

doi: 10.13241/j.cnki.pmb.2018.10.019

IL-17 和 VEGF 在慢性鼻 - 鼻窦炎患者鼻息肉组织中的表达及相关性研究 *

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摘要 目的:探讨慢性鼻 - 鼻窦炎患者鼻息肉组织中白介素-17(IL-17)、血管内皮生长因子(VEGF)的表达,并分析 IL-17、VEGF 表达水平的相关性。**方法:**以我院 2015 年 1 月~2017 年 12 月期间收治的慢性鼻 - 鼻窦炎患者 95 例为研究对象,按患者有无鼻息肉分为伴鼻息肉(观察 1 组)49 例和不伴鼻息肉(观察 2 组)46 例。另选取同期在我院进行治疗的鼻中隔偏曲患者 40 例为对照组。所有患者均进行鼻内镜手术治疗,并在术中取其较窄侧的鼻甲黏膜作为检测标本,采用免疫组化 SP 法检测各组织标本中的 IL-17、VEGF 的表达水平,并分析 IL-17、VEGF 表达水平的相关性。**结果:**观察 1 组患者 IL-17、VEGF 的阳性表达率分别为 93.88%(46/49)、85.71%(42/49),均高于观察 2 组患者 IL-17、VEGF 的阳性表达率[76.09%(35/46)、65.22%(30/46)]以及对照组患者 IL-17、VEGF 的阳性表达率[5.00%(2/40)、2.50%(1/40)],差异均具有统计学意义($P<0.05$)。观察 1 组患者 IL-17、VEGF 的表达水平分别为 (38.92 ± 5.34) 个/LP、 (33.21 ± 4.87) 个/LP,均高于观察 2 组患者 IL-17、VEGF 的表达水平 $[(28.19\pm 4.56)$ 个/LP、 (21.28 ± 4.03) 个/LP]以及对照组患者 IL-17、VEGF 的表达水平 $[(9.31\pm 2.76)$ 个/LP、 (7.19 ± 1.95) 个/LP],差异均具有统计学意义($P<0.05$)。经 Spearman 相关性分析结果显示,观察 1 组患者、观察 2 组患者中,IL-17 与 VEGF 的表达水平呈正相关性($P<0.05$)。**结论:**慢性鼻 - 鼻窦炎患者鼻息肉组织中 IL-17、VEGF 的表达显著升高,且 IL-17 与 VEGF 表达水平呈明显的正相关性,表明 IL-17、VEGF 可能共同参与鼻息肉的发生与发展过程。

关键词:慢性鼻 - 鼻窦炎;鼻息肉;白介素-17;血管内皮生长因子;相关性

中图分类号:R765.21 文献标识码:A 文章编号:1673-6273(2018)10-1901-04

Expression and Correlation of IL-17 and VEGF in Nasal Polyps of Patients with Chronic Rhinosinusitis*

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ABSTRACT Objective: To investigate the expression of interleukin-17 (IL-17) and vascular endothelial growth factor (VEGF) in nasal polyp tissue of patients with chronic rhinosinusitis, and to analyze the correlation between IL-17 and VEGF expression levels. **Methods:** 95 patients with chronic rhinosinusitis who were treated in our hospital from January 2015 to December 2017 were selected as the research subjects. According to whether the patients had nasal polyps, they were divided into nasal polyps (Observation group 1) with 49 cases and no nasal polyps (Observation group 2) with 46 cases. In addition, 40 patients with nasal septum deviation who were treated in our hospital over the same period were selected as control group. All patients were underwent endoscopic surgery, and the nasal concha mucous membrane at the narrower side of patients was taken as a test specimen during the operation. The expression levels of IL-17 and VEGF in all tissue specimens were detected by immunohistochemical SP method, and the correlation of IL-17 and VEGF expression levels was analyzed. **Results:** The positive rates of IL-17 and VEGF in Observation group 1 were 93.88% (46/49) and 85.71% (42/49), respectively, which were all higher than those of [76.09% (35/46), 65.22% (30/46)] in Observation group 2 and [5.00% (2/40) and 2.50% (1/40)] in the control group, the differences were statistically significant ($P<0.05$). The expression levels of IL-17 and VEGF in Observation group 1 were (38.92 ± 5.34) amount/LP and (33.21 ± 4.87) amount/LP, respectively, which were all higher than those of $[(28.19\pm 4.56)$ amount/LP, (21.28 ± 4.03) amount/LP] in Observation group 2 and $[(9.31\pm 2.76)$ amount/LP, (7.19 ± 1.95) amount/LP] in the control group, the differences were statistically significant ($P<0.05$). The results of Spearman correlation analysis showed that there was a positive correlation between the expression levels of IL-17 and VEGF of patients in Observation group 1 and Observation group 2 ($P<0.05$). **Conclusion:** The expression of IL-17 and VEGF in the nasal polyp tissue of patients with chronic rhinosinusitis is increased significantly, and the expression level of IL-17 is significantly positively correlated with VEGF expression, it is suggested that IL-17 and VEGF may

