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# MMP2 和 MMP9 在粘膜内胃癌中表达及其临床病理意义

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**摘要 目的:**观察基质金属蛋白酶(MMP)家族成员 MMP2 和 MMP9 在粘膜内胃癌中的表达及其与淋巴结转移的相关性。**方法:**研究病例为病理诊断为粘膜内胃癌的档案病例，应用免疫组织化学技术检测 MMP2 和 MMP9 在粘膜内胃癌中表达的临床病理意义,特别是与淋巴结转移的相关性。**结果:**临床病理分析结果显示有淋巴结转移的 IMGC 病例肿块直径要显著大于无淋巴结转移的 IMGC。有淋巴结转移 IMGC 中低分化腺癌发生率要显著高于无淋巴结转移组。有淋巴结转移 IMGC 中淋巴管侵犯发生率要显著高于无淋巴结转移组。免疫组化结果显示,MMP2 在正常胃粘膜上皮和粘膜内胃癌中的阳性表达率分别是 7%和 43.93%,有显著性差异(P<0.01),MMP9 在正常胃粘膜上皮和粘膜内胃癌中的阳性表达率分别为和 23%和 48.48%,无显著性差异(P>0.05)。MMP9 在淋巴结转移组中的阳性率(87.5%)显著高于无淋巴结转移组(36%),在有淋巴管侵犯病例中的表达率(83.3%)显著高于无淋巴管侵犯的病例(30%),差异均有统计意义(P<0.05);而 MMP2 的表达与有无淋巴结转移及淋巴管侵犯均无显著相关性(P>0.05)。**结论:**MMP9 可能作为预测粘膜内胃癌是否有淋巴结转移的标志物,但需要结合组织分化、肿块大小和淋巴管侵犯等临床病理特点综合判断。MMP2 可能与粘膜内胃癌的发生有关而作为早期诊断的指标。

**关键词:**基质金属蛋白酶;粘膜内胃癌;淋巴结转移;临床病理学
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# Clinicopathological Significancer of MMP2 and MMP9 Expression in the Intramucosal Gastric Carcinoma

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**ABSTRACT Objective:** To investigate the expression of MMP2 and MMP9 in the intramucosal gastric carcinoma and its correlation with the lymphatic metastasis. **Methods:** Samples involved in this study were diagnosed as intramucosal gastric carcinoma by clinicopathological daignosis. The MMP2 and MMP9 expression were assayed by immunohistochemical technique; the correlation of which with lymphatic metastasis were analyzed. **Results:** Clinicopathological feature were that lump size was larger in IMGC with lymph node metastasis than that in IMGC without lymph node metastasis. The incidence of Poorly poorly differentiated IMGC was higher in IMGC with lymph node metastasis than that in IMGC without lymph node metastasis. The incidence of Lymphatic permeationwas higher in IMGC with lymph node metastasis than that in IMGC without lymph node metastasis. Immunohistochemical results showed that positive rate of MMP2 in normal mucosal epithelial and intramucosal gastric carcinoma were 7% and 43.93% with significant difference (P<0.01),positive rate of MMP2 in normal mucosal epithelial and intramucosal gastric carcinoma were 23% and 48.48% without significant difference(P>0.05). The positive rate of MMP9 expression was higher in IMGC with lymph node metastasis(87.5%)than that in the IMGC without lymph node metastasis (36%); the positive rate of MMP9 expression was higher in IMGC with lymphatic permeation (83.3%) than in the IMGC without lymphatic permeation (30%). No significant correlation of MMP2 expression with the lymph node metastasis and lymphatic permeation was found (P>0.05). **Conclusion:** MMP9 expression could be used as a biomarker for the prediction of lymph node metastasis in IMGC, which should be analyzed combined with tisuue diferentiation, lump size and lymphatic permeation. MMP2 could be associated with development of intramucosal gastric carcinoma and become an index for early daignosis.

