·专题研究：中医药干预肺癌的基础与临床研究·

基于“分子－证候”双维度探讨不同亚型小细胞肺癌的中医精准辨治思路*

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摘要：小细胞肺癌（small cell lung cancer，SCLC）是一种侵袭性极强的神经内分泌肿瘤，目前小细胞肺癌最常见的亚型分类主要为基于转录因子所定义的 SCLC－A、SCLC－N、SCLC－P、SCLC－I 等。本文首次系统构建了 SCLC 分子分型与中医证型的映射关系，提出“分子－证候共演化”假说。设计“分型－辨证－复方”精准用药方案，将 SCLC 分子分型与中医辨证论治有机结合，可在一定程度上突破传统治疗的局限性，为个体化精准治疗提供新范式。同时也可在分子层面揭示中医证型的生物学基础（如 SCLC－I 亚型与“阴虚内热、正虚邪恋证”的免疫微环境关联），突破中医理论“抽象化”的瓶颈。虽然这一理论框架需要进一步的基础研究及临床验证，但其整合思维有望为肿瘤治疗提供一定的参考意义。未来需建立分子分型与中医证型的动态关联模型，开发标准化疗效评价体系，开展多中心临床研究，验证基于“分子－证候”双维度的“分型－辨证－复方”模式的可行性。

关键词：小细胞肺癌；分子分型；中医辨证；精准诊疗；分子；证候；辨病；辨型；辨证

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Precise TCM Diagnosis and Treatment Approaches for Different Subtypes of Small Cell Lung Cancer in "Molecular－Syndrome" Dual Dimensions

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Abstract: Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine tumor. Currently, the most common subtype classification of SCLC is mainly based on transcription factors, defined as SCLC－A, SCLC－N, SCLC－P, SCLC－I, and other subtypes. This paper systematically constructs, for the first time, the mapping relationship between SCLC molecular subtypes and traditional Chinese medicine (TCM) syndromes and proposes "molecular－syndrome co－evolution" hypothesis. A precise medication scheme of "syndrome recognition－syndrome differentiation－compound formula" is designed, organically combining SCLC molecular subtyping with TCM syndrome differentiation and treatment. This can, to some extent, overcome the limitations of traditional treatment and provide a new paradigm for individualized precision therapy. At the same time, it can reveal the biological basis of TCM syndromes at the molecular level (for example, the association of the SCLC－I subtype with the immune microenvironment of "Yin deficiency with internal Heat, deficiency of the body's Zheng Qi with lingering Evil Factors" syndrome), breaking through the bottleneck of TCM theory's "abstractness". Although this theoretical framework requires further basic research and clinical validation, its integrative thinking is expected to provide certain reference value for tumor treatment. In the future, it is necessary to establish a dynamic correlation model between molec-

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ular subtypes and TCM syndromes, develop a standardized efficacy evaluation system, and conduct multicenter clinical studies to verify the feasibility of the "molecular – syndrome co – evolution" model based on the dual dimensions of "molecule – syndrome".

Key words: small cell lung cancer; molecular subtyping; TCM syndrome differentiation; precision diagnosis and treatment; molecular; syndrome; disease differentiation; type differentiation; syndrome differentiation

