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小细胞肺癌外周血生物标记物的研究进展

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摘　要

小细胞肺癌(small cell lung cancer, SCLC)是一种低分化且具有侵袭性的源于支气管粘膜或腺上皮内的神经内分泌肿瘤，其特点包括：生长迅速、侵袭性强、广泛转移、预后差且易复发。SCLC的临床治疗往往因疾病的侵袭性而复杂化，许多患者表现为胸内肿物和/或广泛转移的衰弱症状，且侵袭性强，预后较差，5年生存率 < 7%，所以很大一部分接受顺铂联合依托泊苷治疗的患者总是经历治疗失败和肿瘤复发。而靶向治疗及免疫治疗的问世使得一小部分患者从免疫治疗中获得了新的契机，所以寻找更加快速切且有效的诊断及预后生物标志物，提高肺癌患者生存率及生活质量、延长生存期。但目前尚缺乏对SCLC的诊断及预后有提示意义的简单易得、快速准确的实验室指标，本文将对SCLC患者外周血诊断及预后生物标志物的研究进展作一综述。

关键词

小细胞肺癌，预后，外周血炎性指标，分子生物学指标

Advances in Peripheral Blood Biomarkers of Small Cell Lung Cancer

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Abstract

Small cell lung cancer (SCLC) is a poorly differentiated and invasive neuroendocrine tumor originating from bronchial mucosa or glandular epithelium. It is characterized by rapid growth, strong invasivity, extensive metastasis, poor prognosis, and easy recurrence. The clinical treatment of SCLC is often complicated by the aggressiveness of the disease. Many patients present with debili-

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tating symptoms of intrathoracic masses and/or extensive metastasis with strong aggressiveness, poor prognosis, and 5-year survival rate < 7%. Therefore, a large proportion of patients receiving cisplatin combined with etoposide always experience treatment failure and tumor recurrence. However, the advent of targeted therapy and immunotherapy has provided a small number of patients with new opportunities from immunotherapy. Therefore, more rapid and effective diagnostic and prognostic biomarkers are sought to improve the survival rate and quality of life of lung cancer patients, and prolong the survival period. However, there is still a lack of simple, easy, rapid and accurate laboratory indicators that have suggestive significance for the diagnosis and prognosis of SCLC. This paper will review the research progress of peripheral blood diagnosis and prognostic biomarkers of SCLC patients.

Keywords

Small Cell Lung Cancer, Prognosis, Peripheral Blood Inflammatory Index, Molecular Biological Index

1. 引言

全球癌症范围内肺癌的患病率及死亡率呈现持续性的攀升趋势[1]，5 年生存率 < 7% [2]，其中小细胞肺癌属于肺癌中的常见类型，约占所有肺癌的 15% [3]，据报道，全球每年有 25 万例 SCLC 新发病例和至少 20 万例死亡[4]。尽管 SCLC 最初对化疗和放疗敏感，但在治疗后通常会出现复发或者转移，只有大约 5%的患者有延长生存期机率即在诊断后存活 5 年[5] [6]。对于延长期疾病患者，中位生存期约为 10 个月。而且 SCLC 的治疗方案在过去 40 年几乎没有变化，同时生存率也没有得到改善很大[7]，一部分接受顺铂/依托泊苷治疗的患者总是经历治疗失败和肿瘤复发[8]。靶向治疗及免疫治疗的问世使得 SCLC 治疗出现了新的契机，部分患者从免疫治疗及靶向治疗中获得了一定的益处，所以尽早的诊断及干预能够在一定程度上延长患者寿命[9]。现在肺癌的临床诊断方式主要包括影像学、病理细针穿刺活检、支气管镜等，而小细胞肺癌早期诊断更加局限，体检时影像学不易发现[10]，而病理活检和支气管镜检查虽然能够诊断早期患者，但存在有创、取材不到位导致漏诊的风险[11] [12]。目前 SCLC 缺乏采样简单、经济适用且无创伤的对诊断及预后有提示意义的实验室指标，而患者外周血中的生物标记物成为目前较理想的一类肿瘤检测方式，本文将对 SCLC 患者外周血诊断及预后生物标志物的研究进展作一综述。

