·综　述·

肺癌合并肺结核的机制研究及诊治进展

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[摘　要]　肺癌及肺结核是呼吸系统的常见病,两者在发病机制上存在许多相关性。肺结核导致的瘢痕、慢性炎症、免疫功能异常可增加肺癌风险。肺癌的肿瘤微环境处于免疫抑制状态,利于结核分枝杆菌免疫逃逸。肺癌的免疫治疗也可影响结核发展。如何早期识别肺癌合并结核、选择合适的治疗方法是目前的诊疗难点。了解肺癌合并肺结核的发病机制有助于寻找新的诊治方法。文章重点就肺癌合并结核的发病机制、诊疗策略进行综述,以对其进行早期诊断、精准治疗。

[关键词]　肺癌;肺结核;发病机制;诊治

[中图分类号]　R734.2　　[文献标志码]　A　　[文章编号]　1007-4368(2022)05-746-06

doi:10.7655/NYDXBNS20220524

Advances in the pathogenesis, diagnosis and treatment of lung cancer with pulmonary tuberculosis

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[**Abstract**]　Lungcancer and pulmonary tuberculosis are two common diseases in respiratory system, which are correlated in pathogenesis. Scars, chronic inflammation and abnormal immunity in lung induced by tuberculosis increase the risk of lung cancer. The immunosuppressive status in lung cancer tumor microenvironment enhances immune evasion of *Mycobacterium tuberculosis*. Additionally, immunotherapy in lung cancer in fluences the development of tuberculous. Therefore, the main challenge in clinic practice is early diagnosis and therapeutics for lung cancer with pulmonary tuberculosis. Understanding the pathogenesis of lung cancer with pulmonary tuberculosis is helpful to develop new diagnostic and therapeutical methods. This article summarizes the pathogenesis, diagnosis and treatment of lung cancer with pulmonary tuberculosis for itsearly diagnosis and precision therapy.

[**Key words**]　lung cancer; tuberculosis; pathogenesis; diagnosis and treatment

[J Nanjing Med Univ, 2022, 42(05): 746-750, 758]

肺癌是威胁人类健康的重大疾病,尽管近年来其发病率及死亡率有下降趋势,但仍居恶性肿瘤前列,57%的肺癌患者确诊时已发生转移,其5年生存率仅为6%[1]。由结核分枝杆菌(*Mycobacterium tuberculosis*,MTB)导致的结核病是全球第十大死因,我国是结核高负担国家,患者数量占全球的8.4%,2019年我国约有83.3万新发病例和3.1万死亡病例[2]。肺结核可增加肺癌风险,而肺癌可导致患者体内休眠期的MTB重新激活[3-4]。肺癌的发生与慢性炎症反应、免疫失衡相关;肺结核可导致肺内瘢痕组织增生、慢性炎症及免疫功能异常,两者发病机制密切相关。肺癌合并肺结核给临床诊疗工作

[基金项目]　国家科技重大专项(2018ZX10722301-002);国家自然科学基金(81870054,81800090,82002438)

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带来诸多挑战,如何对其进行早期识别以及选择合适的治疗方法是目前的诊治难点。本文将对肺癌合并肺结核的发病机制、诊疗策略、预后评估进行综述,以期为早期诊断、精准治疗提供新思路。

1 肺癌合并肺结核发生机制的研究进展

肺结核可增加肺癌发生风险,诊断结核10年后患者的肺癌风险仍然为非结核患者的3倍,合并结核的肺癌患者死亡率也显著升高,约为未感染结核者的8倍[4]。相较于肉瘤、白血病、淋巴瘤等恶性肿瘤,肺癌患者感染结核的风险更高,且诊断时往往处于晚期[3,5]。一项全基因组关联研究进一步支持结核可导致肺癌的观点,通路分析发现结核相关基因集与亚洲非吸烟女性肺腺癌相关(P=0.016),其中FHAD1、ZFPM2、HLA-DQA1、DLG2基因的相关性最强,孟德尔随机化研究发现结核感染与肺腺癌呈正相关[6]。研究发现,小鼠肺结核病灶内肺泡细胞发生鳞状上皮化生,大部分鳞状细胞表现出高增殖活性[7],将其以皮下或腹腔注射方法转移至同基因受体小鼠体内,可观察到每组各有1只(1/5)小鼠形成肿瘤[7]。

