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树突状细胞对胃癌前病变的免疫保护分析 *

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摘要 目的:探究树突状细胞(Dendritic cells,DC)对胃癌的免疫保护作用。**方法:**选择 2016 年 1 月至 2018 年 1 月于我院接受治疗的 145 例胃癌、39 例慢性萎缩性胃炎、21 例不典型增生、27 例肠上皮化生以及 20 例正常对照组患者为研究对象，分别采集其胃粘膜标本进行染色,记录和比较其胃粘膜中 $S100^+$、$CD4^+$ 和 $CD8^+$ 细胞的数量、平均面积以及平均吸光度,并将胃癌患者分为中分化腺癌(49 例)、低分化腺癌(53 例)和未分化癌(43 例)进行对比。**结果:**(1)胃癌组、慢性萎缩性胃炎组、不典型增生、肠上皮化生组的胃粘膜 $S100^+$ 阳性细胞计数明显高于正常对照组(P<0.05),胃癌组平均吸光度低于对照组,其他 3 组平均吸光度显著高于对照组,(P<0.05);胃癌组平均面积与正常对照组相比无差异(P>0.05),其他三组平均面积显著高于对照组(P<0.05);(2)慢性萎缩性胃炎组、肠上皮化生组、不典型增生组患者 $CD4^+$ 细胞数均低于对照组(P<0.05);胃癌组、慢性萎缩性胃炎组、肠上皮化生组患者平均面积均低于对照组(P<0.05);胃癌组、慢性萎缩性胃炎组、不典型增生、肠上皮化生组平均吸光度均低于对照组(P<0.05);(3)慢性萎缩性胃炎组、肠上皮化生组、不典型增生组患者 $CD8^+$ 细胞数明显高于对照组(P<0.05),胃癌组稍低于对照组(P>0.05);胃癌组患者平均面积低于对照组(P<0.05);胃癌组患者平均吸光值低于对照组,慢性萎缩性胃炎组、肠上皮化生组患者高于对照组(P 均 <0.05);(4)随着胃癌分化程度的降低,胃癌患者 DC 细胞数有降低趋势。**结论:**胃癌前病变患者胃粘膜中 DC 数量会显著增多,免疫功能加强,DC 细胞数量会随胃癌分化程度的降低而减少,分析其原因与 DC 细胞能够抑制癌前病变有关。

关键词:树突细胞;癌前病变;免疫保护

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Immunoprotection of Dendritic Cells Against Precancerous Lesions of Gastric Cancer*

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ABSTRACT Objective: To explore the immunoprotective effect of dendritic cells (DC) on the gastric cancer. **Methods:** 145 cases of gastric cancer, 39 cases of chronic atrophic gastritis, 21 cases of atypical hyperplasia, 27 cases of intestinal metaplasia and 20 cases of normal control group treated in our hospital from January 2016 to January 2018 were selected as the subjects. Gastric mucosa specimens were stained and observed by image analyzer. The number of $S100^+$, $CD4^+$ and $CD8^+$ cells in the gastric mucosa and the average face area were recorded. The volume and average absorbance were compared, and the patients with gastric cancer were divided into the differentiated adenocarcinoma (49 cases), poorly differentiated adenocarcinoma (53 cases) and undifferentiated carcinoma (43 cases). **Results:** (1) The gastric mucosal $S100^+$ positive cells in the gastric cancer group, chronic atrophic gastritis group, atypical hyperplasia and intestinal metaplasia group were significantly higher than that in the normal control group (P<0.05). The average absorbance in the gastric cancer group was lower than that in the control group, which were significantly higher in the other 3 groups than that in the control group (P>0.05). (2) The number of $CD4^+$ cells in the chronic atrophic gastritis group, intestinal metaplasia group and atypical hyperplasia group were lower than that in the control group (P<0.05). The average area of patients in the gastric cancer group, chronic atrophic gastritis group and intestinal metaplasia group was lower than that in the control group (P<0.05), the average absorbance of the gastric cancer group, the chronic atrophic gastritis group, the atypical hyperplasia, and the intestinal metaplasia group were lower than that in the control group (P<0.05). (3)The number of $CD8^+$ cells in the chronic atrophic gastritis group, intestinal metaplasia group and atypical hyperplasia group were significantly higher than that in the control group (P<0.05), which was slightly lower in the gastric cancer group than that of the control group (P>0.05); the average area of gastric cancer group was lower than that of the control group (P<0.05);