2. 外周血炎症指标

1863 年 Rudolf Virchow 等研究中发现肿瘤组织被白细胞浸润，将癌症的起源与炎症联系在一起[13]，随后 Dvorak 研究进一步证实肿瘤和炎症反应之间紧密相关[14]。随着肿瘤学研究的深入，越来越多的文献报道，免疫炎症反应在肿瘤发生发展中发挥重要作用，即触发免疫系统的细胞通路导致细胞因子、趋化因子和其他炎症介质的过度释放[15] [16]，但是机体的细胞因子和趋化因子检测方法较为复发，无法用常规简单、经济的方法检测，所以目前提出了 3 类简化指标来监测机体的炎症反应，其包含血小板与淋巴细胞比值(PLR)、中性粒细胞与淋巴细胞比值(NLR)和格拉斯哥预后评分[17] [18] [19]，通过检测外周血中表达细胞因子和趋化因子的细胞成分如特定的血细胞计数作为标记物进行研究。

2.1. 中性粒细胞计数、淋巴细胞计数及其比值

中性粒细胞产生于位于骨髓静脉窦处的造血索，来源于髓系祖细胞[20]，一直被认为是具有促炎功能的抵抗入侵病原体的第一道防线，现如今研究表明，中性粒细胞具参与急性损伤和修复、慢性炎症、肿瘤及自身免疫的发生等特殊功能的炎症细胞[21]。组织癌变之后巨噬细胞有了新的身份即肿瘤相关巨噬细胞(TAM)，TAM 分泌趋化因子使中性粒细胞聚集在“促进基因突变”的肿瘤微环境中，在细胞因子 TNF、IL-8 等的介导下分化为不同的类型的中性粒细胞，释放活性氧、VEGF 以及白介素等物质调控肿瘤细胞的代谢，抑制免疫反应的同时促进肿瘤转移、增值及肿瘤血管的生成[22] [23]。Manfroi 等人研究 DLBCL 的预后时提出中性粒细胞促进肿瘤的发生转移[24]。淋巴细胞是由淋巴器官产生的，主要存在于淋巴管中循环的淋巴液中，淋巴细胞作为肿瘤监测和清除的核心在肿瘤免疫微环境能够正负项调节免疫应答；T 淋巴细胞通过产生细胞因子、细胞毒性酶穿孔素、颗粒酶 B 等途径抑制癌细胞增殖、转移[25]。同时可以分泌免疫抑制因子和生长因子，如 IL-6、VEGF 等抑制自然杀伤细胞等，从而使肿瘤细胞逃脱免疫监视。Ruan、Silatha Sakamuru 等人研究表明当免疫反应被抑制时，可以出现肿瘤治疗相关性和非肿瘤治疗相关性的导致淋巴细胞减少症，均影响小细胞肺癌的预后[26] [27]。

中性粒细胞与淋巴细胞比值(neutrophil to lymphocyte ratio, NLR)是目前公认的可反映机体全身炎症反应的重要指标，被认为是转化淋巴细胞和中性粒细胞之间的有利或不利影响的替代标志物[28]；当肿瘤细胞侵入机体时产生防御反应，中性粒细胞相对增加或淋巴细胞相对减少，导致外周血高 NLR 的出现，最终机体的免疫功能难以识别过度增生形成的肿瘤细胞，使肿瘤出现转移或浸润[29]。Karantanos 等的研究表明，非小细胞癌及结直肠癌等实体瘤的生存期及预后不良与外周血的高 NLR 相关[29] [30]。

2.2. 血小板计数、淋巴细胞计数及其比值

1865 年 Armand Trousseau 首次研究表明肿瘤可诱发机体形成静脉血栓[31] [32]，揭示癌症和血栓之间的关系。血小板存在于血管外的肿瘤微环境中直接接触癌细胞[33]，激活时分泌转化生长因子 β (TGF-β)、血管内皮生长因子(VEGF)等因子诱导肿瘤生长，促进肿瘤新生血管的形成[34] [35] [36]；同时血小板诱导肿瘤细胞 MMP-9 的表达以及血小板包裹肿瘤细胞，避免在血性转移途径中被免疫系统的监视及杀伤，减少凋亡信号[37]。Demers、Abdulrahman 等人多项研究表明乳腺癌、卵巢癌及肾癌等实体瘤的死亡率和高血小板计数成正相关[38] [39] [40]。

