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· 综述 ·

肿瘤肺转移前微环境的研究进展及靶向治疗策略

Research progress on tumor pre-metastatic niche in the lung and targeted therapy strategies

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[摘要] 肿瘤转移是复杂的动态过程, 具有器官选择性, 其中肺是常见的转移部位。肺转移与肿瘤患者预后不良密切相关, 因此, 研究肿瘤肺转移前微环境(PMN)的特征和机制对于改善患者的预后至关重要。研究表明, 原发肿瘤能驯化PMN的形成以促进肿瘤细胞的转移与定植, 甚至决定肿瘤转移的器官选择性。在肺部, 原发肿瘤来源的分泌因子与基质细胞、免疫细胞等之间的相互作用为肿瘤细胞的定植创造了有利条件, 形成了以基质重塑、免疫抑制、血管生成及通透性增加、代谢重编程为主要特征的肺PMN。本综述聚焦于肺PMN的形成因素及其促转移机制, 探讨了靶向肺PMN在肿瘤转移预测、诊断或治疗中的潜在应用, 为肿瘤治疗提供了新策略。

[关键词] 肺转移前微环境; 肿瘤; 基质重塑; 免疫抑制; 血管生成; 代谢重编程

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近年来, 恶性肿瘤的发病率和病死率逐年上升, 肿瘤转移是癌症致死的主要原因^[1]。转移是一个复杂的动态过程, 肿瘤细胞局部侵袭周围组织, 继而渗入血管或淋巴管并在其内存活并转运, 最后外渗至次生组织定植^[2]。然而, 大部分肿瘤的扩散不是随机的, 总是倾向于转移到特定器官, 这说明肿瘤细胞与器官特异性转移靶点之间相互作用的重要性。已有研究^[3]表明, 原发肿瘤能够通过促进转移前微环境(pre-metastatic niche, PMN)的形成来支持肿瘤转移。PMN是指肿瘤尚未形成转移前, 已经通过原发肿瘤分泌的细胞因子、趋化因子或外泌体等, 动员和募集骨髓源性细胞(bone marrow-derived cell, BMDC)至预转移的靶器官, 形成以免疫抑制、基质重塑等为特征的微环境, 有利于肿瘤细胞的定植。肺具有丰富的毛细血管网络, 是多种肿瘤例如乳腺癌、胃肠道肿瘤、黑色素瘤、肾癌等的常见转移部位。目前, 关于肺PMN形成及其特征的研究越来越多, 许多小鼠模型也已被用于肺转移的研究之中。本文旨在总结肺PMN的形成因素及其促转移特征, 为发掘可能的肿瘤转移治疗靶点提供参考依据。

1 肺PMN的形成因素

肿瘤源性分泌物质、免疫细胞、基质细胞是肺PMN形成的三个关键因素。肿瘤源性分泌物质作为肺PMN的始动因素, 能招募多种免疫细胞到肺组织中, 诱导基质细胞活化。免疫细胞、基质细胞通过分泌细胞因子等促进肺组织局部炎性、抑制性微环境的形成。免疫细胞与基质细胞之间复杂的相互作用诱导重编程, 致使细胞表型或功能发生适应性改变。

1.1 肿瘤源性分泌物质

肿瘤源性分泌物质主要包含肿瘤源性分泌因子(tumor-derived secreted factor, TDSF)和细胞外囊泡(extracellular vesicle, EV), 能动员、招募免疫抑制性细胞到肺组织, 诱导免疫细胞和基质细胞重编程, 促进肺PMN的形成。

