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经肺炎衣原体感染的 SD 大鼠的病理学特征变化分析研究 *

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摘要 目的:探讨与分析大鼠肺炎衣原体感染后的病理学特征变化。**方法:**研究时间为 2019 年 5 月到 2020 年 2 月。将 30 只斯泼累格·多雷(Sprague Dawley, SD)大鼠随机分为 2 组 - 实验组与对照组, 每组各 15 只大鼠。实验组大鼠从鼻腔吸入 40 μ L 含 1×10^3 感染颗粒的肺炎衣原体, 对照组吸入等剂量的无菌磷酸液缓冲液。观察与检测大鼠一般行为、血液学指标与病理学变化情况。**结果:**实验组肺实变面积达 25 %~50 %, 细支气管和小血管周围出现小灶性淋巴细胞及单个核细胞聚集, 肺泡腔有大量炎性渗出, 肺泡壁伴随有充血, 支气管周围见大量嗜中性粒细胞浸润。小鼠一般行为表现为活力下降, 毛发皱乱, 进食和饮水减少, 进食明显减少。接种后 3 d, 实验组的白细胞总数、中性粒细胞比例高于对照组, 淋巴细胞比例低于对照组($P < 0.05$); 实验组的血清白细胞介素-6(IL-6)、肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)浓度都显著高于对照组($P < 0.05$); 实验组的肺炎衣原体 IgG 抗体相对表达水平显著高于对照组($P < 0.05$); 实验组的血清血管内皮生长因子(Vascular endothelial growth factor, VEGF)、D-二聚体(D-dimer, D-D)表达水平都显著高于对照组($P < 0.05$)。**结论:**大鼠肺炎衣原体感染后伴随有肺组织病理损伤, 也可诱发 VEGF 与 D-D 的表达, 促进肺组织炎症细胞浸润, 可导致大鼠白细胞总数、中性粒细胞比例增加, 促进炎症因子的释放。

关键词:大鼠; 肺炎衣原体; 肺组织病理; 炎症细胞; 中性粒细胞

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Study on Pathological Features of SD Rats Infected by Chlamydia Pneumoniae*

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ABSTRACT Objective: To explore and analyze the pathological characteristics of rats after Chlamydia pneumoniae infection. **Methods:** The study period were from May 2019 to February 2020. 30 Sprague Dawley (SD) rats were randomly divided into experimental group (n=15) and control group (n=15). The rats in the experimental group were inhaled 40 μ L Chlamydia pneumoniae containing 1×10^3 infectious units per mL from the nasal cavity, and the control group were inhaled equal dose of sterile phosphate buffer solution. The general behavior, hematological parameters and pathological changes of the rats were observed and detected. **Results:** In the experimental group, the lung consolidation area WERE reached 25 % ~50 %, and there were small focal lymphocytes and mononuclear cells agglomerated around the bronchioles and small blood vessels, large amount of inflammatory exudation in the alveolar cavity, and congestion accompanied by alveolar walls. The general behavior of the mice manifested themselves as a decline in vitality, hair crumpled, eating and drinking reduced, and eating significantly reduced. 3 days after inoculation, the total number of white blood cells and the proportion of neutrophils in the experimental group were higher than those in the control group, and the proportion of lymphocytes were lower than that in the control group ($P < 0.05$). The concentrations of IL-6, TNF- α were significantly higher than those in the control group ($P < 0.05$), the relative expression levels of IgG antibodies to Chlamydia pneumoniae in the experimental group were significantly higher than those in the control group ($P < 0.05$). The serum VEGF, D-D expression levels in the experimental group were significantly higher than those in the control group ($P < 0.05$). **Conclusion:** After chlamydia pneumoniae infection, the rats are accompanied by pathological damage to the lung tissue and are promoted infiltration of inflammatory cells in the lung tissue, which can lead to an increase in the total number of white blood cells and the proportion of neutrophils in the rats so as to induce the expression of VEGF and D-D and promote the release of inflammatory factors.