**Key words:** Matrix metalloproteinase; Intramucosal gastric carcinoma; Lymph node metastassis; Clinicopathology
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## 前言

早期胃癌是指腺癌细胞限于粘膜层或粘膜下层,无论淋巴结有无转移。粘膜内癌(intramucosal gastric carcinoma,IMGC)即指腺癌细胞限于粘膜层的早期胃癌。早期胃癌的发生率占胃癌切除标本约 20%～60%不等,预后较好。在早期胃癌中,出现肝转移或腹膜播散的情况极少,因此最重要的预后因素是淋巴结的转移情况,而大部分有淋巴结转移的病例都是癌细胞浸润到粘膜下层的病例[1-5],IMGC 出现淋巴结转移极少,有报道粘膜内癌淋巴结转移率大致为 1.9～3.4%。所以,是否有无淋巴结转移对于患者治疗方式的选择至关重要[6,7]。基质金属蛋白酶(matrix metalloproteinase,MMPs) 是一类能降解细胞外间质的蛋白酶家族,具有促进肿瘤侵袭和播散的能力[8-10]。研究显示,MMPs 与胃癌的侵袭、转移和生存状态密切相关[11-16]。MMP2(72kDa 明胶酶,IV 型胶原酶)和 MMP9(92kDa 明胶酶,IV 型胶原酶)是 MMP 家族重要成员,主要通过消化基底膜中Ⅳ型胶原纤维来介导血管侵袭和转移。本研究旨在探讨 MMP2 和 MMP9 在粘膜内胃癌中的表达及其与淋巴结转移的相关性和临床病理意义。

## 1 材料与方法

### 1.1 实验材料

胃癌标本取自冷水江市人民医院和湖南省肿瘤医院病理科 2008 年 1 月到 2011 年 12 月的档案病例, 年龄 35～70 岁,中位年龄 54 岁。所有病例均经普外科进行胃部分切除。IMGC 诊断是通过病理学取材、连续切片和显微镜下观察而确诊的。16 例 IMGC 有淋巴结转移,50 例 IMGC 无淋巴结转移,组织组织学分级分为高分化腺癌(22 例)、中分化腺癌(10 例)、低分化腺癌(34 例)。此外,需考虑的其它组织学特点包括粘膜肌有无累及、血管有无侵犯,病理诊断经两位高级病理医师复验确定。

### 1.2 主要试剂和仪器

MMP2(4D3)鼠单克隆抗体(sc-53630)和 MMP9 鼠单克隆抗体 (sc-6480 )均为 Santa Cruz 公司产品。柠檬酸盐抗原修复液 (粉剂)(0.01M,pH 6.0,MVS-0066),0.01M PBS(pH7.2-7.4)。DAB 显色试剂盒(Kit-0015)和 ElivisionTM plus Polyer HRP (鼠 / 兔) Kit-9902 免疫组化试剂盒均为福建迈新生物技术公司产品。格兰仕家用微波炉用于抗原微波修复。

### 1.3 免疫组织化学技术

本研究使用免疫组化技术检测 MMP-2 和 MMP-9 表达。切片厚度为 4 μm,60℃ 烤片 4rs、二甲苯脱蜡、梯度酒精脱水,3%过氧化氢处理抑制内源性过氧化酶活性室温孵育 20 min,柠檬酸抗原修复液中进行微波修复, 非免疫血清室温孵育 20 min,滴加 MMP2,MMP9 抗体(滴度 1:100)4℃ 过夜,PBS 洗三次,使用 ElivisionTM plus Polyer HRP (鼠 / 兔) Kit-9902(福州迈新产品),具体操作按试剂盒说明书进行。DAB 显色,苏木素复染,脱水及烤干切片,中性树脂封片,显微镜下观察和判断结果。

### 1.4 统计学方法分析

实验数据用 SPSS 11.0 统计软件包, 组间率的比较采用卡方检验,以 P<0.05 为差异具有统计学意义。

## 2 结果

### 2.1 粘膜内胃腺癌的临床病理特征分析

对 66 例粘膜内胃癌(IMGC)的临床病理学资料进行分析发现,淋巴结转移的 IMGC 病例肿块直径要显著大于无淋巴结转移的 IMGC。有淋巴结转移 IMGC 中低分化腺癌发生率要显著高于无淋巴结转移组(P<0.05)。有淋巴结转移 IMGC 中淋巴管侵犯发生率要显著高于无淋巴结转移组,见表 1。而淋巴结转移组和无淋巴结转移组年龄、性别、静脉侵犯比较无显著性差别(P>0.05)。