1.1.1 TDSF

肿瘤细胞及其驯化的基质细胞能分泌大量的趋化因子/细胞因子或蛋白、酶促进肺PMN形成。例如, 原发肿瘤分泌的血管内皮生长因子-A(vascular endothelial growth factor-A, VEGF-A)。研究^[4]发现, 肿瘤细胞过表达VEGF-A后, 在转移前能诱导前哨淋巴结和淋巴管的生成。VEGF-A也是重要的中介因子, 其介导的血管和淋巴管生成是端粒重复结合因子2(telomeric repeat-binding factor 2, TRF2)、血管生成素样蛋白2(angiopoietin-like protein 2, ANGPTL2)促进肿瘤转移的关键因素^[5-6]。肺泡巨噬细胞通过上调趋化因子CCL12的表达募集更多的髓源性抑制细胞(myeloid-derived suppressor cell, MDSC), 进而促进肿瘤肺转移^[7]。

炎性细胞因子表达上调和炎性微环境的形成是肺PMN形成的特征之一。CCL2在非小细胞肺癌、乳腺癌等易转移肿瘤组织中高表达^[8], 是乳腺癌复发^[9]的早期指标。IL-6和CXCL8在肺转移患者中的表达

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水平高于其原发肿瘤^[10]。S100家族是肿瘤细胞与基质细胞相互作用的重要信号分子,促进炎症微环境的形成^[11],是肿瘤肺转移的重要驱动因子^[12]。非转移性乳腺癌MCF-7细胞在转染S100A4后出现转移表型^[13]。S100A8、S100A9在转移前肺内积聚,诱导血清样淀粉蛋白3(serum amyloid A3, SAA3)的表达^[14]。使用抗S100A8和S100A9单抗治疗后,小鼠肺转移显著减少^[15]。

1.1.2 EV

原发肿瘤分泌的EV是肿瘤细胞和基质细胞在局部和PMN发生信息交换的重要介质,能调节基质重塑、血管生成等多种病理过程以促进PMN的形成^[16]。EV中包含来自其母细胞的RNA、DNA、蛋白质、代谢物、miRNA等。NOVO等^[17]发现,P53突变的肿瘤细胞可以产生EV;KONG等^[3]发现,从人唾液腺样囊性癌组织中分离的原代肿瘤相关成纤维细胞(cancer-associated fibroblast, CAF)产生的EV也参与了肺PMN的形成。

EV通过受体与靶细胞的相互作用,或与细胞膜的直接融合或内吞参与肿瘤细胞、基质细胞、免疫细胞之间的信息交换^[18]。肿瘤外泌体RNA能通过与Toll样受体3(TLR3)结合靶向肺上皮细胞^[19]。黑色素瘤来源的外泌体通过重编程骨髓来源的DC,促进肺PMN的形成^[20]。脂肪肝中肝细胞源性的EV能增强致癌YAP信号转导,促进M2型巨噬细胞浸润,形成免疫抑制性微环境,促进肿瘤生长和转移^[21]。高转移性肝癌细胞来源的miR-1247-3p外泌体能直接激活成纤维细胞中 $\beta 1$ 整合素/NF- κ B信号通路^[22]。胰腺癌来源的外泌体FGD5-AS1能激活STAT3/NF- κ B通路促进巨噬细胞极化^[23]。结直肠癌细胞分泌的miR-146a-5p和miR-155-5p外泌体能激活CAF,促进肿瘤进展和肺转移^[24]。

1.2 免疫细胞

免疫细胞如中性粒细胞、MDSC、巨噬细胞等被募集到肺,驱动肺PMN的形成。在固有免疫反应中,中性粒细胞能直接吞噬病原体等发挥杀伤效应,然而,中性粒细胞也能促进肿瘤细胞迁移、侵袭、外渗等,对肺PMN的形成至关重要。中性粒细胞在肺中聚集累积形成炎症微环境^[25-26]。研究^[27]发现,CD62L^{dim}嗜中性粒细胞亚群经由CXCL12/CXCR4信号通路特异性募集到肺组织,利于肺PMN的形成。N2型中性粒细胞能分泌脂蛋白2,诱导肿瘤间质上皮转化^[28]。CD11b⁺/Ly6G⁺中性粒细胞能抑制NK细胞功能,分泌IL-1 β 和基质金属蛋白酶(matrix metalloproteinase, MMP)促进肿瘤细胞外渗^[29]。此外,由活化的中性粒细胞释放的蛋白质和DNA-组蛋