Key words: Rats; Chlamydia pneumoniae; Lung histopathology; Inflammatory cells; Neutrophils

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前言

衣原体(Chlamydia)是一类革兰氏染色阴性、专性细胞内寄

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生的原核细胞型微生物,可感染人、畜、家禽等属于人畜共患病类病原菌^[1,2]。衣原体仅能在真核细胞内进行增殖,可引起非典型肺炎,还可引起社区获得性肺炎、中耳炎、咽炎、支气管炎、鼻窦炎的发病^[3,4]。已有研究显示肺炎衣原体(*Chlamydia pneumoniae*, Cpn)不仅只感染黏膜表面,也与反应性关节炎、多重硬化症、动脉粥样硬化、心血管疾病等多种疾病有关,严重影响患者的身心健康^[5,6]。并且多数肺炎衣原体感染者早期无临床症状或者症状不明显,因此未能及时采取相应的治疗措施,致使肺炎衣原体在体内的持续存在,造成人体多系统的慢性病理损害^[7,8]。目前,尚无有效的疫苗用于肺炎衣原体感染的预防,其具体的作用机制也不十分明确,其毒力物质也不清楚^[9,10]。VEGF是血管新生重要的正调控因子之一,在肺炎的发生机制中具有重要的调节作用。多种疾病如心脑血管疾病、严重感染等都可引起D-二聚体(D-dimer, D-D)升高^[11,12]。对肺炎衣原体感染宿主的病理学机制的研究对指导治疗肺炎衣原体疾病有重要价值^[13,14]。本文建立了大鼠肺炎衣原体感染模型,探讨了大鼠肺炎衣原体感染后的病理学特征变化,并分析了炎症细胞因子变化情况,旨在进一步探索肺炎衣原体的致病性及其可能的致病机制。现总结报道如下。

1 材料与方法

1.1 研究材料

研究时间:2019年5月到2020年2月。

实验菌种:肺炎衣原体大鼠肺炎毒株-CWL-029由本实验室保存。

实验动物:30只SD大鼠、清洁级、6~8周龄、体重 230 ± 20 g,由实验动物中心提供,所有大鼠饲料、饮用水、垫料均为清洁级,按实验动物中心操作规程进行,遵守动物福利与伦理要求。主要试剂:辣根过氧化物酶(Horseradish peroxidase, HRP)标记羊抗鼠二抗购自上海生工公司,酶联免疫检测试剂盒购自武汉三鹰公司,鼠抗衣原体-单克隆抗体购于美国生物应用公司。

1.2 动物分组与处理

1.2.1 肺炎衣原体的繁殖 CWL-029株在喉癌细胞(HEp-2细胞)培养基中繁殖,培养基组为含有10%胎牛血清的1640培养基(无双抗)。对细胞培养生长的病原体已进行离心纯化,再悬浮于二磷酸蔗糖无菌缓冲液中,制成浓度为 1.12×10^8 感染颗粒/mL。

1.2.2 大鼠接种 将30只SD大鼠随机分为两组-实验组与对照组,每组各15只大鼠。将大鼠置于麻醉机中(麻醉药物为异氟烷),实验组大鼠从鼻腔吸入 $40\mu\text{L}$ 含 1×10^8 感染颗粒的肺炎衣原体,对照组吸入等剂量的无菌磷酸液缓冲液,待大鼠呼吸平稳后将大鼠从箱中取出平放。

1.3 观察指标

(1)实验期间记录与观察大鼠的常规行为,包括对刺激的反应、活动、进食、外观等。(2)至预定实验结束时取摘取大鼠眼球血,分为两管,其中一管抗凝后进行白细胞计数与分类;另外一管静置于 37°C 10 min后,2000 rpm离心10 min,采用酶联免疫法检测血清IL-6、TNF- α 、VEGF、D-D水平。(3)打开大鼠胸腔,分离并取下肺组织,固定24 h后进行石蜡包埋,切片后进行苏木素-伊红(HE)染色,观察肺组织病理改变。(4)提取肺组织蛋白,测定蛋白质浓度,使用裂解缓冲液将所有蛋白质样品调整至均匀浓度,跑胶转膜后常温封闭2 h,孵育肺炎衣原体抗体 4°C 过夜,洗涤3次后,然后孵育二抗常温2 h,采用化学发光法检测肺炎衣原体抗体表达水平。