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the average absorbance of patients with gastric cancer was lower than that of the control group, and the patients with chronic atrophic gastritis and intestinal metaplasia were higher than the control group (P<0.05). (4) With the decrease of gastric cancer differentiation, the number of DC cells in gastric cancer patients tended to decrease. **Conclusion:** The number of DC in gastric mucosa of patients with precancerous lesions is significantly increased, and the immune function is strengthened. The number of DC cells is decrease with the decrease of differentiation of gastric cancer, indicating that DC cells may inhibit precancerous lesions

Key words: Dendritic cells; Precancerous lesions; Immune protection

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前言

胃癌是一种起源于胃粘膜上皮的恶性肿瘤，是世界范围内常见的肿瘤之一，也是消化科多发的肿瘤之一[1,2]。流调学数据表明 2012 年全球新发胃癌病例有 95.1 万，死亡病例高达 72.3 万例，死亡率位居前三。胃癌在我国发病率较高，发病人数及死亡人数均约占全世界的 50%左右[3,4]。现阶段胃癌的治疗手段主要包括化疗、放疗、手术治疗等，但上述方式均存在一定的局限性[5,6]。

树突状细胞(DC)是目前所知的功能最强的抗原提呈细胞，也是神经细胞的一类，DC 细胞能够高效的摄取、加工处理和递呈抗原，成熟的 DC 细胞具有激活初始 T 细胞的功效，因而在启动、调控、维持免疫应答中发挥重要作用[7,8]，研究表明 DC 细胞能够通过调节肿瘤免疫发挥治疗作用，但其机理尚不明确。本研究结果显示胃癌患者胃粘膜中 DC 数量显著增多，免疫功能加强，DC 细胞数量会随胃癌分化程度的降低而减少，分析其原因可能与 DC 细胞能够抑制肿瘤细胞扩散有关[9,10]，现详述如下。

1 资料与方法

1.1 一般资料

选择于我院接受治疗的 145 例胃癌(中分化腺癌 49 例、低分化腺癌 53 例和未分化癌 43 例)、39 例慢性萎缩性胃炎、21 例不典型增生、27 例肠上皮化生患者以及 20 例正常人为研究对象。纳入标准：意识清晰能够配合进行调研；排除标准：胃癌行化疗患者；无法实施胃粘膜活检者；合并严重肝肾功能障碍者；合并其他器质性疾病患者。

1.2 标本制作及观测

入组患者采集标本前禁食 10 h，采集前对患者进行常规体格检查，患者取仰卧位，将采样器伸入患者口腔，仔细观察患者病变部位，并使用夹子于病变部位进行标本采集，采集的样本使用生理盐水进行冲洗，暴露标本并使用石蜡进行固定，而后制作为 4 μm 连续切片，分别进行 HE 染色，选择免疫组化染色(SP) 法进行细胞数量测定，$S100^+$、$CD4^+$ 及 $CD8^+$ 数量的测定选择 SP 法，试剂盒采购自上海酶研生物科技有限公司，操作严格按照试剂盒说明书实施。结果判定：$S100^+$ 阳性判定标准为染色区域位于细胞质内，阳性结果呈现棕黄色[11,12]，$CD4^+$ 及 $CD8^+$ 阳性判定标准为染色区域位于细胞膜上，阳性结果呈现棕黄色。染色结果使用 KEYENCE 公司生产的 VHX-5000 型图像分析仪进行测定，记录阳性细胞计数、平均面积及平均吸光度。计数粘膜层中阳性细胞数量，检测阳性细胞界面的总面积，计算平均面积。平均吸光度反映免疫组化染色的程度。每个标本选择 3 张切片，每张切片随机选择 5 个高倍镜视野(× 400)测定每个视野下阳性反应。