* 基金项目:江苏省第十四批“六大人才高峰”高层次人才选拔培养资助项目(WSW-094)

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(收稿日期:2018-01-07 接受日期:2018-01-30)

participate in the occurrence and development of nasal polyps.

Key words: Chronic rhinosinusitis; Nasal polyp; Interleukin-17; Vascular endothelial growth factor; Correlation

Chinese Library Classification(CLC): R765.21 **Document code:** A

Article ID: 1673-6273(2018)10-1901-04

前言

慢性鼻-鼻窦炎为鼻窦的慢性化脓性炎症,通常表现为多个鼻窦同时受累。慢性鼻-鼻窦炎的出现可加重患者的呼吸道感染症状,严重者有可能引起颅眼肺并发症,导致视力改变,严重影响患者的生活质量。鼻息肉是指赘生于鼻腔或鼻窦黏膜处的突起的增生组织,通常伴随着慢性鼻-鼻窦炎共同出现,对患者呼吸道的结构与功能有着严重的不良影响^[1-3]。患者临床表现为鼻腔阻塞、鼻内分泌物增多,同时还会引起患者面部的疼痛、肿胀,并对患者的嗅觉功能有一定的影响^[4,5]。目前,对于鼻息肉发生发展的机制研究尚未完全明确,大部分观点认为鼻息肉的发生、进展与环境、遗传、炎症反应等因素有一定关联。近几年相关研究显示^[6-8],鼻息肉组织生长过程中,有大量的新生血管形成,促进和加速鼻息肉组织的增生。鼻息肉组织的增生过程还与机体的炎症反应有关,在鼻息肉组织的增生扩张过程中伴随着多种炎性细胞因子的浸润。白介素-17(Interleukin-17, IL-17)是临床常见的炎症细胞因子,与机体炎症反应水平有关,而血管内皮生长因子(Vascular endothelial growth factor, VEGF)是血管通透因子,与新生血管的形成紧密相连^[9,10]。为此,本研究检测鼻息肉组织的 IL-17、VEGF 阳性表达率和表达水平,并分析二者在鼻息肉组织中的相关性,以期对鼻息肉的发病机制研究提供参考。

1 资料与方法

1.1 临床资料

以我院 2015 年 1 月~2017 年 12 月期间收治的慢性鼻-鼻窦炎患者 95 例为研究对象,纳入标准:①患者经诊断符合慢性鼻-鼻窦炎相关诊断标准^[11],即患者中鼻道或嗅裂有黏脓性分泌物,中鼻道黏膜充血、水肿或有鼻息肉,影像学检查:CT 扫描显示窦口鼻道复合体或鼻窦黏膜病变;②患者均进行鼻内镜手术治疗;③患者入组前 1 个月未进行相关激素类药物治疗。排除标准:①鼻内其他病变患者,如变应性鼻炎、细菌感染性鼻炎等;②支气管哮喘患者;③不能耐受本研究手术治疗患者。将 95 例患者按有无鼻息肉分为伴鼻息肉(观察 1 组)49 例和不伴鼻息肉(观察 2 组)46 例。观察 1 组男性 27 例、女性 22 例,患者年龄 28~59 岁,平均年龄(43.82±10.21)岁;观察 2 组男性 26