1.4 统计方法

选择SPSS 23.00软件对本研究所有数据进行分析,所有实验结果数据都以 $(\bar{x}\pm s)$ 表示,比较用t检验, $P<0.05$ 表示差异有显著性。

2 结果

2.1 两组大鼠一般情况及组织病理学特征对比

对照组:(1)一般情况:均无明显异常表现;(2)病理特征:肺部无明显异常改变,支气管旁偶见淋巴细胞浸润,毛细血管周围少量嗜中性粒细胞浸润。

实验组:(1)接种后3 d内可见动物活力下降,毛发皱乱,进食和饮水减少,进食明显减少;(2)肺实变面积达25%~50%,肺泡腔有大量炎性渗出,肺泡壁充血,伴有较多嗜中性粒细胞浸润,细支气管和小血管周围出现小灶性淋巴细胞及单个核细胞聚集,支气管周围见大量嗜中性粒细胞浸润。

2.2 白细胞总数及分类对比

接种后3 d,实验组大鼠的白细胞总数、中性粒细胞比例均显著高于对照组,而淋巴细胞比例低于对照组($P<0.05$),见表1。

表1 两组白细胞总数及分类对比 $(\bar{x}\pm s)$

Table 1 Comparison of total number and classification of white blood cells between two groups $(\bar{x}\pm s)$

Groups	n	Total white blood cells ($\times 10^9/\text{L}$)	Neutrophil ratio (%)	Proportion of lymphocytes (%)
Experimental group	15	$6.52\pm 0.18^*$	$33.09\pm 2.41^*$	$2.00\pm 0.14^*$
Control group	15	5.42 ± 0.13	27.49 ± 3.19	1.10 ± 0.08

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

2.3 细胞因子表达对比

接种后3 d,实验组大鼠血清中IL-6、TNF- α 浓度均显著高于对照组($P<0.05$),见表2。

2.4 VEGF、D-D表达水平对比

接种后3 d,实验组大鼠血清中VEGF、D-D表达水平均显

著高于对照组($P<0.05$),见表3。

2.5 肺炎衣原体IgG抗体表达水平对比

接种后3 d,实验组的肺炎衣原体IgG抗体相对表达水平显著高于对照组($P<0.05$),见表4。

表 2 两组炎症因子含量对比(pg/mL, $\bar{x} \pm s$)

Table 2 Comparison of content of inflammatory factors between two groups (pg/mL, $\bar{x} \pm s$)

Groups	n	IL-6	TNF- α
Experimental group	15	22.15 $\pm$ 1.44*	49.78 $\pm$ 3.14*
Control group	15	15.90 $\pm$ 2.24	36.09 $\pm$ 2.81

表 3 两组 VEGF、D-D 含量对比($\bar{x} \pm s$)

Table 3 Comparison of VEGF and D-D content between two groups ($\bar{x} \pm s$)

Groups	n	VEGF (pg/mL)	D-D (μ g/L)
Experimental group	15	341.73 $\pm$ 19.32*	96.30 $\pm$ 2.13*
Control group	15	141.80 $\pm$ 18.66	79.24 $\pm$ 1.44

表 4 两组肺炎衣原体 IgG 抗体表达水平对比($\bar{x} \pm s$)

Table 4 Comparison of IgG antibody expression levels of Chlamydia pneumoniae between two groups ($\bar{x} \pm s$)

Groups	n	Chlamydia pneumoniae IgG antibody
Experimental group	15	6.11 $\pm$ 0.14*
Control group	15	1.83 $\pm$ 0.22