小细胞肺癌(small cell lung cancer, SCLC)占肺癌的 13% ~15%,是侵袭性极强的神经内分泌肿瘤,5 年生存率约为 7%[1-2]。SCLC 具有增殖迅速、凋亡失衡、早期易转移扩散等特征,约 70% 的患者最初诊断为广泛期[3]。虽然小细胞肺癌初始治疗取得了显著进展[4],但仍存在缺乏有效生物预测标志物、化疗耐药、免疫抑制及个体治疗差异等问题[5],这些都表明 SCLC 仍处于精准医疗的范畴之外。出现上述现象的潜在原因之一就是 SCLC 各亚型之间存在显著的异质性[6],近年来,该领域的研究也引发了广泛关注。SCLC 分子分型特征与其临床实践之间的关系十分复杂,最初 Carney 等[7]发现,根据肿瘤细胞的生物学行为和神经内分泌(neuroendocrine, NE)表型,SCLC 可分为典型的 NE 干细胞样和 Non – NE 干细胞样变异。近年相关研究则强调了神经母细胞特异性转移因子(achaete – scute homolog 1, ASCL1)、神经内分泌因子 1(neurogenic differentiation factor 1, NEUROD1)、POU2 类同源框 3(POU domain class 2 transcription factor 3, POU2F3)和 Yes 相关蛋白 1(Yes – associated protein 1, YAP1)等转录因子,在定义 SCLC 不同分子亚型中的重要性[8-9],但是关于 SCLC – Y 亚型的定义存在诸多争议[10-11]。此外,还有多项研究提及 SCLC – I(inflammation)[12]、SCLC – TN(triple negative)[13]、SCLC – AN(ASCL1 +/NEUROD1 +)[13-14]、免疫富集亚型(immune enriched, IE)和免疫耗竭亚型(immune depleted, ID)[15]等。

在 SCLC 各亚型的治疗策略方面,西医也处于探索及开发阶段,缺乏对 SCLC 常见分子亚型的生物学特点、治疗方式及预后的总结,SCLC 各亚型也存在生存获益不一,治疗预后欠佳等问题。中医药作为肺癌行之有效的治疗手段之一,一方面,可通过“扶正祛邪”动态调整机体整体状态[16-17],弥补西医“分型固定化”的不足;另一方面,若可明确 SCLC 分子分型与中医证型的相关性,通过建立“分子 – 证候”双维度诊疗模式,可实现“精准打击肿瘤”与“整体调节机体”的结合,可突破传统治疗的局限性,提升单纯西医治疗效果,为个体化精准治疗提供新范式。

1　不同亚型 SCLC 生物学特性及治疗靶点

针对 SCLC 常见的分子分型,对已知靶点、西医治疗方式及不同分型所表现出来的典型特征,所对应的中医证候、病机治则等进行总结(图 1)。目前基于转录因子定义的 SCLC – A、SCLC – N、SCLC – P、SCLC – I 亚型为常见的 SCLC 分子分型。高表达 ASCL1 被定义为 SCLC – A 亚型,ASCL1 在神经内分泌细胞的分化中发挥至关重要的作用[18],与 SCLC 的发生密切相关[19]。SCLC – A 亚型增殖活跃,化疗治疗敏感但易复发,并常伴 TP53、RB1 缺失及白细胞介素 – 6(interleukin – 6, IL – 6)、肿瘤坏死因子 – α(tumor necrosis factor – α, TNF – α)等促炎因子的释放。但 SCLC – A 亚型免疫微环境呈现明显的“冷肿瘤”特征,即免疫细胞浸润不足且功能受抑制,可能与 IL – 6 和 TNF – α 驱动的慢性炎症及免疫耗竭相关[20-22]。目前,已知的关于 SCLC – A 治疗靶分子主要包括 Delta 样配体 3(delta – like ligand 3, DLL3, DLL3)[23-24]、B 细胞淋巴瘤因子 – 2(B – cell lymphoma 2, BCL – 2)[25]、环腺苷酸反应元件结合蛋白(cAMP response element binding protein, CREBBP)[26]、性别决定区 Y 框蛋白 2(SRY – box transcription factor 2, SOX2)[27]、赖氨酸特异性去甲基化酶 1(lysine – specific demethylase 1, LSD1)[28]等(图 1)。SCLC – N 亚型高表达 NEUROD1,同样具有高神经内分泌特征。研究表明,NEUROD1 的表达对 SCLC 细胞的增殖和迁移至关重要,故 SCLC – N 亚型可表现为侵袭性强、转移发生率高[29-31]。在治疗方面,致癌基因 Myc 为 NEUROD1 的下游靶点[32],Owonikoko 等[33]发现 Myc 基因扩增可能与极光激酶 A(aurora kinase A, AURKA)抑制剂治疗 SCLC – N 亚型的敏感性提高有关,而 AURKA 和 c – Myc 抑制剂的联合策略也可能提高这一特定亚型的治疗效果[34]。