血小板与淋巴细胞比值(platelets to lymphocytes ratio, PLR)与 NLR 一样，可以反映机体防御能力与免疫炎症之间的相对变化，一般认为淋巴细胞相对减少或血小板相对增多则出现高 PLR 值。2014 年 Templeton 等人使用 meta 分析来结合 20 项研究探索 PLR 在 12754 名实体瘤中的预后，发现高 PLR 和多种实体瘤的生存率之间成负相关，即 PLR 值越高说明其抗肿瘤能力越低，肿瘤负荷越重，预后越差[41]。El Asmar 等人研究证实，NLR 和 PLR 是预测实体肿瘤和肿瘤手术不良结局的预后工具[42]；NLR 和 PLR 除了预测肿瘤患者预后不良的结局，还可以用于肿瘤的早期诊断，研究表明在胃癌早期 PLR、NLR 等炎症指标明显高于胃癌传统指标 CA199 的值，且表明在男性胃癌患者中 NLR、PLR 联合检测更能提高诊断效能[43]。

2.3. C-反应蛋白

C-反应蛋白(C-reactive protein CRP)是机体防御反应时，由肝脏或者上皮细胞合成的、多种促炎症细胞因子(IL-1a、IL-6 以及肿瘤坏死因子等)调节合成的保护机体急性时相的一种最主要、最敏感的炎性标记物[44]。由 Tiuett 和 Francis 首次发现急性患者的血清能和肺炎链球菌的荚膜 C-多糖发生沉淀反应[45]。在正常情况下，机体内含量较少，当机体受到炎症及肿瘤性的刺激时产生大量炎症因子，2 h 可升高，4~8

h 迅速上升达到高峰进一步刺激细胞过度增值，最终损伤 DNA 复制[46]；同时其介导的炎症反应在正常基因中插入癌基因以此促进肿瘤的发生发展[47]。有 Takaki、杨佳程、Nakayama [48] [49] [50]等多人的研究表明，肺癌、胰腺癌以及肾癌等多种实体瘤患者的血清 CRP 水平与肿瘤患者的预后不良相关，血清中 CRP 水平越高，患者的预后越差，生存期越短。在临床工作中，我们可以将外周血 CRP 检测作为评估肿瘤患者诊断及预后的一种常规项目。

血清学肿瘤标记物是目前与临床相关的最常见检测方法，血清学检查在临床上应用较为普遍，检测方法无创且安全、简便且经济，因此 NLR、PLR、C-反应蛋白相较于其他炎性指标具有更高的使用价值；但临床上肿瘤单项标记物检测灵敏度低、特异性较差，可在多种实体瘤中检测出来，只能作为辅助指标与 SCLC 其他生物指标联合检测提高临床恶性肿瘤患者的检出率，从而为 SCLC 的诊断及预后提供更多的理论依据。

3. 分子生物学标志物

3.1. miRNA

miRNA 是由 21~23 个核苷酸组成的单链非编码 RNA，在 1993 年 Ambros 和 Ruvkun [51] [52]报道了第一个 miRNA，之后 miRNA 时代花了 8 年时间才真正开始，当时有 3 个小组从线虫、果蝇和人类中鉴定出了数十个小 RNA [53] [54] [55]。生物信息学研究预测，超过 30%的人类基因是 miRNAs9 的靶向基因，它们影响一系列不同的生物程序，包括细胞发育、分化、凋亡和增殖，同时调控造血和促癌作用[56] [57]。现已证明，位于靶基因中的 3'非编码区中的单核苷酸可调控 miRNA 与靶基因的结合，进而调控小细胞肺癌发生、发展[58]。近年来，随着各种高通量测序平台应用于分析 miRNA 基因全基因组表达，越来越多的报道已经证明 miRNA 在癌症中的异常表达表现为成熟或前体 miRNA 转录本相对于相应正常组织的表达水平上调或下调，且已在淋巴瘤、乳腺、结直肠及前列腺恶性癌症中被发现,具有诊断、预后和治疗潜力[59] [60] [61] [62]。目前我们已知多种 miRNA 影响小细胞肺癌的预后，如 miR-338、miR-101 和 miR-98 等的高表达，Du [63]等通过比较支气管表皮细胞、小细胞肺癌细胞和非小细胞肺癌细胞中 miR-338、miR-101 和 miR-98 的表达量，小细胞肺癌中表达量最高，因而对异常表达的 miRNA 进行定量可能成为小细胞肺癌诊断和预后的可靠方法。这种 miRNA 分子群可能不仅仅在淋巴结组织中存在[63]，在外周血循环中同样可以检测到相应的 miRNA，其表达水平同样与小细胞肺癌的预后密切相关。