### 2.2 MMP2 和 MMP9 的表达与粘膜内胃腺癌淋巴结转移及淋巴管侵犯的相关性

免疫组织化学结果显示:MMP2 和 MMP9 阳性信号定位于癌细胞胞浆。MMP2 或 MMP9 表达阳性的判断标准是超过 10%的癌细胞胞浆着色,见图 1。MMP2 在正常胃粘膜上皮和粘膜内胃癌中的阳性表达率分别是 7%和 43.93%,有显著性差异(P<0.01),MMP9 在正常胃粘膜上皮和粘膜内胃癌中的阳性表达率分别为和 23%和 48.48%,无显著性差异(P>0.05)。MMP9 在淋巴结转移组中的阳性率(87.5%)显著高于无淋巴结转移组(36%)(P<0.05)。而 MMP2 在淋巴结转移组和无淋巴结转移组中的表达率比较无显著性差异(P>0.05),见表 2。MMP9 在有淋巴管侵犯病例中的表达率(83.3%)显著高于无淋巴管侵犯病例(30%),差异有统计学意义(P<0.05),MMP2 在有淋巴管侵犯病例和无淋巴管侵犯病例中的表达率比较无显著性差异(P>0.05),见表 3。

## 3 讨论

粘膜内胃癌(intramucosal gastric carcinoma,IMGC)根据有无淋巴结转移可选择不同的治疗方法, 如果没有淋巴结转移,可选择内镜下黏膜切除术,因该法对患者的损伤最小且有较高的生存期,已被普遍接受用于 IMGC 的治疗,但其应用标准较为严格,如粘膜内癌、直径小于 2 cm 的隆起型病变、直径小于 1 cm 的凹陷型病变、高分化腺癌等[17-20];如果有淋巴结转移,则要选择胃部分切除及淋巴结清扫的治疗方法。但诊断是否存在淋巴结转移存在一定的困难。本研究通过检测粘膜内胃癌中 MMP2 和 MMP9 的表达并分析其与淋巴结转移的相关性分析, 旨在探讨 MMP2 和 MMP9 在粘膜内胃癌淋巴结转移中的临床意义。

本研究的临床病理结果发现有淋巴结转移 IMGC 肿块平均直径显著大于无淋巴结转移的 IMGC,低分化腺癌在有淋巴结转移的 IMGC 中较无淋巴结转移的 IMGC 更常见。关于 IMGC 中淋巴结转移的途径,淋巴管浸润应该是第一步和关键步骤。在本研究中有淋巴结转移 IMGCs 的淋巴管浸润百分率显著高于无淋巴结转移 IMGC。本研究淋巴结转移 IMGC 病例中,除了 1 例外,所有其它病例的肿块直径均大于 2.0 cm ,肿块直径也显著大于无淋巴结转移 IMGC。随着肿块体积增加,癌细胞进入粘膜内淋巴管的机会也增加。

癌细胞进入淋巴管需要特异性的酶降解淋巴管壁,癌细胞降解和侵入淋巴管壁的能力不能直接通过 HE 染色进行判断。

基质金属蛋白酶(MMPs)在增加肿瘤侵袭和转移方面具有重要作用,MMP 表达与癌症晚期相关,MMP2 和 MMP9 血清学水平也与胃癌的侵袭和转移相关。本研究证明了 MMP9 与淋巴管侵袭和淋巴结转移密切相关，但 MMP2 没有显示出与

**表 1 胃粘膜内癌的临床病理特点**

Table 1 The clinicopathological features of intramucosal gastric carcinoma

| | 淋巴结转移(Lymph node metastasis) | | |
|---|---|---|---|
| | 阴性(Negative) (n=50) | 阳性(Positive) (n=16) | P |
| | | | >0.05 |
| 性别(Sex) | | | |
| 男性(Male) | 34 | 7 | |
| 女性(Famale) | 16 | 9 | |
| 平均年龄(Average age, year) | 55.3 ± 6.7 | 53.9 ± 8.6 | >0.05 |
| 肿块平均大小(Average size,cm) | 2.10± 1.11 | 4.21 ± 1.14 | <0.01 |
| 组织学分级(Histological type) | | | <0.01 |
| 高分化腺癌(Well differentiation) | 21 | 1 | |
| 中分化腺癌(Moderately differentiation) | 7 | 3 | |
| 低分化腺癌(Poorly differentiation) | 22 | 12 | |
| 淋巴管浸润(Lymphatic permeation) | | | <0.01 |
| 有 | 2 | 7 | |
| 无 | 48 | 9 | |
| 静脉侵犯(Venous permeation) | | | |
| 有 | 0 | 0 | >0.05 |
| 无 | 50 | 16 | |