在 Non – NE 亚型方面,SCLC – P 亚型依赖转录因子 POU2F3 的高表达,具有低神经内分泌特征。在单细胞转录组分析中,SCLC – P 亚型显示出较弱的上皮 – 间充质转化(epithelial – to – mesenchymal transition, EMT)特征,更多与上皮状态而非间充质

状态相关，从而可能限制了其迁移能力[35]，表现出相对“惰性”的生长特征。在治疗预后方面，部分研究表明，SCLC－P 亚型比 NE 亚型的 SCLC 有更好的生存预后[13,36]。目前 SCLC－P 亚型特异性治疗靶点的研究，主要集中在聚腺苷二磷酸核糖聚合酶（poly ADP－ribose polymerase inhibitor，PARP）抑制剂[37]、胰岛素样生长因子 1 受体（insulin－like growth factor 1 receptor，IGF1R）[38]，SRY 盒 9 转录因子（SRY－box transcription，SOX9）[39]等。SCLC－I 亚型患者以上 3 种转录因子均表现为低表达，往往高表达免疫检查点分子，其免疫微环境中 $CD8^+$ T 细胞等免疫细胞浸润显著，通常呈现炎症状态，也预示其在免疫检查点抑制剂联合治疗中能有更多的获益[40]。但是另一方面，由于 T 细胞免疫共抑制受体的表达同时上调，导致 T 细胞的功能可能因抑制性信号过强而被限制[41]。此外，还有研究表明，布鲁顿氏酪氨酸激酶抑制剂（Bruton's tyrosine kinase，BTK）（如伊布替尼）具有潜在治疗 SCLC－I 的敏感性[42]。

