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非小细胞肺癌组织 MMP-2、MMP-9 的表达与组织学类型及临床分期的关系*

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摘要 目的:探究非小细胞肺癌组织基质金属蛋白酶-2(MMP-2)、基质金属蛋白酶-9(MMP-9)的表达及其与患者组织学类型及其临床分期的关系。**方法:**选取2014年1月至2017年1月于我院进行就诊并确诊为非小细胞肺癌的96例患者为实验组,另选取30例肺良性病变患者为对照组,使用免疫组织化学的方法检测患者肺癌组织或肺良性病变组织中MMP-2、MMP-9的表达,并分析MMP-2、MMP-9的表达与患者组织学类型及临床分期之间的关系。**结果:**非小细胞肺癌组织MMP-2及MMP-9表达水平显著高于肺良性病变组织($P<0.05$)。非小细胞肺癌鳞癌组织MMP-2、MMP-9表达明显高于腺癌和腺鳞癌($P<0.05$),而鳞癌与腺鳞癌组织MMP-2、MMP-9表达相比差异无统计学意义($P>0.05$)。随着非小细胞肺癌临床分期的增加,癌组织MMP-2及MMP-9表达逐渐上升,各分期比较差异均具有统计学意义($P<0.05$)。**结论:**MMP-2、MMP-9在非小细胞肺癌组织中的表达水平明显上调,以鳞癌最高,且与临床分期显著相关,提示其对组织学类型、临床分期、病情评估和预后判断均具有一定的参考意义。

关键词:非小细胞肺癌;基质金属蛋白酶-2;基质金属蛋白酶-9;组织学类型;临床分期

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Relationship between the Expression of MMP-2 and MMP-9 in Non-small Cell Lung Cancer and the Histological Type and Clinical Stage*

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ABSTRACT Objective: To explore the expression of matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9) and their correlation with the histological type and clinical stage of non-small cell lung cancer. **Methods:** A total of 96 cases of patients with NSCLC diagnosed as non-small cell lung cancer admitted in our hospital from January 2014 to January 2017 were selected as the experimental group, 30 cases of patients with benign lung disease were selected as the control group. The expressions of MMP-2 and MMP-9 in lung cancer tissues were detected by immunohistochemical method. The relationship between MMP-2, MMP-9 expressions and histological type and clinical stage of non-small cell lung cancer patients were analyzed. **Results:** The expression of MMP-2 and MMP-9 in non-small cell lung cancer tissue were significantly higher than those in the lung benign lesion tissue ($P<0.05$). The expression of MMP-2 and MMP-9 in non-small cell lung cancer squamous cell carcinoma was significantly higher than those in the adenocarcinoma and adenosquamous carcinoma ($P<0.05$), while there was no significant difference between squamous cell carcinoma and adenosquamous carcinoma ($P>0.05$). The expression of MMP-2 and MMP-9 in lung cancer tissue were significantly increased with the increase of non-small cell lung cancer stage ($P<0.05$). **Conclusions:** The expression of MMP-2 and MMP-9 in non-small cell lung cancer tissues was significantly up-regulated, which was the highest in squamous cell carcinoma, they may contribute to the prognostic prediction and evaluation of histological type and clinical stage.

Key words: Non-small cell lung cancer; Matrix metalloproteinase-2; Matrix metalloproteinase-9; Histological type; Clinical stage

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前言

随着近些年居民饮食结构和生活方式的改变,癌症的发病率呈现逐年递增趋势,癌症是一类起源于上皮组织的恶性肿瘤,因其具有异常细胞分化和增殖性,且易发生转移和浸润,发展至后期会对人体正常组织产生严重破坏,进而导致患者死亡

[1,2]。肺癌是呼吸系统中最常见的恶性肿瘤之一,其发病率具有恶性肿瘤首位,其中非小细胞癌为最为常见的病理类型。统计数据显示,2012年全球癌症发病数为1.41亿例,而肺癌发病例数为1600万,约占总数的12.9%,同年死于肺癌的人数高达1600万例[3-5]。

非小细胞型肺癌包括鳞状细胞癌(鳞癌)、腺癌、大细胞癌,

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与小细胞癌相比其癌细胞生长分裂较慢,扩散转移相对较晚,约占所有肺癌的80%^[6,7]。虽然近些年对肺癌的治疗手段不断更新,但肺癌患者仍会或早或晚的死于肺癌的复发和转移,究其原因肺癌具有较高的转移和侵袭性,大大增加了其治疗难度^[8,9]。近年研究表明MMP-2及MMP-9与非小细胞肺癌的发展密切相关^[10,11]。因此,本研究主要探讨了非小细胞肺癌组织MMP-2、MMP-9的表达及其与组织学类型及其临床分期的相关性,现详述如下。