例、女性 20 例,患者年龄 27~61 岁,平均年龄(44.95±10.89)岁。另选取同期在我院进行治疗的鼻中隔偏曲患者 40 例为对照组,其中男性 24 例、女性 16 例,患者年龄 29~60 岁,平均年龄(44.57±11.56)岁。所有患者均进行鼻内镜手术治疗,并在术中取较窄侧的鼻甲黏膜作为检测标本。三组患者的基线资料比较无统计学差异($P>0.05$),组间均衡可比。所有患者均签署知情同意书,研究方案经医院伦理学委员会批准。

1.2 方法

所有患者手术切除的标本在 4%多聚甲醛中固定,脱水后用石蜡包埋,染色前采用 RM3255 型自动病理切片机(德国徕卡仪器公司)进行连续切片,厚度为 5 μm 。将切好的切片置于 DFZ-6021 型电热恒温箱(上海合恒仪器设备有限公司)中进行烤片 30 min,温度为 60℃,使切片能够黏附在载玻片上,然后采用二甲苯进行脱蜡处理,加入 3%双氧水溶液对内源性的酶类物质进行灭活,灭活时间为 5~10 min,再加入枸橼酸盐缓冲液于微波炉中进行抗原修复。按照 SP 试剂盒操作说明对各组织标本进行免疫组化染色,SP 试剂盒购自上海哈灵生物有限公司。在 CX-21 型光学显微镜(日本奥林巴斯公司)下观察 IL-17、VEGF 的阳性细胞数,并计数阳性率,阳性率判断标准为:显微镜视野下出现棕黄色或棕褐色的特异性着色的颗粒状物质即为阳性,否则为阴性。将显微镜调节值低倍镜视野($\times 100$)下,选出每个标本下 10 个阳性细胞数较多的视野进行计数,计算每个标本中的 IL-17、VEGF 表达水平。

1.3 统计学方法

采用专业统计学软件包 SPSS 20.0 进行数据的统计与处理,计数资料以[n(%)]表示,组间比较用 χ^2 检验,计量资料用($\bar{x}\pm s$)表示,两组间比较用 t 检验,多组间比较采用单因素方差分析,IL-17、VEGF 相关性分析采用 Spearman 相关性分析,当 $P<0.05$ 时认为差异有统计学意义。

2 结果

2.1 三组患者 IL-17、VEGF 阳性表达率比较

三组 IL-17、VEGF 的阳性表达率整体比较,差异有统计学意义($P<0.05$),观察 1 组、观察 2 组患者 IL-17、VEGF 的阳性表达率均显著高于对照组患者,且观察 1 组患者高于观察 2 组患者,差异均具有统计学意义($P<0.05$),见表 1。

表 1 三组患者 IL-17、VEGF 阳性表达率比较[n(%)]

Table 1 Comparison of positive rates of IL-17 and VEGF of patients in three groups[n (%)]

Groups	n	IL-17 positive	VEGF positive
Observation group 1	49	46(93.88)* [#]	42(85.71)* [#]
Observation group 2	46	35(76.09)*	30(65.22)*
Control group	40	2(5.00)	1(2.50)
χ^2	-	79.742	64.895
P	-	0.000	0.000

Note: compared with the control group, * $P<0.05$; compared with observation group two, [#] $P<0.05$.

2.2 三组患者 IL-17、VEGF 表达水平比较

三组患者的 IL-17、VEGF 表达水平整体比较,差异有统计学意义($P<0.05$)。观察 1 组、观察 2 组患者 IL-17、VEGF 的表达

水平均显著高于对照组患者,且观察 1 组患者高于观察 2 组患者,差异均具有统计学意义($P<0.05$),见表 2。

表 2 三组患者 IL-17、VEGF 表达水平比较(个/LP, $\bar{x} \pm s$)

Table 2 Comparison of IL-17 and VEGF expression levels of patients in three groups (amount/LP, $\bar{x} \pm s$)

Groups	n	IL-17	VEGF
Observation group 1	49	38.92 $\pm$ 5.34* [#]	33.21 $\pm$ 4.87* [#]
Observation group 2	46	28.19 $\pm$ 4.56*	21.28 $\pm$ 4.03*
Control group	40	9.31 $\pm$ 2.76	7.19 $\pm$ 1.95
F	-	27.362	21.074
P	-	0.000	0.000

Note: compared with the control group, * $P<0.05$; compared with observation group two, [#] $P<0.05$.