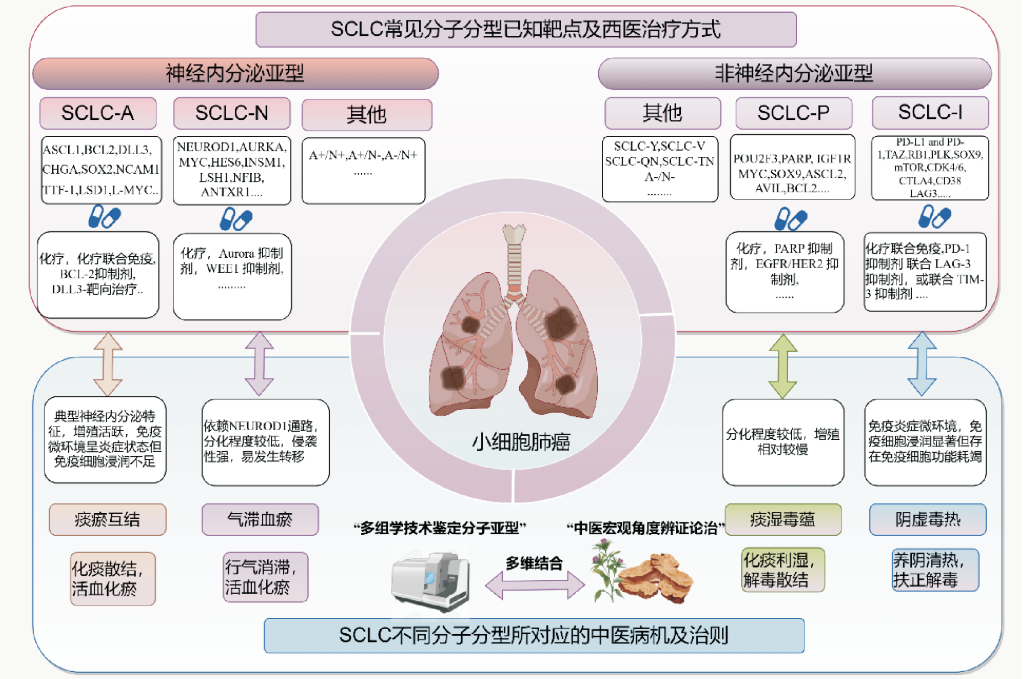


图 1　基于“分子－证候”双维度探讨 SCLC 分子分型的中西医治疗示意图

此外，随着多组学及综合空间分析等研究发展，SCLC 也出现了其他新兴的分型。如 Huo 等[43]基于蛋白组学将 SCLC 分为 S－Ⅰ（化疗获益）、S－Ⅱ（化免获益）和 S－Ⅲ亚型。Liu 等[44]将 SCLC 分为非负矩阵分解－1（non－negative matrix factorization－1，nmf1）、nmf2、nmf3 和 nmf4 亚型，并描述了各亚型的分子特征和潜在治疗策略。其他新型预测因子包括高迁移率族蛋白 3（high－mobility group box 3，HMGB3）、RE1 沉默转录因子（RE1 silencing transcription factor，REST）[15,45]和免疫生态位 MT2[46]等鉴定，也成为 SCLC 亚型及预后研究的一个重要方面，这也为 SCLC 精准诊疗的临床实践提供了更多依据。

2　“分子－证候”双维度下 SCLC 的中医辨证论治

2.1　中医对小细胞肺癌病因病机的整体认识　在中医治疗方面，根据 SCLC 病症特点可归于肺积、息贲、咳嗽、咯血等范畴。中医认为，肺癌全身属虚，局部属实。“虚”指肺、脾、肾等脏腑虚衰及气血阴阳虚损[47]，“实”指痰热瘀毒等郁阻于肺，久则酿生癌毒积块[48]。郁仁存教授、林洪生教授认为，邪毒是 SCLC 的重要病因，癌毒较盛，易于流窜，病性以痰瘀毒结为主，而正虚贯穿疾病始终，是 SCLC 发生和进展的根本原因[49－50]。相较于 NSCLC，治疗 SCLC 可在益气养精的基础上，加大抗癌祛邪力度。SCLC 证型变化多端，临床辨证论治时应结合西医治疗情况，随证诊治。

2.2　不同分型 SCLC 的中医证型特征及治则治法　SCLC－A 亚型有典型的神经内分泌特征，肿瘤细胞增殖活跃且易进展及复发，免疫微环境呈现炎症状态，但免疫细胞浸润不足。在机制研究方面，黄芩素可通过抑制 IL－6 和 TNF－α 的表达，缓解癌症

引起的骨痛[51]。香砂六君子汤合除痰解毒中药可促进 NK 细胞活化且抑制免疫逃逸，提示中医药可在一定程度上改善炎症因子驱动的 SCLC－A 亚型的慢性炎症及免疫耗竭，提高免疫微环境的免疫细胞浸润[52]。从中医理论而言，痰浊阻滞气机，血行不畅形成瘀血，“痰瘀胶结”致病理产物积聚，从而促进肿瘤细胞快速增殖[53]。肿瘤微环境的“炎症”和“免疫抑制”状态对应中医“痰热壅盛”所致“正气受损”，导致免疫细胞功能受损[54]。故考虑 SCLC－A 亚型以痰瘀互结为主，痰热内盛及正气受损为辅。推断临床多见咳嗽痰黏、舌质紫暗，脉涩或滑数。宜采用化痰散结联合活血祛瘀法，临证可选用半夏泻心汤加减联合桃红四物汤等。SCLC－N 亚型也表现出神经内分泌失调特征，且易发生侵袭及转移。中医认为，气滞血瘀是导致气血运行失调的主要原因，这种失调可能会增加肿瘤细胞转移的风险。气滞血瘀与微循环功能障碍、肿瘤转移等密切相关，晚期肿瘤患者血小板聚集和血液高黏滞性可能促进肿瘤细胞的扩散[55]。研究表明，如槐耳颗粒提取物可通过下调 N－cadherin 等 EMT 相关蛋白，抑制肺癌细胞转移[56]。对于 SCLC－N 亚型而言，中医临证时多采用行气消滞、活血化瘀解毒等法，方药多选用柴胡疏肝散、血府逐瘀汤等，根据患者症状，随症加减[57]。

