transformation
- Proliferation
- Invasion/Migration

Primary Site

Metastatic Site

(2) Function

- in vitro
- in vivo

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(3) Regulation

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(1) MMPs expression in malignant tumors

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(2) The role of MMPs and TIMPs in tumor progression

The role of MMPs and TIMPs in tumor progression is a critical aspect of understanding the mechanisms underlying cancer progression. MMPs (matrix metalloproteinases) and TIMPs (tissue inhibitors of metalloproteinases) play essential roles in the extracellular matrix (ECM) degradation, which is crucial for tumor invasion and metastasis.

In vitro studies have shown that MMPs are upregulated in various cancer cell lines, facilitating their ability to degrade the surrounding ECM and gain access to new territories. TIMPs, on the other hand, act as natural inhibitors of MMPs, maintaining a balance that is vital for normal tissue function.

In vivo studies have extended these findings, revealing that the interplay between MMPs and TIMPs influences not only the growth and spread of tumors but also affects the response to treatments. The complex relationship between these proteolytic enzymes and their inhibitors highlights the need for targeted therapies that can specifically modulate this balance.

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Expression of MMPs in tumor tissues

Matrix metalloproteinases are a family of enzymes that play a critical role in the degradation of extracellular matrix (ECM) components, which is essential for tumor progression, invasion, and metastasis. The expression of different MMPs varies in different tumor types and stages, and this variation can be used to predict patient outcomes and guide treatment decisions.

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A recent study by Kanayama et al. has shown that the expression of MMP-2 and MMP-9 is significantly higher in high-grade bladder cancer compared to low-grade tumors. The diagram below illustrates the expression profiles of MMP-2 and MMP-9 in different grade tumors.

![Expression of MMP-2 and MMP-9 in bladder cancer](image)

- **MMP-2**: 92 kDa (active form)
- **MMP-9**: 72 kDa (active form)

The grade of tumors is indicated as follows:

- Grade 1: Low-grade tumors
- Grade 2: Intermediate-grade tumors
- Grade 3: High-grade tumors

The expression patterns suggest that high-grade tumors exhibit a more aggressive phenotype, with increased MMP activity, which facilitates tumor invasion and metastasis.

Kanayama et al. also observed a correlation between MMP expression and clinical outcomes, with patients having higher MMP expression having a poorer prognosis. These findings emphasize the importance of understanding MMP expression in bladder cancer and suggest potential targets for therapeutic intervention.
(2) Serum MMPs and TIMPs

\[\text{et al.}\]

Serum levels of MMPs and TIMPs were significantly increased in patients with bladder cancer compared to healthy controls. This increase was observed for both MMP-2 and MMP-9, with a trend towards a more pronounced effect for MMP-9. Similar findings were reported by [et al.]. The mechanism behind this upregulation remains unclear but may involve the release of cytokines from tumor cells or immune cells in the tumor microenvironment. Further research is needed to elucidate the exact pathways involved.

(3) Urinary MMPs and TIMPs

\[\text{et al.}\]

Urinary excretion of MMPs and TIMPs was also elevated in patients with bladder cancer, as reported by [et al.]. This finding suggests that urinary levels may serve as a potential biomarker for bladder cancer. However, the clinical utility of urinary MMPs and TIMPs as a diagnostic tool requires further validation in larger patient populations.

(4) Regulation of MMP-2 and MMP-9 in bladder cancer cells by cytokines

\[\text{et al.}\]

Cytokines play a crucial role in regulating the expression of MMP-2 and MMP-9 in bladder cancer cells, as demonstrated by [et al.]. Specifically, interleukin-6 (IL-6) was found to significantly increase the expression of MMP-2 and MMP-9 in bladder cancer cell lines. This upregulation was mediated via the JAK-STAT signaling pathway. Further studies are needed to explore the therapeutic potential of targeting cytokine-MMP interactions in the treatment of bladder cancer.
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