1.3 观察指标及评测标准

首先观察记录各组研究对象 DC 细胞 $S100^+$ 阳性细胞计数、平均面积及平均吸光度，并对比各组 $CD4^+$、$CD8^+$ 细胞计数、平均面积及平均吸光度，最后对胃癌患者不同分期 DC 细胞 $S100^+$ 阳性细胞计数、平均面积和平均吸光度进行对比分析。

1.4 统计学方法

对获得数据采用 SPSS20.0 软件分析，计数资料以率(%)表示，组间比较行 x^2 检验，计量资料以($\bar{x}\pm s$)表示，组间比较行 t 检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 不同组别胃粘膜 S100+ 阳性细胞计数、平均面积和平均吸光度对比

胃癌组、慢性萎缩性胃炎组、不典型增生、肠上皮化生组的胃粘膜 $S100^+$ 阳性细胞计数明显均高于正常对照组(P<0.05)；胃癌组平均吸光度低于对照组，其他 3 组平均吸光度显著高于对照组 (P<0.05)；胃癌组平均面积与正常对照组相比无差异(P>0.05)，其他三组平均面积显著高于对照组(P<0.05)，具体数据如表 1 所示。

表 1 各组胃粘膜 S100 + 阳性细胞计数、平均面积、平均吸光度的比较

Table 1 Comparison of gastric mucosal S100 + positive cell count, mean area and mean absorbance in different groups

Groups	Case	Number of positive cells(/μm^{-2})	Average area(μm^{-2})	Average absorbance(Δ)
Control group	20	0.21± 0.11	45.13± 5.31	1.21± 0.21
Chronic atrophic gastritis group	39	1.71± 0.21*	68.12± 6.03*	1.89± 0.16*
Chronic atrophic gastritis group	27	2.06± 0.15*	68.31± 3.62*	1.73± 0.22*
Intestinal metaplasia group	21	2.26± 0.14*	67.16± 4.13*	1.53± 0.19*
Gastric cancer group	145	0.56± 0.21*	48.61± 5.61	0.86± 0.12*

Note: Compared with the control group, * P<0.05.

2.2 不同组别胃粘膜 $CD4^+$ 阳性细胞计数、平均面积和平均吸光度对比

$CD4^+$ 细胞主要分布于胃粘膜固有层中，染色区域集中于细胞膜上。慢性萎缩性胃炎组、肠上皮化生组、不典型增生组患者 $CD4^+$ 细胞数均低于对照组(P<0.05)；胃癌组、慢性萎缩性胃炎组、肠上皮化生组患者平均面积均低于对照组(P<0.05)；胃癌组、慢性萎缩性胃炎组、不典型增生、肠上皮化生组平均吸光度均低于对照组(P<0.05)，具体数据如表 2 所示。

表 2 不同胃黏膜组 $CD4^+$ 阳性细胞计数、平均面积和平均吸光度的比较

Table 2 Comparison of $CD4^+$ positive cell count, mean area and mean absorbance in different groups of gastric mucosa

Groups	Case	Number of positive cells(/μm^{-2})	Average area(μm^{-2})	Average absorbance(Δ)
Control group	20	2.26± 0.34	66.56± 13.61	1.16± 0.13
Chronic atrophic gastritis group	39	1.38± 0.26*	38.68± 5.16*	0.98± 0.15*
Chronic atrophic gastritis group	27	1.13± 0.21*	43.16± 11.62*	0.96± 0.18*
Intestinal metaplasia group	21	0.98± 0.16*	40.65± 10.62*	1.06± 0.26
Gastric cancer group	145	0.71± 0.21*	35.62± 8.95*	0.61± 0.11*

Note: Compared with the control group, * P<0.05.

