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烟草及$PM_{2.5}$影响肺癌免疫治疗的研究进展

郑彩华，黄媚，冼桂兰，朱志国，周秋丽，朱淦，朱卓豪，
陈智，戴金玄，庞学鑫，李碧慧*

（桂林医科大学第二附属医院肿瘤内科，广西 桂林 541199）

【摘要】肺癌作为全球癌症相关死亡的首要原因，其发生与多种环境因素密切相关。吸烟、空气污染等环境危险因素会对肺部细胞造成不同程度的损伤，并引发炎症反应。在这一过程中，机体的免疫系统会被激活，试图清除受损细胞和潜在的癌变细胞。然而，环境因素的持续作用可能会导致免疫应答异常。一方面，烟草中的有害物质可直接损伤免疫细胞，抑制免疫细胞的增殖与功能，从而削弱免疫系统对肺癌细胞的识别和清除能力。另一方面，空气污染中的细颗粒物（$PM_{2.5}$）可进入肺组织，激活炎症信号通路，促使炎症因子大量释放，诱导免疫抑制微环境的形成，使肺癌细胞得以逃避免疫监视。这些环境因素通过影响肺癌的免疫应答，在肺癌的发生发展中扮演着重要角色。本文综述烟草及$PM_{2.5}$与肺癌及免疫治疗的关系，旨在为肺癌的预防和治疗提供新的思路。

【关键词】烟草；细颗粒物；肺癌；免疫治疗

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Impact of tobacco and PM2.5 on lung cancer immunotherapy

Zheng Caihua, Huang Mei, Xian Guilan, Zhu Zhiguo, Zhou Qiuli, Zhu Gan, Zhu Zhuohao, Chen Zhi, Dai Jinxuan, Pang Xuexin, Li Bihui*

(Department of Oncology, The Second Affiliated Hospital of Guilin Medical University, Guilin 541199, Guangxi, China)

【**Abstract**】Lung cancer remains the leading cause of cancer-related mortality worldwide, with its etiology closely associated with multiple environmental risk factors. Environmental risk factors, such as smoking and air pollution, induce varying degrees of damage to pulmonary cells and trigger inflammatory responses. During this process, the body's immune system is activated to eliminate damaged cells and potential malignant cells. However, prolonged exposure to these environmental factors may disrupt normal immune function. On the one hand, harmful components in tobacco directly damage immune cell viability and functionality, thus diminishing the immune system's ability to recognize and eliminate lung cancer cells. On the other hand, fine particulate matter (PM2.5) in polluted air penetrates pulmonary tissues, activates inflammatory signaling pathways, promotes excessive release of pro-inflammatory cytokines, fostering an immunosuppressive microenvironment that enables cancer cells to evade immune surveillance. These environmental factors play a critical role in lung cancer initiation and progression by modulating immune responses. This review focuses on the interplay between

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通信作者：李碧慧（1980-），女，广西贵港人，主任医师，教授，主要从事肺癌免疫治疗研究，E-mail：99743925@qq.com

tobacco/PM2.5 exposure, lung cancer, and immunotherapy, aiming to propose novel strategies for lung cancer prevention and therapeutic innovation.

【**Keywords**】Tobacco; PM2.5; Lung cancer; Immunotherapy

随着中国人口老龄化的不断加剧，肺癌的发病率呈现上升趋势，2022年世界卫生组织国际癌症研究机构数据表明，肺癌在中国癌症发病谱和死因谱中均位列第一，其发病例数占中国癌症发病总数的22.0%，死亡例数占癌症死亡总数的28.5%。从全球范围看，中国肺癌发病和死亡病例分别占全球总数的42.8%和40.3%，疾病负担极为突出[1]。由于肺癌早期临床表现隐匿且病程进展迅速，多数患者在确诊时已处于晚期阶段，导致5年生存率低于20%[2]。因此，如何预防肺癌发生，延缓肺癌进展是全球亟待解决的难题。深入解析肺癌致病机制发现，其发生发展与环境暴露因素（包括烟草、大气细颗粒物等）密切相关[3-5]。近年来，免疫治疗领域进入新发展阶段，程序性死亡受体-1（Programmed Cell Death Protein 1，PD-1）/程序性死亡配体-1（Programmed Cell Death Ligand 1，PD-L1）抑制剂作为免疫检查点抑制剂（Immune Checkpoint Inhibitors，ICIs）的典型代表，已逐步应用于临床实践，不仅显著延长了晚期非小细胞肺癌（Non-Small Cell Lung Cancer，NSCLC）患者的总生存期，更在围手术期新辅助/辅助治疗中展现出潜在治愈可能[6-7]。本文将论述烟草、大气细颗粒物（Particulate Matter 2.5，$PM_{2.5}$）如何影响肺癌的发生发展及其影响免疫应答过程的机制，以期对肺癌的预防和治疗提供新的思路。