3.2. 乳酸脱氢酶

乳酸脱氢酶(lactate dehydrogenase, LDH)是一种存在于机体所有组织细胞胞质内的糖酵解酶[64]，通常由肝、脾和骨髓中的巨噬细胞通过受体介导的内吞作用清除[65]，当肿瘤生长过程中肿瘤微环境中的免疫系统发生改变时，可能是导致这些患者血清中 LDH 水平高的原因。此外，正常细胞在绝大多数情况下进行有氧氧化获得能量，有氧存在使氧化更加充分，效率更高。只在无氧的情况下例如从事剧烈运动才动用不考虑氧气可用性的无氧氧化，效率低，释放能量较少[65]。而在许多肿瘤细胞中，代谢转移到摄取高葡萄糖和生成高乳酸，取代有氧氧化而不考虑氧的可用性，这种现象被称为“Warburg effect”[66]，所以微环境通过诱导营养物质清除机制来维持癌细胞的增值，使肿瘤细胞被迫适应，使其不得不依赖肿瘤细胞的糖酵解，而 LDH 是糖酵解途径中关键酶之一[67]，常见的有 LDH-A 和 LDH-B 两种亚基组成，两种亚基构成五种不同的同工酶(LDH1、LDH2、LDH3、LDH4 和 LDH5)，LDH-A 是主要存在于骨骼肌中，对丙酮酸具有较高的亲和力，有利于丙酮酸转化为乳酸；相比之下，LDH-B 主要存在于心肌中，将乳酸转化为丙酮酸，丙酮酸在线粒体中进一步氧化，其中心、肾以 LDH1 为主，肺以 LDH3、LDH4 为主，骨骼肌以 LDH5 为主[68]。相关研究表明，LDH 可能与肿瘤负荷在一定程度上存在关联[69]，在弥漫大 B

细胞瘤国际预后评分指标中，LDH 值被认为是最具有独立预后因素的重要指标之一[70]。

3.3. 血管内皮因子

1989 年 VEGF 克隆和测序首次描述 VEGF 蛋白家族引起了巨大的轰动[71]，其成员包括：VEGF (或 VEGF-a)，VEGF-b，VEGF-c 和 VEGF-d，VEGF-f，胎盘生长因子(PlGF)，及其受体 VEGFR-1，VEGFR-2 和 VEGFR-3 [72]。VEGF-a 是正常和异常状态下许多血管生成过程所必需的二聚糖蛋白[73]，是所有 VEGF 家族成员中最具有特征性的血管生成因子[74]，它至少存在于 9 种同型二聚体异构体中(含有 121、145、148、162、165、165b 183、189 或 206 个氨基酸) [75]。小细胞肺癌患者高转移传播能力与其丰富的血管生长有关，其机理包括：① VEGF 具有刺激血管内皮细胞增殖产生组织因子促进增生；② 在低氧情况下，诱导内皮细胞的表达，激发 V3 因子的释放，改变细胞外基质有利于血管生长；③ VEGF 增加血管通透性的能力[76]。Salven 等[77]的研究结果表明 SCLC 患者血清中 VEGF 表达水平与患者不良预后显著相关，VEGF 表达水平越高，患者预后越差，生存期越短；刘军[76]等人通过研究 42 例 SCLC 患者、良性肺部疾病以及健康人的 VEGF 的浓度，表明 SCLC 患者血清 VEGF 的浓度显著高于良性肺部疾病患者和健康人的血清 VEGF 的浓度。

4. 展望

近年来，随着 SCLC 的肿瘤标志物相继报道，多项研究表明 NSE 和 ProGRP 作为小细胞肺癌患者肿瘤标志物，它们的灵敏度分别为是 42%、76% [78] [79]，作为单一的检测指标难以为小细胞肺癌的诊断及预后提供更加精准的预判。NLR、PLR、CRP 等外周血炎性指标虽然简单易测、价格易接受，可以在临床上大规模使用，但其易受外界因素干扰，特异性低，需要大样本回顾性或前瞻性研究来进一步确定；而刘军[72]等通过实验数据表明，血清 VEGF 和血清 NSE 联合检 SCLC 的阳性率为 54.1%，提高了 NSE 单独检测 SCLC 的阳性率，所以需要在临床工作中寻找更加具有经济价值和社会价值的生物标记物进行联合检测，提供更加精准的预判，根据疾病分层给予患者个体化、标准化得治疗，提高肺癌患者生存周期及生活质量。

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