**表 2 粘膜内胃癌中 MMP2 和 MMP9 表达与淋巴结转移的相关性分析**

Table 2 Correlation of the MMP2 and MMP9 expressions with lymph node metastasis in the intramucosal gastric carcinoma

| | 无淋巴结转移组 Lymphatic metastasis group (n=50) | 淋巴结转移组 Non lymphatic metastasis group (n=16) | P |
|---|---|---|---|
| MMP9 | | | 0.025 |
| 阴性(Negative) | 32(64%) | 2 (12.5%) | |
| 阳性(Positive) | 18(36%) | 14(87.5%) | |
| MMP2 | | | >0.05 |
| 阴性(Negative) | 27 (54%) | 10 (62.5%) | |
| 阳性(Positive) | 23(46%) | 6 (37.5%) | |

MMP9 相同的作用。研究发现 MMP9 的基质降解作用比 MMP2 高出近 25 倍,MMP9 在粘膜内胃癌转移中的作用比 MMP2 更强[21-24]。此外,MMP2 在粘膜内癌中的表达率显著高于正常粘膜组,说明与胃癌发生有关,可能作为胃癌早期诊断标志物，而 MMP9 在粘膜内癌和正常粘膜中的表达无显著性差异,可能提示其表达不是肿瘤发生的早期事件。

综上所述,本研究将肿瘤体积、分化、淋巴管侵犯等临床病理特征与淋巴结转移相联系，并进一步证实 MMP9 表达与淋巴管侵袭和淋巴结转移存在相关性，这些结果提示 MMP9 可能作为粘膜内胃癌进展的标志物,通过检测胃癌患者活检标本中 MMP9 表达的可能为是否存在淋巴结转移以及手术方式的选择提供依据。

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表 3 粘膜内胃癌中 MMP2 和 MMP9 表达与淋巴管侵犯的相关性

Table 3 Correlation of the MMP2 and MMP9 expressions with lymphatic permeation in the intramucosal gastric carcinoma

| | 无淋巴管侵犯组 Lymphatic vessel invasion group (n=60) | 淋巴管侵犯组 Non lymphatic vessel invasion group (n=6) | P |
|---|---|---|---|
| MMP9 | | | 0.027 |
| 阴性(Negative) | 42(70%) | 1(16.6%) | |
| 阳性(Positive) | 18(30%) | 5(83.3%) | |
| MMP2 | | | >0.05 |
| 阴性(Negative) | 36(60%) | 2(33.3%) | |
| 阳性(Positive) | 24(40%) | 4(66.7%) | |

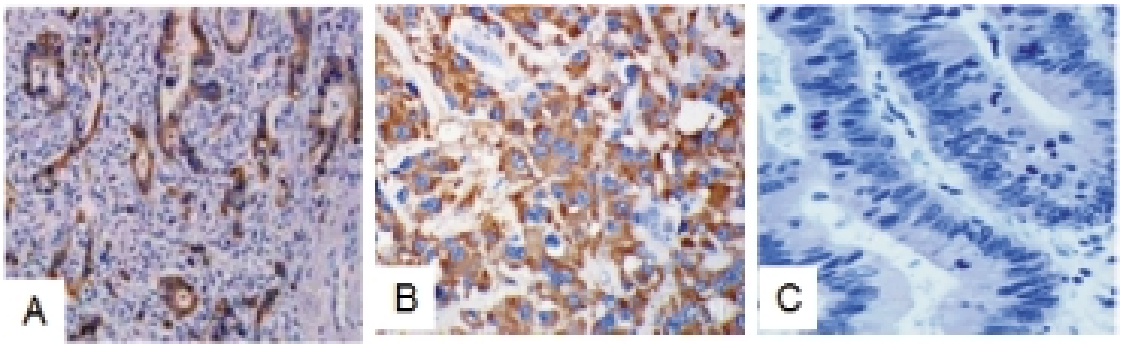


图 1 MMP2 和 MMP9 在胃粘膜内腺癌中的表达(200×)

Fig.1 MMP2 and MMP9 expressions in the intramucosal gastric carcinoma(200×)

A: MMP2 在粘膜内胃癌中的表达(MMP2 expression in IMGC)

B: MMP9 在粘膜内胃癌中的表达(MMP9 expression in IMGC)

C: 空白对照组(blank control)

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