1 环境因素与肺癌的关系

肺癌发生发展与多种环境致癌物的暴露密切相关。流行病学研究证实，环境暴露贡献度约占肺癌总归因风险的70%～85%，其致病过程涉及多阶段、多通路的复杂生物学机制[8]。

1.1 传统环境致癌物的致病作用

研究表明，烟草是环境导致肺癌的主要原因[9]。大规模队列研究显示，每日吸烟量≥20支的个体，肺鳞癌发病风险比高达28.6（95%*CI*：22.4～35.8）[10]。对于吸烟人群而言，烟草中含有多种致癌物质如多环芳烃及亚硝胺类化合物通过代谢活化形成DNA加合物，诱导支气管上皮细胞恶性转化[11]。

1.2 新兴环境污染物的潜在风险

气候变化加剧了大气污染物的致癌效应，野火释放的$PM_{2.5}$可穿透肺泡气血屏障，诱发端粒酶逆转录酶异常表达[12]。体外实验证实，$PM_{2.5}$通过ROS-Akt-DNMT3B通路介导的启动子高甲基化诱导*P53*的表观遗传沉默，提示表观遗传调控在环境致癌中的关键作用[13]。此外，电子烟气溶胶中含有的甲醛缩甘油被证实具有致突变性，动物模型显示其可导致肺泡Ⅱ型上皮细胞Ki-67增殖指数升高至（23.5±3.2）%[14]。

由上不难得知，吸烟及$PM_{2.5}$与肺癌的发生发展密切相关，深入了解肺癌的致病机制，从环境方面入手对肺癌预防具有重要意义。

2 免疫治疗在肺癌中的地位

肿瘤细胞常通过表达免疫检查点分子，像PD-L1、细胞毒T淋巴细胞相关抗原4（Cytotoxic T Lymphocyte-Associated Antigen-4，CTLA-4），这些分子能与免疫细胞（如T细胞）结合，抑制免疫细胞的活性，引起免疫逃逸。因此抑制PD-L1与免疫细胞的结合，可显著提高抗肿瘤疗效，近年来以PD-1/PD-L1单抗为代表的免疫检查点抑制剂在肺癌治疗中取得了显著进展。

2.1 晚期NSCLC免疫治疗现状

NSCLC在肺癌病例中占比达85%，其中约2/3患者初诊时已处于晚期阶段[15]。对于驱动基因阴性的晚期NSCLC，PD-1/PD-L1抑制剂已成为一线标准治疗方案。对于PD-L1高表达（TPS≥50%）的患者，单药免疫治疗（如帕博利珠单抗、阿替利珠单抗）与传统化疗相比，可显著提高客观缓解率（Objective Response Rate，ORR）、无进展生存期（Progression Free Survival，PFS）和总生存期（Overall Survival，OS），同时减少了3级以上不良反应发生率[16]。Keynote-042和Impower110研究证实了单药治疗的长期生存获益，且中国人群数据与全球结果一致[16-17]。此外，纳武利尤单抗、替雷利珠单抗等药物也在二线治疗中获批单药适应证。

联合治疗模式进一步扩大了免疫治疗的适用性。免疫+化疗方案（如帕博利珠单抗、卡瑞利珠单抗等联合化疗）不受PD-L1表达限制，显著改善患者生存，已被广泛纳入指南[18]。双免疫联合（如纳武利尤单抗+伊匹木单抗）在CheckMate 227研究中显示5年生存率提升，但需精准筛选获益人群（如*STK11*/*KEAP1*突变患者）[19]。对于驱动基因阳性NSCLC（如*EGFR*突变），靶向治疗耐药后免疫