3 讨论

衣原体直径约为 0.4 μ m,能通过细菌滤器,且具有独特的双相发育周期。肺炎衣原体的基因组大小在 1.06 Mb~1.43 Mb 之间,脱氧核糖核酸呈双链封闭环状结构^[15,16]。肺炎衣原体为衣原体的主要类型,与兽类嗜衣原体、豚鼠嗜衣原体、猫嗜衣原体等共同组成嗜衣原体属。肺炎衣原体除了引起机体发生急、慢性呼吸系统疾病外,也可诱发心血管疾病的发生^[17,18]。本研究显示接种后 3 d,实验组的白细胞总数、中性粒细胞比例高于对照组,淋巴细胞比例低于对照组;实验组的血清 IL-6、TNF- α 浓度都显著高于对照组,与王华丽^[19]的研究类似,研究肺炎嗜衣原体蛋白酶样活性因子(CPAF)的 181~400 aa 基因(CPAFm)的重组蛋白在 BALB/c 小鼠体内引起的肺部炎症改变及对炎症细胞因子 TNF- α 和 IL-6 的水平的影响,结果显示,实验组 BALB/c 小鼠的肺组织出现中性粒细胞,淋巴细胞等炎症细胞浸润,对照组与正常组 BALB/c 小鼠肺组织未见明显病理改变。鼻内滴入重组蛋白实验组 BALB/c 小鼠 BALF 中白细胞总数明显高于对照组,鼻内滴入和尾静脉注射重组蛋白实验组 BALF 中炎症因子 IL-6、TNF- α 的水平明显高于对照组。表明肺炎衣原体感染后可导致大鼠白细胞总数、中性粒细胞比例增加,也可促进炎症因子的释放。从机制上分析,IL-6 和 TNF- α 是重要的促炎介质,能够反映机体炎症状态。IL-6 主要与炎症反应、组织损伤关系,也具有一定的细胞免疫、体液免疫和促凝血作用^[20]。两者都可通过分泌或旁分泌刺激其他细胞因子产生,可作用于血管内皮细胞使之表达黏附因子,诱发抗原提呈细胞表面免疫分子的表达,刺激内皮细胞、中性粒细胞、单核巨噬细胞等进一步释放脂质介质,激活补体、吞噬细胞、杀伤细胞的活性,使炎症进一步恶化^[21,22]。肺炎衣原体感染可刺激刺激血管内皮细胞分泌 IL-6 和 TNF- α ,引起炎症反应,从而直接损害肺泡表面活性物质,造成肺损伤^[23]。本研究也显示接种后 3 d,实验组的血清 VEGF、D-D 表达水平都显著高于对照组,陈晓

宇^[24] 的利用肺炎衣原体体外感染人脐静脉内皮细胞系 EA.hy926 细胞模型,结果显示肺炎衣原体感染组和 VEGF 处理组的细胞膜 VE 钙粘素表达水平与正常对照组明显减少。从机制上分析,VEGF 能作用于内皮细胞表面的受体,增强血管的通透性,促使形成新生血管^[25]。D-D 是反映抗体凝血与纤溶状态的指标,经纤溶酶水解所产生的一种特异性降解产物,心脑血管疾病、严重感染等都可引起 D-D 升高^[26]。

肺炎衣原体具有感染能力,通过吞饮作用进入胞内后形成包-涵体,再次感染新的易感细胞^[27,28]。本研究显示接种后 3 d,实验组的肺炎衣原体抗体相对表达水平显著高于对照组;实验组肺实变面积达 25%~50%,细支气管和小血管周围出现小灶性淋巴细胞及单个核细胞聚集,肺泡腔渗出大量炎症因子,支气管周围浸润大量嗜中性粒细胞,目前还没有相关的研究。从机制上分析,肺炎衣原体感染可损伤和破坏局部组织,引起内皮细胞和组织损伤,促进嗜中性粒细胞和淋巴细胞混合浸润,造成组织溶解和破坏^[29,30]。当前研究显示肺炎衣原体感染可导致肺泡隔增宽,促进纤维母细胞增生,呼吸道局部感染比血行感染更为严重,导致机体其他器官发生继发性损伤^[31,32]。另外,本研究也存在一定的不足,未对两组大鼠接种后不同时间点病理学特征变化的相关指标进行分析,且大鼠样本数量较少,将在后续研究中进行深入探讨。

总之,大鼠肺炎衣原体感染后伴随有肺组织病理损伤,促进肺组织炎症细胞浸润,可导致大鼠白细胞总数、中性粒细胞比例增加,也可诱发 VEGF 与 D-D 的表达,促进炎症因子的释放。

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