1.1 结核瘢痕可能诱导肺癌的发生

在肺部瘢痕组织上发生的恶性肿瘤称肺瘢痕癌,瘢痕与肺癌在解剖位置上有较强的相关性,97.6%的瘢痕与肿瘤病灶位于同一肺叶[8]。肺结核经初步治疗后约1/5的患者存在肺内瘢痕,结核所致瘢痕占肺瘢痕癌的30%~57%[9]。瘢痕组织可引起淋巴管阻塞,导致致癌物质滞留[10];纤维化还可导致慢性炎症,上皮细胞损伤、DNA复制失调,利于肿瘤的发生[11]。但有学者发现,大多数肺瘢痕癌中,瘢痕在肿瘤之后出现,为肿瘤组织反复坏死、修复的结果,这与“肺瘢痕癌”的定义矛盾,且肺瘢痕癌的色素沉着、胸膜皱缩及瘢痕状外观可能是肺泡塌陷的结果[12]。

1.2 结核慢性炎症引起肺癌的发生

MTB被巨噬细胞吞噬后,可阻止溶酶体的融合与酸化,导致MTB在机体内持续增殖并分泌靶抗原,引起慢性炎症[13]。结核相关的慢性炎症可导致细胞增殖、DNA损伤、血管生成等,为肺癌的发生、发展提供有利环境。

慢性炎症为肿瘤微环境提供多种炎症介质,如肿瘤坏死因子(tumor necrosis factor,TNF)、干扰素(interferon,IFN)、白细胞介素(interleukin,IL)、转化生长因子-β(transforming growth factor-β,TGF-β)、环氧化酶2(cyclooxygenase-2,COX-2)等,促进癌症发生发展[14]。MTB感染后,巨噬细胞产生大量活性氧(reactive oxygen species,ROS)、活性氮(reactive nitrogen species,RNS)杀灭MTB。同时,细胞内抗氧化系统被激活,以减少组织损伤。但随着感染的持续,ROS、RNS不断增加,抗氧化剂无法成比例产生,引起平衡失调[13]。慢性炎症可破坏细胞外基质、损伤组织,诱导细胞增殖与组织修复。细胞增殖易导致基因突变的发生。ROS与低剂量RNS参与调节磷脂酰肌醇3-激酶/蛋白激酶B、丝裂原活化蛋白激酶等细胞增殖信号通路,促进细胞增殖[15-16]。MTB的分枝杆菌磷酸酶PtpA可进入宿主细胞核,调节与细胞增殖及迁移相关的基因表达,如MK167[17]。

ROS、RNS可引起DNA损伤、表观遗传学改变,导致基因组不稳定,原癌基因激活、抑癌基因失活[15-16]。ROS、RNS还影响DNA修复,如过氧亚硝酸盐引起DNA修复蛋白失活,使突变在细胞中不断累积[14]。正常情况下,DNA损伤细胞会激活p53分子发生凋亡,该信号通路可被NF-κB通路拮抗,p53基因突变或功能异常是原发性肺癌最常见的分子改变。结核感染时,上皮及巨噬细胞中NF-κB通路通过氧化应激、Toll样受体、TNF-α等多种途径激活,抑制p53对DNA损伤的检测和修复,导致基因突变积累并诱导肿瘤发生[7]。

MTB感染所致的慢性炎症产生的促血管生成作用利于肺癌发生发展。IL-1、IL-6、TNF-α、COX-2等炎症介质可促进血管生成[18]。斑马鱼模型发现,MTB表面海藻糖二霉菌酸酯的环丙烷化促进巨噬细胞中血管内皮生长因子(vascularendothelial-growth factor,VEGF)信号激活,诱导结核肉芽肿内血管生成增加[19]。ROS也可通过多种机制调节VEGF信号的传导,如诱导缺氧诱导因子1的表达、抑制脯氨酰羟化酶、激活VEGF相关信号通路、调节COX-2等[15]。

上皮-间充质转化(epithelial-mesenchymal transition,EMT)可引起肿瘤细胞迁移及侵袭能力增加,结核感染可能促进肿瘤细胞发生EMT。研究发现,肺腺癌细胞系A549与感染MTB的单核细胞系共培养可引起TNF-α、IL-1β、IL-6表达增加,诱导A549发生EMT并增加其侵袭性,但这些炎症细胞因子诱导EMT的具体机制仍待研究[20]。ROS、RNS也可促进肿瘤细胞增殖、侵袭,但在某些情况下表现为肿瘤抑制作用,这可能与ROS、RNS的种类、剂量、来源、时空分布等因素相关,了解不同种类、来源、时空分

布ROS、RNS的功能可能有助于理解MTB导致的氧化与抗氧化紊乱对癌症的影响[15-16]。

1.3 结核免疫功能异常促进肺癌的发生与发展

当体细胞发生突变时，免疫系统可识别、清除突变细胞，发挥免疫监视作用。突变的细胞通过多种方式逃避免疫系统的监视，不断增殖，导致肿瘤发生。MTB通过多种途径抑制机体免疫功能，避免被免疫系统识别、清除，为肺癌的发生发展创造有利条件。