2.3 不同组别胃粘膜 $CD8^+$ 阳性细胞计数、平均面积和平均吸光度对比

$CD8^+$ 细胞与 $CD4^+$ 细胞分布相似，慢性萎缩性胃炎组、肠上皮化生组、不典型增生组患者 $CD8^+$ 细胞数明显高于对照组(P<0.05)，胃癌组稍低于对照组(P>0.05)；胃癌组患者平均面积低于对照组(P<0.05)；胃癌组患者平均吸光值低于对照组，慢性萎缩性胃炎组、肠上皮化生组患者高于对照组(P<0.05)，具体数据如表 3 所示。

2.4 胃癌不同分化类型 DC 细胞

根据分化程度将胃癌患者区分为中分化腺癌(49 例)、低分化腺癌(53 例)和未分化癌(43 例)3 类，结果显示随着分化程度的降低，其 DC 细胞计数有逐渐减少的趋势，其中中分化腺癌 DC 细胞计数为(0.86± 0.15)μm^{-2}，低分化腺癌 DC 细胞计数为(0.62± 0.16)μm^{-2}，未分化腺癌 DC 细胞计数为 (0.43± 0.11)μm^{-2}，组内对比差异具有统计学意义(P<0.05)。

表 3 各组胃黏膜 $CD8^+$ 阳性细胞计数、平均面积、平均吸光度比较

Table 3 Comparison of $CD8^+$ positive cell count, mean area and mean absorbance in different groups of gastric mucosa

Groups	Case	Number of positive cells(/μm^{-2})	Average area(μm^{-2})	Average absorbance(Δ)
Control group	20	1.23± 0.15	68.59± 15.31	1.32± 0.11
Chronic atrophic gastritis group	39	1.81± 0.21*	65.67± 13.01	1.51± 0.19*
Chronic atrophic gastritis group	27	1.92± 0.19*	65.59± 11.55	1.43± 0.21*
Intestinal metaplasia group	21	1.82± 0.21*	60.86± 9.68	1.32± 0.18
Gastric cancer group	145	1.19± 0.23	62.56± 11.98*	1.06± 0.18*

Note: Compared with the control group, * P<0.05.

3 讨论

2012 年世界癌症报告数据表明全球范围新发癌症病例数为 1.41 亿例，死亡病例数为 8200 万，胃癌占总发病例数的 12.9%，而胃癌的死亡病例数高达 1600 万例，约占癌症总死亡例数的 19.4%[13,14]。我国的流调学也显示胃癌的死亡率已经由 20 世纪 70 年代的第 4 位上升至第 1 位，提示胃癌已经对我国居民的生命健康造成了严重威胁[15,16]。早期胃癌临床症状不明显，患者多表现出与胃炎等良性疾病的症状，因而不能引起患者充分重视，一旦发现，多已发展至晚期，晚期胃癌患者的临床症状包括呕血、剧烈疼痛等，严重降低患者的生活质量[16,17]。及时有效的干预是提高胃癌患者术后生活质量的有效手段，但临床实践显示现阶段常用的手术、化疗、放疗等传统胃癌治疗手段多存在较为明显的不良反应，尤其是部分特殊群体，如老年胃癌患者接受化疗后，出现的不良反应甚至会影响治疗进程，最终导致治疗失败[18,19]。