2.3 IL-17 与 VEGF 相关性分析

经 Spearman 相关性检验显示,观察 1 组、观察 2 组患者中,IL-17 与 VEGF 的表达水平呈正相关性($r=0.562, 0.491$; $P=0.000, 0.000$)。

3 讨论

慢性鼻-鼻窦炎是耳鼻喉科常见的一种炎症性疾病,该病发生后对患者的鼻腔、呼吸道功能均产生不良影响,并且多数慢性鼻-鼻窦炎患者还会伴发鼻息肉,且鼻息肉的出现会加重患者的病情,并且还会致使患者的鼻部正常功能及呼吸道功能受到不利影响^[12-14]。由于鼻息肉存在的危害性,临床上对其关注度在不断提高,目前已有大量的研究在寻求有效方法以降低鼻息肉在患者中的发生率^[15,16]。鼻息肉的发生及发展是一个多种因素、多种细胞因子参与的经过多个步骤反应的病理学结果。其发生机制为患者出现鼻粘膜上皮细胞损伤、上皮增生以及间质水肿,并在体内炎症细胞因子紊乱的诱导下,鼻粘膜出现大量的血管增生和扩张,从而导致鼻息肉组织的增生^[17-19]。因此,可以推测慢性鼻-鼻窦炎患者新生血管的异常增生及炎症因子水平异常升高可能是影响鼻息肉组织发生发展的关键因素。VEGF 可以反映患者体内的新生血管的生长状态,IL-17 为患者体内具有代表性的重要炎症细胞因子,其水平可反映患者体内炎症反应的程度^[20-22]。

本研究结果显示,观察 1 组、观察 2 组患者 IL-17、VEGF 的阳性表达率、表达水平均显著高于对照组患者,且观察 1 组患者高于观察 2 组患者($P<0.05$)。表明慢性鼻-鼻窦炎患者中伴发鼻息肉时,IL-17、VEGF 表达有明显的上调,IL-17、VEGF 可能参与了鼻息肉组织的发病过程。对其原因进行分析,可能是因为 IL-17 作为炎症因子,可诱导机体产生大量的促炎症细胞因子,如 IL-1 β 、IL-6、IL-8、环氧合酶-2(COX-2)、细胞黏附因子(CAM)等,增加这些炎症因子的活性,并参与到鼻息肉组织的结构重塑中,从而介导了鼻息肉组织的增生过程^[23-25]。VEGF 在体内的水平升高时可与血管内皮细胞中的 FLT、FLK/KDR 受体结合,增加了内皮细胞的增生能力,使得血管内皮细胞不断的增殖、分裂,从而诱导加速病理性新生血管的形成^[26,27]。在鼻息肉组织的发生发展过程中,VEGF 通过增加鼻粘膜血管的通透性,使患者鼻粘膜血浆渗出量增加,加重患者鼻

黏膜的水肿症状,加速患者新生血管的形成,从而影响鼻息肉的发生发展过程^[28,29]。观察 1 组患者、观察 2 组患者中,IL-17 与 VEGF 的表达呈正相关性,其原因可能是鼻息肉中 IL-17 的高表达导致炎症细胞因子的激活和上调,作用于患者鼻黏膜引起血管内皮细胞生长因子的高表达,从而使得两者的表达呈现明显的正相关性^[30]。

综上所述,在慢性鼻-鼻窦炎患者鼻息肉组织 IL-17、VEGF 呈高表达,且 IL-17 与 VEGF 表达水平呈明显的正相关性,表明 IL-17、VEGF 可能共同参与鼻息肉的发生与发展过程。这为鼻息肉发病机制的研究以及鼻息肉的临床诊治提供了一定的理论依据。

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