单药疗效有限，但免疫联合化疗及抗血管生成治疗（如阿替利珠单抗+贝伐珠单抗+化疗的ABCP方案）可延长生存[20]。

2.2 广泛期小细胞肺癌免疫治疗现状

小细胞肺癌（Small-Cell Lung Cancer，SCLC）可分为局限期SCLC（Limited-Stage Small-Cell Lung Cancer，LS-SCLC）和广泛期SCLC（Extensive-Stage Small-Cell Lung Cancer，ES-SCLC），约80%的患者在首次确诊时已处于ES-SCLC[21]。ES-SCLC预后极其不佳，5年生存率仅有5%～10%[21]。PD-1/PD-L1单抗在ES-SCLC中的应用，突破了该领域几十年来一线治疗的瓶颈，让患者的预后获得一定程度的改善。目前，阿替利珠单抗、度伐利尤单抗等PD-L1单抗联合依托泊苷+铂类化疗已成为一线标准方案[22]。IMpower133研究显示，阿替利珠单抗联合化疗显著延长中位OS和PFS[23]。CASPIAN和CAPSTONE-1研究则进一步验证了度伐利尤单抗、阿得贝利单抗的疗效[24-25]。值得注意的是，尽管Keynote-604中帕博利珠单抗联合化疗未显著改善OS[26]，但斯鲁利单抗、特瑞普利单抗等PD-1单抗在RATIONALE-312、EXTENTORCH等研究中展现出生存获益[22,27]。

免疫联合抗血管生成药物的探索为ES-SCLC带来新突破。ETER701研究显示，贝莫苏拜单抗+安罗替尼+化疗的联合方案使ORR达81.3%，中位OS提升至19.2个月（对照组11.89个月），尽管3～4级不良反应增加，但仍可耐受[28]。然而，双免疫治疗或后续免疫维持治疗的疗效尚不明确，需更多临床研究验证。

免疫治疗在肺癌治疗中的作用不可忽视，仍有约20%～30%的患者对免疫治疗无初始反应，我们仍需寻找更多的潜在影响免疫治疗疗效的机制，通过对机制层面的了解，针对性地阻断不利因素，可进一步提高免疫治疗疗效，从而改善患者的预后。

3 环境因素影响免疫应答的机制

3.1 引起炎症反应

环境因素在肺癌免疫中扮演着关键角色，其通过引发炎症反应对肺癌免疫产生深远影响。研究表明，烟草烟雾中的尼古丁、焦油等有害物质进入肺部后，会直接损伤肺上皮细胞，导致细胞损伤和死亡。受损的细胞会释放大量的损伤相关分子模式（Damage-Associated Molecular Patterns，DAMPs），如高迁移率族蛋白B1等；这些DAMPs作为危险信号，可激活肺部的固有免疫细胞，使其释放炎症因子，如TNF-α、IL-1β等；这些炎症因子会进一步招募更多的免疫细胞到炎症部位，形成炎症级联反应[29]。$PM_{2.5}$也能引发类似的炎症反应。$PM_{2.5}$进入肺部后，可被巨噬细胞吞噬，吞噬过程中会释放大量的活性氧（Reactive Oxygen Species，ROS）和炎症因子[30]。ROS具有强氧化性，能损伤细胞DNA和细胞膜，导致细胞功能障碍和死亡，进而加重炎症反应[31]。炎症因子则能促进炎症细胞的浸润和活化，使炎症反应持续加剧[31]。

长期的炎症反应会形成慢性炎症微环境。在这种环境中，炎症因子持续高水平表达，会抑制免疫细胞的活化和功能，导致免疫细胞无法有效识别和清除肺癌细胞[32]。同时，慢性炎症还会促进癌症相关成纤维细胞（Cancer-Associated Fibroblasts，CAFs）的活化，CAFs会分泌大量的细胞外基成分和生长因子，为肺癌细胞的生长和转移提供有利条件[33]。

3.2 直接损伤免疫细胞

环境因素对免疫细胞功能的影响是导致免疫应答异常的关键因素。免疫细胞作为机体免疫系统的重要组成部分，其功能正常与否直接关系到机体对肺癌细胞的识别和清除能力。吸烟对免疫细胞功能的影响尤为显著。香烟中的有害物质能直接损伤免疫细胞，如抑制淋巴细胞的增殖和分化，降低吞噬细胞的吞噬能力[34]。淋巴细胞是机体适应性免疫的核心细胞，其增殖和分化受阻会导致机体无法产生足够的抗体和效应T细胞来对抗肺癌细胞。吞噬细胞作为固有免疫的重要组成部分，其吞噬能力下降会使机体对肺癌细胞的早期识别和清除能力减弱。空气污染中的$PM_{2.5}$等污染物也会影响免疫细胞的功能。$PM_{2.5}$能抑制树突状细胞（Dendritic Cells，DCs）的成熟，使其抗原呈递能力下降，从而影响T细胞的激活和抗肿瘤免疫应答[35]。DCs是连接固有免疫和适应性免疫的桥梁，其功能受损会导致机体对肺癌细胞的免疫应答减弱。