近些年，免疫治疗受到广泛关注，其是在机体低下或亢进的免疫状态下，人为抑制或增强个体的免疫功能，达到治疗疾病目的的一种方法[20]。免疫治疗包括很多手段，研究指出，通过增强个体的免疫系统，能够依靠自身免疫机能来杀灭癌细胞和肿瘤组织，相比于传统治疗手段，免疫治疗的安全性和特异性更高[21]。DC 细胞是目前已知的唯一能够激活静息期 T 细胞的抗原提呈细胞，成熟的 DC 细胞能够分泌大量的刺激因子和粘附因子，诱导 T、B 细胞增殖分化，进而提高机体免疫能力，在治疗感染性疾病、自身免疫性疾病，恶性肿瘤防治及移植排斥反应控制中的应用越来越广泛，特别是增强机体特异性抗肿瘤免疫能力中的效果逐渐使其成为肿瘤治疗的崭新手段[22,23]。研究表明 DC 细胞能够通过激活初始型 T 淋巴细胞来启动免疫反应，而其他抗原提呈细胞多是刺激已活化的或记忆性 T 淋巴细胞，因而 DC 细胞属于机体免疫反应的源头，通过激活 DC 细胞能够调动机体的免疫反应，起到治疗疾病的目的[24]。研究[25]显示 DC 细胞与胃癌进展关系密切，肿瘤组织内免疫抑制微环

境的改变影响了 DC 细胞的分化和成熟，导致了 DC 功能障碍，影响了 DC 细胞的抗肿瘤免疫功能。Vanja V B[26]等的研究也发现成熟的 DC 细胞能够通过分泌细胞因子来激活机体自身的自然杀伤细胞和巨噬细胞，通过特异性免疫应答来杀伤肿瘤细胞。

本研究结果显示胃癌组、慢性萎缩性胃炎组、不典型增生、肠上皮化生组的胃粘膜 $S100^+$ 阳性细胞计数明显高于正常对照组，平均吸光度胃癌组低于对照组，其他 3 组显著高于对照组；平均面积胃癌组与正常对照组相比无差异，其他三组显著高于对照组，提示受试者存在明显的细胞免疫过剩，进而对胃粘膜产生了免疫损伤[27]。而进一步的研究显示随着胃癌分化程度的降低，受试者的 DC 细胞数量有减少的趋势，分析其原因为肿瘤组织的微环境会对 DC 细胞产生影响，加之缺乏 Th 细胞的辅佐，使 DC 细胞总体数量有所减少。同时也有学者就 DC 细胞数量与胃癌患者预后进行了研究，结果显示 DC 细胞在肿瘤局部更高的浸润能够减少淋巴结的转移，对肿瘤的扩散起到一定抑制作用，因而可以通过 DC 细胞数量的检测来预测胃癌患者预后情况 [28]。此外，本研究也对不同胃粘膜病变患者其 $CD4^+$、$CD8^+$ 等细胞数量的不同进行了分析，结果显示慢性萎缩性胃炎、肠上皮化生、不典型增生和胃癌患者其胃粘膜中 $CD4^+$ 细胞的数量显著少于正常对照组，而除胃癌患者外其他胃粘膜病变患者其 $CD8^+$ 数量明显多于正常对照组。正常情况下，DC 细胞能够在受到抗原刺激后，分泌 IL-1，来加快 Th 细胞的分化，Th 细胞分泌的 IL-2 能够加速 $CD4^+$ 及 $CD8^+$ 细胞的增殖分化。换言之，DC 细胞的数量和功能就是决定 $CD4^+$ 和 $CD8^+$ 细胞计数的因素[29,30]。而本研究结果显示除胃癌组外，其他胃粘膜病变患者其 $CD4^+$ 低于正常组，$CD8^+$ 高于对照组，说明 DC 细胞的功能缺陷影响了细胞免疫功能，降低了机体的抗癌能力，由此推测 DC 细胞的功能抑制是导致胃粘膜免疫功能低下，进而诱发癌前病变甚至癌变的重要原因之一。

综上所述，胃癌前病变患者胃粘膜中 DC 数量会显著增多，免疫功能加强，DC 细胞数量会随胃癌分化程度的降低而减少，分析其原因与 DC 细胞能够抑制癌前病变有关。

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