白复合物组成的网状结构中性粒细胞胞外诱捕网(neutrophil extracellular trap, NET)也参与了肿瘤生长与转移^[30]。

MDSC是调节免疫反应的未成熟髓细胞,在小鼠肺转移模型中,MDSC是原发肿瘤切除后PMN形成的关键因素^[31]。粒细胞样MDSC(G-MDSC)^[32-33]、单核样MDSC(mo-MDSC)^[7]、CD11b⁺ Ly6C⁺单核细胞^[34]等被招募到肺组织,诱导局部微环境改变,促进肺转移。此外,巨噬细胞也是肿瘤细胞免疫逃逸、侵袭与转移的始动因素之一,在转移前肺中浸润增加^[35]。巨噬细胞被诱导极化为M2型肿瘤相关巨噬细胞(TAM)后,能促进血管和淋巴管生成、免疫抑制等致肿瘤肺转移^[36-37]。

1.3 基质细胞

肺内基质细胞(如成纤维细胞、上皮细胞、内皮细胞等)受到原发肿瘤或免疫细胞等来源的分泌因子的调控,表型或功能发生改变,通过细胞因子或相互作用使得被募集到肺的免疫细胞等呈转移性表型,营造利于肿瘤细胞定植与扩增的微环境。肺成纤维细胞可被诱导重编程,分化为CAF,分泌TGF- β 、IL-33^[38-39],促进骨肉瘤、乳腺癌肺转移。内皮细胞高表达BCL-2^[40]、S100A6^[41]或SLIT2^[42]等,与肿瘤肺转移呈正相关。肿瘤细胞能激活静止的上皮细胞,使其发生上皮间质转化,提高细胞迁移与侵袭能力^[43]。此外,肺上皮细胞表面的TLR3受体能识别原发肿瘤来源的信号,释放细胞因子而促进肿瘤肺转移^[19]。

2 肺PMN的促转移机制

肺PMN的形成利于肿瘤细胞在肺组织中定植,其主要特征为基质重塑、免疫抑制、血管生成及血管通透性增加、代谢重编程等。基质重塑和血管通透性增加能促进肿瘤细胞的附着和渗入,激活细胞内信号通路,同时大量免疫抑制性细胞的富集,能通过抑制免疫监视和免疫杀伤功能,形成抑制性微环境。此外,代谢物质累积和血管生成更能促进肿瘤细胞的存活和迁移。

2.1 基质重塑

肺组织的细胞外基质(extracellular matrix, ECM)在原发肿瘤释放的细胞因子、激活的基质细胞、募集的免疫细胞等调控下发生显著变化^[44]。TGF- β 可诱导ACAT2和波形蛋白在小鼠转移前肺中表达^[45],在含小窝蛋白-1(caveolin-1, CAV-1)的外泌体刺激下,肺上皮细胞中炎症趋化因子的表达增加,促进肺成纤维细胞中胶原蛋白-C分泌,致使ECM沉积^[37]。在肿瘤细胞到达前,肺募集的单核MDSC分泌

IL-1 β , 上调E-选择素的表达, 促进肺转移^[46]。N2型中性粒细胞分泌的脂钙蛋白2(lipocalin 2, LCN2)能诱导肿瘤细胞间质上皮转化^[28], 促进肿瘤细胞在肺中定植。COL10A1也是上皮间质转化的潜在诱导剂, 敲除COL10A1后, 肺转移被抑制^[47]。肺基质重塑重要特征之一是纤维连接蛋白(fibronectin, FN)的累积, 利于免疫抑制细胞的黏附及肿瘤细胞的定植。肺部表型改变的血管周围细胞KLF4(Kruppel-like factor 4)基因表达增加, 利于建立富含FN的促转移微环境^[48]; 敲除IGF2BP1能抑制肺中FN的积累, 阻断肺PMN的形成^[49]。