结核感染为肿瘤微环境提供具有免疫抑制作用的细胞因子，如TGF-β、IL-10、前列腺素E等。MTB可分泌哺乳动物细胞入侵蛋白（mammalian cell entry，Mce）影响免疫功能，Mce2E、Mce3E可抑制巨噬细胞表达TNF、IL-6，抑制免疫功能[21]。$CD4^+$ T细胞包括Th1细胞、Th2细胞、Th17细胞、调节性T细胞（Treg），结核可能通过干扰Th1/Th2、Th17/Treg平衡促进肿瘤发生发展。Th1细胞分泌IL-2、IFN-γ、TNF-α等细胞因子，促进免疫系统发挥抗肿瘤作用，Th2细胞可抑制Th1细胞的抗肿瘤作用，Th1/Th2失衡引起肺癌发生发展[22]。结核患者体内Th1/Th2免疫失衡，其机制尚不清楚，可能与Notch信号通路相关，研究发现抑制Notch信号通路可降低结核患者外周血Th2细胞比例，逆转Th1/Th2比值[23]。Th17细胞分泌多种促炎细胞因子，如IL-17A、IL-17F、IL-22等。Th17细胞对肺癌发生的影响尚有争议，研究发现IL-17可促进血管生成与肿瘤生长、侵袭。但最新数据显示Th17细胞具有抗肿瘤作用，其可诱导肿瘤部位的T细胞募集，并激活$CD8^+$T细胞[22]。Treg细胞与Th17细胞作用相反，有免疫抑制功能。结核患者Treg细胞数量增加，MTB可通过诱导Treg细胞增加促进小鼠非小细胞肺癌（non-small cell lung cancer，NSCLC）生长[24]。此外，巨噬细胞也参与肿瘤的发生。巨噬细胞可分为M1型与M2型，M1型巨噬细胞促进炎症与免疫反应，发挥抗肿瘤作用；M2型巨噬细胞抑制炎症与免疫反应，促进血管生成，诱导肿瘤细胞的增殖、迁移、侵袭[25]。MTB可促进巨噬细胞M2型极化，但机制尚不清楚，可能与IL-1受体相关激酶、IL-4、IL-10、早期分泌性抗原靶蛋白6等相关[26]。结核可诱导M2型巨噬细胞的CD209表达增加，发挥抗炎作用，肺癌细胞利用CD209减少T细胞活化与增殖、抑制Th1细胞的功能等，逃避免疫监视[27-28]。

1.4 肺癌及其治疗促进结核的发展

肺癌可为结核的增殖、传播创造有利环境，导致潜伏期结核重新激活。Li等[29]发现，NSCLC患者肿瘤组织及胸腔积液中IL-4、IL-10、TGF-β1等Th2型及免疫抑制细胞因子的mRNA表达水平较高，利于结核免疫逃逸。

免疫治疗为晚期肺癌治疗提供新途径，程序性死亡受体-1（programmedcell death-1，PD-1）抑制剂为常见的免疫检查点抑制剂（immune checkpoint inhibitor，ICI）。PD-1与程序性死亡受体配体-1（programmed cell death ligand1，PD-L1）相互作用，在免疫反应中起“刹车”作用[30]。肿瘤细胞表面的PD-L1与PD-1相互作用，拮抗T细胞活化的双信号，抑制转录因子活化，引起T细胞活化被抑制，导致肿瘤细胞免疫逃逸[31]。MTB也可诱导PD-1/PD-L1表达，通过PD-1/PD-L1途径逃避免疫监视[32]。阻断PD-1/PD-L1可增强$CD8^+$T细胞的细胞毒性，利于控制结核感染[32]。另有研究发现，活动性结核中$IFN\text{-}\gamma^+TNF\text{-}\alpha^+CD4^+$T细胞减少，PD-1抑制剂可增加$IFN\text{-}\gamma^+TNF\text{-}\alpha^+CD4^+$T细胞，并促进IFN-γ与TNF-α释放，减少巨噬细胞坏死，抑制MTB播散[33]。根据这些理论，ICI可能利于结核控制，但临床研究发现ICI治疗中可发生MTB激活[34]，其机制尚不清楚，可能与免疫重建炎症综合征（immunereconstitution inflammatory syndrome，IRIS）类似。PD-1缺陷小鼠感染MTB后存活率显著降低，MTB大量增殖，多种炎症因子的表达水平增加，剧烈的炎症反应促进结核发展[35]。也有研究发现，虽然接受ICI治疗的癌症患者结核发病率为普通人群8倍，但是ICI与结核发生风险无显著相关性，在ICI治疗中发生的MTB激活可能与癌症而非ICI相关[36]。