1 资料与方法

1.1 一般资料

选取2014年1月至2017年1月于我院进行就诊并确诊为非小细胞肺癌的96例患者为实验组,包括男性45例,女性51例,年龄35-64岁,平均年龄(42.36±10.15)岁,鳞癌36例,腺癌35例,腺鳞癌25例,I期26例,II期30例,III期27例,IV期13例。另选取30例肺良性病变患者为对照组,其中男性15例,女性15例,年龄34-63岁,平均年龄(41.96±11.56)岁,支气管扩张10例,肺脓肿12例,肺结核瘤7例,炎性假瘤1例。两组患者一般资料如性别、年龄等比较差异均无统计学意义($P>0.05$),具有可比性。

病例纳入标准:①实验组患者均经病理检查证实为非小细胞肺癌;②病历资料齐全者;③意识清醒能够配合进行调研者;④患者及其家属对本次调研过程、方法、原理清楚明白并签署知情同意书。排除标准:①合并精神疾病患者;②合并其他器质性疾病如冠心病、肾衰竭等;③前期已进行抗癌治疗者;④依从性差者;⑤干预过程中死亡病例;⑥患者或其家属主动要求退出

调研者。

1.2 免疫组化检测

所有研究对象均进行肺部组织石蜡包埋,而后使用湖北康龙电子科技有限公司生产的生物组织切片机进行组织切片,切片厚度4 μm,使用鼠抗人MMP-2单克隆抗体抗(1:400,上海研生生化试剂有限公司)及MMP-9单抗(1:100,上海扶生实业有限公司)对切片进行处理,操作步骤严格按照说明书进行,而后使用金拓丰仪器公司生产的XDL-7000型连续变倍体视显微镜在400倍镜下对切片进行观察,每个切片取10个视野,每个视野以100个细胞为基数,合计1000个细胞,对视野中被染色为黄色的细颗粒状细胞数进行统计,并计算出其表达水平。

1.3 观察指标及评测标准

观察两组患者阳性细胞数并进行统计,而后进行对比;对实验组患者不同组织学类型患者阳性细胞数进行统计而后进行组内对比;对不同临床分期非小细胞癌患者阳性细胞表达进行记录并进行组内对比。

1.4 统计学方法

使用SPSS22.0进行数据分析,计数资料以率(%)的形式表示,组间比较采用卡方检验,计量资料以($\bar{x}\pm s$)表示,组间比较采用t检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组MMP-2、MMP-9表达的比较

实验组肺癌组织MMP-2及MMP-9相对表达显著高于对照组良性病变肺组织,差异具有统计学意义($P<0.05$),见表1。

表1 两组MMP-2、MMP-9表达的对比($\bar{x}\pm s$)

Table 1 Comparison of the expression of MMP-2, MMP-9 between two groups($\bar{x}\pm s$)

Groups	n	MMP-2(%)	MMP-9(%)
Study group	96	62.35±11.06	66.87±12.17
Control group	30	14.32±2.68	17.63±1.95
P	-	0.000	0.000

2.2 不同组织学类型肺癌组织MMP-2、MMP-9表达的比较

鳞癌组MMP-2及MMP-9表达水平最高,与腺癌和腺鳞癌患者对比差异具有统计学意义($P<0.05$),而鳞癌和腺鳞癌患

者MMP-2、MMP-9表达水平对比差异不具有统计学意义($P>0.05$),见表2。

表2 不同组织学类型患者MMP-2、MMP-9表达比较($\bar{x}\pm s$)

Table 2 Comparison of the expression of MMP-2, MMP-9 between lung cancer patients with different histological types($\bar{x}\pm s$)

Histological types	n	MMP-2(%)	MMP-9(%)
Squamous carcinoma	36	65.26±13.28	66.15±11.86
Adenocarcinoma	35	54.29±10.38*	55.26±11.26*
Adenocarcinoma carcinoma	25	53.27±12.06*	52.98±11.83*

Note: compared with squamous carcinoma, * $P<0.05$.