此外, 基质重塑还伴随与ECM修饰相关的酶如MMP、赖氨酸氧化酶(lysyl oxidase, LOX)等异常表达, 内皮细胞中VEGF/MMP2/MMP9和闭合蛋白(occludin)的表达增加与肿瘤转移相关^[50]。赖氨酰氧化脱氢酶2(lysyl oxidase like 2, LOXL2)能促进FN的产生、上调MMP9和CXCL12的表达, 催化胶原蛋白和弹性蛋白交联, 促进基质重塑和组织硬化, 增强肺组织中BMDC的募集并诱导 γ 黏连蛋白表达^[51-52]。

2.2 免疫抑制性微环境

在肺PMN中, 肿瘤细胞或基质细胞释放多种细胞因子调控免疫细胞, 包括免疫抑制细胞的激活和分化、抗原提呈减少、T细胞增殖抑制等, 致使免疫监视、清除功能下降, 营造免疫抑制性微环境, 促进肿瘤免疫逃逸。

原发性肿瘤来源的细胞因子或外泌体能直接动员、募集免疫抑制性细胞到肺组织中。粒细胞集落刺激因子(G-CSF)、CCL2能分别动员和募集Ly6G⁺Ly6C⁺粒细胞、巨噬细胞到肺组织^[33, 53]; IL-6表达上调后能增加CD11b⁺髓样细胞在肺中的浸润^[54], 转移前肺中Gr-1⁺CD11b⁺细胞比例增加后能抑制IFN- γ 产生, 增加促炎因子的分泌, 抑制抗肿瘤免疫^[55]。同时, 外泌体也能直接调控肺组织中免疫细胞的数量及功能。小鼠在长期EV刺激后, 微环境中CD4⁺T细胞和MDSC比例增加, CD8⁺T细胞和NK细胞比例降低, 免疫杀伤功能显著下降^[56]。EV还能诱导小鼠肺泡巨噬细胞IL-10、TGF- β 、CCL22的表达, 抑制巨噬细胞介导的肿瘤杀伤效应^[57]。

肺内基质细胞与免疫细胞间存在复杂的相互作用, 肺泡巨噬细胞能抑制肺内抗肿瘤T细胞功能, 同时其能通过调节肺中TGF- β 的表达来抑制肺内DC的成熟^[58]。内皮细胞能产生促炎细胞因子S100A8和S100A9, 招募CD11b⁺骨髓细胞^[14]。肺上皮细胞表面受体TLR3被肿瘤外泌体激活后, 释放趋化因子招募中性粒细胞到肺中形成PMN, 促进肺转移^[19]。免疫细胞也能通过释放细胞因子调节肺部微环境以支持

肿瘤细胞的存活与增殖。募集的Ly6G⁺中性粒细胞能上调肺组织中MMP9、S100A8/A9、TGF- β 的表达^[59]; 中性粒细胞发生N2转化后能上调转移前肺中PD-L2的表达, 抑制T细胞增殖, 促进免疫抑制性微环境的形成^[60]。

2.3 血管生成及血管通透性增加

新血管生成和血管通透性增加是转移性肿瘤细胞外渗和存活所必需的。研究^[61]表明, 钙调磷酸酶和活化T细胞核因子(nuclear factor of activated T cell, NFAT)能在肿瘤细胞到达肺之前特异性激活肺内皮细胞, 上调NFAT靶点血管生成素2, 致使肺转移增加, 提示血管生成素2是潜在的肺PMN血管生成的开关。