2 肺癌合并肺结核的诊断进展

肺癌和肺结核有相似的临床表现及影像学特点，易误诊、漏诊、延迟诊断。经病理学确诊肺癌合并肺结核多为NSCLC[5]。与单纯肺癌或结核相比，肺癌合并肺结核更易出现咳嗽、咳痰、咯血、发热症状，且CT影像表现为不规则肿块、胸膜增厚的比例更高[37]。虽然增强CT识别肺癌的特异性较普通CT稍强，但仍难以区分活动性结核与肺癌，而^{18}F-脱氧葡萄糖（^{18}F-fluorodeoxy glucose，^{18}F-FDG）在活动性结核及肺癌中的摄取相似，^{18}F-FDG-PET/CT没有足够的特异性区分肺癌及活动性结核[38]，既往有结核病史的肺癌患者易被误诊为活动性结核。另一种新型探针^{18}F-阿法肽Ⅱ（^{18}F-Alfatide Ⅱ）在肺癌及结核中的摄取有显著差异，在结核病灶中的累积显著低

于肺癌病灶,因此^{18}F-Alfatide Ⅱ PET/CT可能在区分肺癌及肺结核方面有良好前景[39]。一些生物标志物有望用于肺癌合并肺结核的诊断,NSCLC患者的外周血循环游离DNA水平及完整性显著高于结核患者,可用于区分NSCLC与结核,且其完整性对NSCLC及结核的区分能力优于糖类抗原125、神经元特异性烯醇化酶及癌胚抗原[40]。此外,血清中人附睾蛋白-4、小分子核糖核酸也有助于在活动性肺结核中诊断肺癌[41]。

3 肺癌合并肺结核的治疗进展

肺癌合并陈旧性肺结核的患者,一般无需行抗结核治疗,仅行抗肿瘤治疗;肺癌合并活动性肺结核应同时进行抗肿瘤和抗结核治疗以提高临床获益。抗结核治疗并不影响化疗效果,也不增加化疗不良反应[42]。具有手术指征的肺癌合并活动性结核患者可在痰涂片阴性后选择手术治疗,围手术期行抗结核治疗不会增加额外的术后风险[43]。手术及化疗前最佳的抗结核治疗时机仍需要进一步研究,目前认为标准四联抗结核治疗2~3周后进行手术或化疗较安全,因为MTB在抗结核治疗2周后迅速减少[44]。抗结核与靶向治疗同步时,需考虑药物之间的相互影响。例如酪氨酸激酶抑制剂(tyrosine kinase inhibitor,TKI),主要由肝细胞的细胞色素P450(cytochrome P450,CYP)氧化代谢,TKI受CYP3A4抑制剂及诱导剂影响较大。利福平是CYP3A4的强诱导剂,可加速TKI类药物如吉非替尼、厄洛替尼的代谢,降低血浆药物浓度,而异烟肼可抑制CYP1A2、2A6、3A4等肝酶活性,延缓药物代谢,增加血浆药物浓度[45]。ICI治疗肺癌合并活动性结核的安全性有待研究,目前暂不推荐结核活动期使用ICI,而抗结核治疗后ICI治疗是否需要恢复及恢复时机仍需进一步研究[45]。抗PD-1治疗后的MTB激活与IRIS类似,而皮质类固醇可降低IRIS的发生风险,可能有潜力治疗ICI导致的活动性结核[34]。

4 肺癌合并肺结核的预后

合并肺结核的肺癌患者死亡率较单纯肺癌或结核高,平均生存期为584 d,其中合并活动性结核的患者生存期更短[5]。研究发现,合并陈旧性肺结核的肺腺癌患者表皮生长因子受体突变率显著升高,易出现外显子19缺失突变,TKI治疗后患者无进展生存期及总生存期较非结核肺腺癌患者短[47]。

综上所述,结核的瘢痕、慢性炎症、免疫功能异常可为肺癌的发生发展创造有利条件,而肺癌的免疫抑制状态及免疫治疗又可影响结核病灶的发展,两者密切相关。ROS、RNS、Th1/Th2、Th17/Treg及巨噬细胞等可能有潜力作为肺癌合并结核的治疗靶点。ICI在结核发病机制中的作用及其导致结核活化后的治疗方法需更多关注。肺癌合并结核的诊断方法及抗结核联合抗肿瘤治疗的安全性和有效性也需深入探索。虽然近年来肺癌合并肺结核的机制研究及诊疗进展有了一定突破,但未来仍需进一步研究,以寻找新的诊断与治疗方法。

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[收稿日期] 2021-12-03
(本文编辑:唐 震)

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[收稿日期] 2022-01-30
(本文编辑:唐 震)