吸烟、$PM_{2.5}$通过多种途径影响免疫细胞的功能，导致机体对肺癌细胞的识别和清除能力下降，为肺癌的发生和发展创造了有利条件。因此，改善环境因素，增强免疫细胞的功能，是预防和治疗肺癌的重要方向。

3.3 干扰细胞信号通路

细胞信号通路是细胞间信息传递的重要途径，在环境因素对肺癌免疫的影响中起着关键作用。环境因素可通过干扰细胞信号通路，导致免疫细胞功能异常，从而影响肺癌免疫。PD-1/PD-L1信号通路是肿瘤免疫中重要的抑制性信号通路。环

境因素如吸烟、空气污染等能诱导肺癌细胞高表达PD-L1[36]。PD-L1与T细胞表面的PD-1结合后，会抑制T细胞的活化和增殖，降低其抗肿瘤活性。JAK/STAT信号通路在炎症和免疫调节中起着重要作用。环境因素可激活JAK/STAT信号通路，导致炎症因子大量释放，诱导免疫抑制微环境的形成。在空气污染中，$PM_{2.5}$能激活JAK/STAT信号通路，使巨噬细胞释放大量的炎症因子，如TNF-α、IL-6等，这些炎症因子会进一步抑制T细胞的活化和功能[37]。NF-κB信号通路是细胞内调控炎症反应的核心通路之一，广泛参与炎症因子（如细胞因子、趋化因子等）的生成和释放[38]。吸烟和空气污染中的有害物质能激活NF-κB信号通路，导致炎症因子大量释放，形成慢性炎症微环境，抑制免疫细胞的功能[38]。Wnt/β-catenin信号通路在肿瘤的发生和发展中起着重要作用。有研究发现，烟草中的有毒物质能激活Wnt/β-catenin信号通路，β-catenin的激活诱导ATF3表达，从而降低CCL4并导致DCs的募集减少；没有DCs，淋巴细胞不会浸润到肿瘤中[39]。同时，肿瘤中的β-catenin还可以通过与肿瘤相关巨噬细胞相互作用、影响调节性T细胞并改变肿瘤微环境中的代谢来创造免疫抑制环境[39]。

细胞信号通路是环境因素影响肺癌免疫的重要机制，深入研究细胞信号通路的变化及其对肺癌免疫的影响，对于开发新的肺癌治疗药物和策略具有重要意义。

4 环境暴露与免疫治疗疗效的临床关联

4.1 烟草对于肺癌免疫治疗的影响

烟草暴露对肺癌免疫治疗疗效的影响在现有研究中存在一定争议。部分研究指出吸烟者从免疫治疗中获益更多，吸烟史与更高的PD-L1表达和更好的免疫治疗反应相关[40-41]。尽管吸烟是肺癌的主要风险因素，但部分临床数据提示吸烟患者可能从单药免疫治疗中获益更多，而非吸烟者可能需要联合化疗和免疫治疗以达到类似疗效[41]。然而部分研究通过Meta分析发现，吸烟状态并不显著影响免疫治疗的ORR或生存获益（PFS/OS），且交互作用无统计学意义（*HR*=0.91，95%*CI*：0.74～1.11，*P*=0.14）[42]。

4.2 $PM_{2.5}$对于肺癌免疫治疗的影响

研究表明，$PM_{2.5}$可能影响NSCLC患者接受PD-1/PD-L1抑制剂免疫治疗的效果。一项针对361名NSCLC患者的研究发现，空气污染暴露与免疫治疗后的PFS存在负相关关系，尤其是暴露于高浓度污染物的患者PFS显著缩短[43]。

5 总结与展望

大量研究明确指出，环境因素对肺癌影响深远。空气污染中的$PM_{2.5}$等污染物，会激活炎症信号通路，形成免疫抑制微环境，抑制T细胞功能[35]。了解这些发现，有助于制定更有效的肺癌预防与治疗方案，对提高患者生存率意义重大。未来在环境因素与肺癌免疫治疗领域，研究方向丰富且挑战并存。一方面，需深入探究不同环境因素对肺癌的精确影响机制，如特定污染物如何作用于特定免疫细胞信号通路。另一方面，要加强环境因素与遗传背景相互作用对肺癌影响的研究，揭示个体差异背后的遗传基础。还应关注环境因素对新型肺癌免疫疗法，如肿瘤疫苗、细胞治疗等的影响，探索更有效的联合治疗方案。开发精准的环境暴露评估技术与个体化的肺癌免疫干预策略，也是重要的研究方向，以实现肺癌的精准预防与治疗，提高患者生活质量。

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（上接第72页）

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