VEGF及其受体是血管生成和可塑的关键因子。VEGF能诱导小鼠肺微血管内皮细胞产生前列腺素2(prostaglandin E2, PGE2), 增强细胞黏附^[62]。无论是体内体外, 肺血管内皮细胞中VEGF、FGF-2、IL-8的表达增加均利于血管生成, 在富含外泌素的外泌体刺激下, CD146⁺肺内皮细胞中VEGFR1的表达上调, 重塑肺血管内皮细胞, 促进肿瘤肺转移^[63]。此外, G-CSF过表达能动员Ly6G⁺Ly6C⁺粒细胞产生Bv8蛋白, 促进血管生成, 诱导形成肺PMN^[33]。

肺血管通透性增加是肿瘤细胞成功定植的关键, 也是后续肿瘤进展、转移的起始。多种分泌因子(包括EGFR、COX2、MMP1、MMP2等)都可诱导原发性肿瘤及肺血管的通透性增加, 促进循环肿瘤细胞外渗和定植^[64]。血管生成素样蛋白4能破坏血管内皮细胞间的连接, 增加肺毛细血管的通透性, 促进肿瘤细胞定植^[65]。近期多项研究^[66]表明, 外泌体能够靶向内皮细胞和黏附分子以破坏内皮屏障的完整性, 外泌体miR-25-3p通过靶向KLF2和KLF4基因调控内皮细胞中VEGFR2、ZO-1、occludin和密封蛋白-5(claudin-5)的表达, 从而增加血管通透性和促进血管生成。miR-375-3p能直接结合claudin-1的3'UTR, 抑制其表达而破坏血管内皮细胞的紧密连接, 促进肺转移^[67]。

2.4 代谢重编程

肿瘤细胞的代谢改变为肿瘤的发生与发展提供了重要的生化基础。代谢物质的累积不仅影响了基质细胞和免疫细胞的功能, 还决定了肿瘤的发生与发展、转移及预后。

通过对小鼠乳腺癌肺转移模型的蛋白质组学分析, 发现早期肺PMN形成涉及糖代谢相关分子改变, 晚期可能由于肺组织重塑、炎症信号增强等使得Ca²⁺信号增强^[68]。乳腺癌来源的EV能通过miR-122下调丙酮酸激酶和葡萄糖转运蛋白的表达, 进而抑制肺

成纤维细胞等对葡萄糖的摄取和利用^[69]。EV信号还能被TLR2识别,经由NF- κ B通路增加葡萄糖摄取,同时上调一氧化氮合酶2表达,抑制线粒体氧化磷酸化,提高乳酸含量,促进NF- κ B下游缺氧诱导因子-1 α (HIF-1 α)的激活,上调巨噬细胞表面PD-L1的表达,通过对糖代谢重编程使巨噬细胞向免疫抑制表型极化^[70]。

肺是富含脂质的环境,棕榈酸在乳腺癌患者转移前肺间质中富集,利用棕榈酸酯合成乙酰辅酶A,同时促进赖氨酸乙酰转移酶2a的表达^[71]。肺成纤维细胞中乙酰辅酶A羧化酶表达下降,致使蛋白质赖氨酸残基乙酰化和脂肪酸合成改变,促使肺成纤维细胞出现衰老和炎症表型^[72]。脂质代谢中花生四烯酸转化为PGE2也是促进PMN形成的重要原因之一。乳腺癌发生时,IL-1 β 能诱导产生大量的PGE2,使DC和单核细胞重编程,进而引发这些细胞功能障碍或转变为免疫抑制性细胞,促进肺转移^[73]。巨噬细胞中参与花生四烯酸代谢的酶CYP4A的表达与乳腺癌患者肺转移和不良预后相关,抑制CYP4A⁺后可以减少VEGFR1⁺髓系细胞募集和FN的表达,从而可以抑制PMN形成,降低肺转移负荷^[74]。

3 靶向肺PMN的诊疗策略

随着对PMN形成机制的不断解析,抑制PMN的形成,从而抑制肿瘤的转移成为可能,并具有良好的应用前景。多种新型检测技术已被应用于预测和表征肿瘤转移的概率,在众多治疗策略中,靶向PMN的治疗策略显得尤为重要,尤其是靶向免疫抑制性微环境 and 外泌体的治疗方法,已成为研究的热点。