2.3 不同临床分期肺癌组织MMP-2、MMP-9表达的比较

如表3所示,MMP-2及MMP-9表达水平I期<II期<III期<IV期,且各组间对比差异具有统计学意义($P<0.05$),见表3。

3 讨论

近些年我国工业化进程不断发展,环境污染问题逐渐凸显,加之居民生活方式和饮食结构的改变,各类呼吸系统疾病

表 3 不同临床分期患者 MMP-2、MMP-9 表达的比较($\bar{x} \pm s$)Table 3 Comparison of the expression of MMP-2, MMP-9 between patient with different clinical stages($\bar{x} \pm s$)

Different clinical stages	n	MMP-2(%)	MMP-9(%)
Stage I	26	22.32± 6.28	26.76± 5.25
Stage II	30	31.69± 5.82*	32.76± 4.96*
Stage III	27	43.98± 6.97**	46.39± 5.62**
Stage IV	13	59.68± 5.28*#^	61.82± 5.61*#^

Note: compared with Stage I, * $P < 0.05$; compared with Stage II satage, $^{\#}P < 0.05$; compared with Stage III, $^{\wedge}P < 0.05$.

的发病率不断上升^[12,13]。肺癌一种较常见的癌症,其发病率和致死率一直位列肿瘤前茅,统计数据显示近些年我国肺癌的发病率和致死率呈现逐年递升趋势,已经成为威胁居民生命健康的重要因素^[14,15]。有研究显示空气污染、吸烟等因素是诱发肺癌发生的重要原因,肺癌的发病率会随着年龄的增长而上升,提示未来肺癌会成为影响我国经济和社会发展的重要影响因素^[16]。

非小细胞肺癌是肺癌中较为常见的病理类型,世界卫生组织(WHO)根据肺癌的组织学类型,将其区分为鳞癌、腺癌、小细胞癌和腺鳞癌等几类,非小细胞肺癌即指除去小细胞癌的组织学类型,该类型约占全部肺癌比例的 80%^[17,18]。相比于小细胞癌,非小细胞癌肿瘤组织分裂速度慢,扩散较晚,但其临床症状不明显,故而约有 75%的患者在发现时已经为中晚期,故而其致死率较高^[19,20]。早期对组织学类型定和临床分期的确定对于后期治疗的开展具有极为重要的意义,传统检查手段主要为病理活检,虽然准确率高,但由于其为有创操作,患者多难以忍受^[21-23]。

MMP-2 及 MMP-9 属于基质金属蛋白酶(MMPs),其主要生理作用包括参与呼吸道粘膜修复、调节其他细胞因子活性、促进血管内皮生长因子(VEGF)释放等。近些年的研究表明^[24,25]MMP-2、MMP-9 具有降解细胞基底膜和细胞外基质的作用,能够加快肿瘤细胞的浸润和转移过程,同时由于其具有促进 VEGF 分泌的作用,也能够促进肿瘤组织新生血管的形成,进一步加快肿瘤组织的转移^[26,27]。有研究者^[28]对 39 例肺癌组织及 8 例正常对照肺组织中 MMP-2 表达进行对比,发现非小细胞癌患者肺癌组织中的 MMP-2 表达水平显著高于对照组, N1-2 肺癌组织中的 MMP-2 表达显著高于 N0 组织肺癌患者,鳞癌患者 MMP-2 水平高于腺癌患者。该学者认为 MMP-2 属于基质金属蛋白酶中分布最广的蛋白酶,当细胞出现恶性病变时,MMP-2 会通过讲解细胞外基质中的胶原蛋白来促进肿瘤细胞的转移和浸润,故而该物质与非小细胞肺癌的临床分期及组织学类型具有一定关联^[29]。有研究者^[30]对 80 例非小细胞肺癌患者及 20 例良性肺病变患者的对比分析,发现 MMP-9 及 MMP-2 在鳞癌中表达水平最高。MMPs 具有较强的细胞基质溶解能力,同时能够通过刺激血管形成成为肿瘤的转移提供条件,因而在预测肺癌预后及判断肺癌分期方面具有较为实际的意义。

本研究结果显示非小细胞肺癌组织 MMP-2、MMP-9 的表达远高于肺良性病变组织,提示 MMP-2、MMP-9 与肺癌的发生相关;同时,非小细胞肺癌鳞癌组织 MMP-2、MMP-9 的表达明显高于腺癌和腺鳞癌组织,且其随着患者临床分期的加重而

逐渐升高,提示 MMP-2、MMP-9 与非小细胞肺癌患者的病情进展相关。

总之,MMP-2、MMP-9 在非小细胞肺癌组织中的表达水平明显上调,以鳞癌最高,且与临床分期显著相关,提示起对组织学类型、临床分期、病情评估和预后判断均具有一定的参考意义。

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