对于 Non－NE 亚型的 SCLC－P 亚型及 SCLC－I 亚型而言，SCLC－P 亚型通常比 NE 亚型具有更好的生存预后，表现出相对“惰性”的生长特征，这与中医理论中的痰湿毒蕴病机相符[58]。PARP、SOX9 等是 SCLC－P 亚型的主要治疗靶点，相关研究表明，黄芪有效成分可通过激活肿瘤细胞 PARP 和细胞外信号调节激酶（extracellular signal－regulated kinase，ERK）信号通路降低肺癌细胞增殖[59]。中医认为痰湿体质通常表现为代谢功能异常[60]，临证可选用二陈汤、黄连解毒汤等方药化痰利湿，解毒散结，可在一定程度上改善 SCLC－P 亚型患者生存质量及预后。SCLC－I 亚型细胞免疫浸润显著但功能耗竭，符合中医正虚不足的特征，且免疫微环境呈现“炎症”状态，考虑病机以阴虚毒热为主，正虚邪恋为辅。研究显示 SCLC－I 亚型对化疗、免疫制剂联合治疗有更好的应答趋势[40]，与中医“扶正祛邪”理念相契合。且相关研究提示益气扶正类中药及单体可以增强免疫细胞功能，改善免疫微环境。中医临证可采用养阴清热解毒法（如沙参麦冬汤合五味消毒饮）调节免疫微环境的炎症状态，配合益气扶正法（如生脉散等）改善 T 细胞等免疫细胞功能[61－62]。

3　基于 SCLC“分子－证候”双维度的中医临床“辨病－辨型－辨证”的精准诊疗

精准医学强调疾病的精准化诊断与治疗，本质在于疾病的个性化治疗。西医学重视基因、蛋白等微观层面对疾病诊疗的预测及指导作用，即辨“病”、辨分子“分型”；中医重视宏观角度针对不同证型的论治，即辨“证型”，三者结合的诊疗模式更符合精准医学理念[63]，是适用 SCLC 等恶性肿瘤的最佳诊疗模式[64]。此外，肺癌发展过程中可能出现与原发肿瘤相关的症状（如癌痛、癌因性疲劳睡眠障碍、抑郁状态等）及治疗相关的症状（如化疗相关恶心呕吐、放射性肺炎、靶向治疗所致皮疹等），此时应结合具体症状治疗，在原发肿瘤控制稳定的情况下进行辨证论治。当 SCLC 患者症状、体征、舌脉象等不明显时，应以辨病为主，中医则重在“扶正祛邪”调控整体状态，并抑制局部肿瘤的增长，“形神同调”预防肿瘤复发转移。若某项特定亚型 SCLC 的症状、体征具有其他突出证候意义时，亦当以“证型”为主而非“分型”为主，例如归结于痰瘀互结证的 SCLC－A 型患者反见盗汗、五心烦热、舌红脉细数等阴虚内热征象时，亦当以阴虚内热证为主运用养阴清热法治疗。基于“辨病－辨型－辨证”精准诊疗 SCLC，有利于中西医结合，优势互补，提高 SCLC 的临床疗效。

4　结语

本文首次系统构建了 SCLC 分子分型与中医证型的映射关系，提出“分子－证候共演化”假说。设计“分型－辨证－复方”精准用药方案，将 SCLC 分子分型与中医辨证论治有机结合，可在一定程度上突破传统治疗的局限性，为个体化精准治疗提供新范式。同时也可在分子层面揭示中医证型的生物学基础（如 SCLC－I 亚型与“阴虚内热、正虚邪恋证”的免疫微环境关联），突破中医理论“抽象化”的瓶颈。虽然这一理论框架需要进一步的基础研究及临床验证，但其整合思维有望为肿瘤治疗提供一定的参考意义。未来需建立分子分型与中医证型的动态关联模型，开发标准化疗效评价体系，开展多中心临床研究，验证基于“分子－证候”双维度的“分型－

辨证－复方”模式的可行性。

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