3.1 靶向PMN的新型检测技术

免疫抑制性细胞被募集至肺是肺PMN形成的关键因素之一。早期研究^[75]表明,表达VEGFR1和VLA-4的BMDC在PMN的定植能促进肿瘤转移。据此,研究者利用高亲和力和正电子发射断层扫描(PET)探针在体内无创观察BMDC聚集和增殖的情况。诸多研究^[76]表明,MDSC释放的S100A8/A9利于血管生成,形成免疫抑制性微环境,是转移的重要诱导因素。基于此,研究者开发了一种S100A8/A9特异性PET探针用于成像,能预测癌细胞倾向的转移器官,其影像信号与随后的转移负荷相关。此外,中性粒细胞在肺内的聚集与肺转移息息相关,因此利用中性粒细胞靶向肽修饰开发了一种活性靶向纳米探针,通过检测肺中性粒细胞浸润程度以早期诊断肺转移^[77]。

3.2 靶向重塑免疫抑制性PMN

肺PMN的典型特征是免疫抑制,免疫抑制性微

环境的形成以免抑制细胞(如MDSC、TAM等)的募集增多、效应性细胞(如杀伤性T细胞和NK细胞)的功能减弱为特征。因此,靶向免疫抑制性细胞亚群、重塑免疫细胞功能是目前主要的治疗策略。

肿瘤转移前,大量MDSC被招募至肺,是肺PMN形成的关键因素,其通过分泌细胞因子、趋化因子、生长因子和外泌体促进ECM重塑、血管渗漏,诱导炎症、免疫抑制^[78]。研究者^[79]联合多维流式、高分辨率组织RNA测序和单细胞RNA测序发现,MDSC相关特征基因和信号通路是肺PMN中最显著上调的特征之一,提出“BMDC介导的免疫抑制是肿瘤转移的中心调控因子”,基于此发现,利用基因工程骨髓细胞在转移进展期间将抗肿瘤细胞因子IL-12输送至局部,逆转肺部的免疫抑制,减少转移负担,提高荷瘤小鼠生存率。MDSC能促进术后炎症区免疫抑制环境的建立,是原发肿瘤切除后PMN形成的主要原因。研究^[31]发现,使用低剂量的DNA甲基化酶抑制剂5-氮杂胞苷和组蛋白去乙酰化酶抑制剂恩替诺特辅助治疗后,能通过下调CCR2和CXCR2抑制MDSC的募集,促进MDSC分化,抑制PMN形成。

利用纳米或胶束颗粒靶向MDSC以抑制其募集是抑制肺PMN形成的一大方向。海绵状中性粒细胞膜包被的纳米系统可通过抑制MDSC的募集和功能,降低肺血管通透性和抑制循环肿瘤细胞的定植而抑制肺PMN的形成^[80]。低毒性低分子量肝素-生育酚琥珀酸酯纳米颗粒通过抑制血管内皮细胞与G-MDSC之间的黏附,阻断其外渗,抑制其在肺内的聚集^[81]。透明质酸包被的壳寡糖-全反式维甲酸胶束颗粒通过阻断MDSC的NF- κ B炎症信号通路以减轻术后炎症反应,抑制PMN的形成^[82]。靶向C肽修饰的低分子量肝素-全反式维甲酸胶束粒子通过竞争性结合抑制MDSC的募集,改善肺部炎症和免疫抑制性微环境^[83]。

3.3 EV在靶向PMN诊疗中的应用

肿瘤细胞来源的EV对细胞间通信至关重要,能促进肿瘤细胞增殖与侵袭,建立适宜肿瘤细胞定植的微环境,其因稳定、多样的特性已成为PMN形成的潜在标志物。血清外泌体miR-126、miR-1290、miR-23a和miR-940是结肠癌早期诊断的潜在标志物^[84]。外泌体中的磷酸甘油酸变位酶1(phosphoglycerate mutase 1, PGAM1)在转移性前列腺癌中表达显著上调,能促进血管生成,是转移性前列腺癌液体活检的标志物^[85]。外泌体中的CAV-1能调节肺上皮细胞中PMN相关基因及炎症趋化因子的表达,促进ECM沉积、肺巨噬细胞M2型极化和血管生成,为预测乳腺癌肺转移提供了新方向^[86]。头颈部

鳞状细胞癌来源的小EV含脱氢酶结构域12(abhydrolase domain containing 12, ABHD12),能激活巨噬细胞AKT-FOXO1通路上调S1PR1表达,促进肺PMN形成,同时靶向S1PR1和PD-1能显著增强抗肿瘤效应,提示ABHD12⁺的小EV是增强抗肿瘤效应的潜在靶点^[87]。

靶向肺PMN的外泌体治疗策略正逐步兴起,巨噬细胞-肿瘤细胞产生的嵌合EV能激活T细胞、提高CD8⁺T细胞/Treg细胞比率,与PD-1免疫检查点阻断疗法联合后显著抑制肿瘤肺转移^[88]。工程外泌体是基于外泌体的靶向性和转运效应设计的药物递送系统^[89],将正常间充质细胞来源的外泌体进行改造,特异性靶向Kirsten大鼠肉瘤病毒癌基因同源物(KRAS),能促进巨噬细胞增殖,延长胰腺癌患者总生存期^[90]。基因修饰后的DC来源的CD47-SST外泌体能更高效地将寡核苷酸递送至特定组织^[91]。因而,根据PMN的不同特征对外泌体进行针对性、特异性改造是阻断、抑制PMN形成和治疗转移的重要方向。

4 结 语

PMN的形成是肿瘤细胞在远端器官成功定植并形成转移的关键。PMN的组成成分复杂,除原发肿瘤来源的分泌物质、肿瘤细胞、基质细胞外是否有其他重要组分?已有研究表明,压力导致的高水平的组织儿茶酚胺能促进肿瘤生长和转移^[92],慢性应激使得FN累积,T细胞浸润减少,显著改变肺微环境^[93],这表明神经系统及其分泌物质同样参与了肺PMN的形成,但其具体的调节通路及机制有待深入探索。

PMN的复杂组成使得其针对性治疗策略缺乏,难以发现原发肿瘤来源的特异性分泌因子。虽然外泌体治疗取得了一定进展,但如何区别肿瘤细胞和正常细胞来源的外泌体仍是难题,外泌体重编程肿瘤细胞和基质细胞的具体机制,是基因层面的改变还是表观修饰层面的,外泌体分泌与原发肿瘤发生发展是否相关等皆有待探究。目前,针对肺PMN的预防、检查、阻断方式仍面临诸多挑战。肺PMN特异性标志物甚少,液体活检、靶向性纳米探针等技术的应用和推广仍在起步阶段,在原发肿瘤切除后,缺乏预测肺PMN形成可能性的方式。

代谢失调是肿瘤细胞的典型特征之一,癌细胞的代谢变化与表观遗传密不可分。表观遗传能调控代谢相关基因的表达,改变代谢酶活性。代谢物能参与细胞间通信,调控表观修饰。随着信息学和分析技术的发展,代谢组学成为发现转移相关特异性标志物的新兴工具。但代谢网络复杂多变,肿瘤细胞从休眠到转移、侵袭阶段,多种代谢途径发生改

变,是否能利用代谢物来预测肿瘤发生发展,判定分期,如何通过代谢改变预测肿瘤偏好转移部位还在探索阶段。总之,肺PMN的形成机制有待深入研究,如何将基础研究成果转化为临床应用,减少肿瘤肺转移发生率仍面临巨大的挑战。

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