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云南省宣威地区肺癌研究进展

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摘 要

肺癌严重危害着人类健康，是一个重大的公共卫生问题。位于云南省东北部的宣威地区是全球肺癌死亡率最高的地区之一。近十几年来，研究人员从不同角度探索与揭示宣威肺癌高发的原因及分子机制，从其特殊的环境因素到遗传易感性、DNA甲基化、非编码RNA等分子机制的研究都取得了显著进展。本文综述了宣威地区肺癌特点及其风险因素研究进展。

关键词

地方性肺癌，易感性，DNA甲基化，非编码RNA

Research Progress of Lung Cancer in Xuanwei Area of Yunnan Province

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Abstract

Lung cancer seriously endangers human health and is a major public health problem. The Xuanwei region in northeastern Yunnan province has one of the highest lung cancer mortality rates in the world. In the past ten years, researchers have explored and revealed the causes and molecular mechanisms of the high incidence of lung cancer in Xuanwei from different perspectives. Significant progress has been made in the study of its special environmental factors to molecular mechanisms such as genetic susceptibility, DNA methylation, and noncoding RNA. This paper reviews the research progress on the characteristics and risk factors of lung cancer in Xuanwei area.

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Keywords

Endemic Lung Cancer, Susceptibility, DNA Methylation, Noncoding RNA

1. 引言

肺癌已成为全球死亡的主要原因之一，从世界范围内来看，肺癌的发病率和死亡率在迅速增加，在男性人口中，肺癌分别以 14.3%的发生率和 21.5%的死亡率位居首位，在女性人口中，肺癌死亡率也高达 13.7%，仅次于乳腺癌[1]。我国云南省肺癌发病率较高，尤其宣威地区，是全国乃至世界肺癌的高发区[2]。本文就云南省宣威地区肺癌特点及其风险因素研究进展做一综述。

2. 云南省宣威地区肺癌特点

云南省宣威地区肺癌的流行有其独特的特点。第一，宣威地区肺癌发病率农村高于城市[3]。第二，宣威人群中女性肺癌发病率远高于男性[4]。农村妇女的肺癌患病率居全国首位，是中国其他地区的 20 倍，也是世界上女性肺癌死亡率最高的地区之一。第三，宣威地区肺癌患者的发病和死亡年龄有年轻化的趋势[5]。第四，宣威地区肺癌流行具有明显的家族聚集性，基因突变及遗传可能在其中发挥着重要作用[6]。

3. 风险因素

3.1. 环境影响

宣威地区有丰富的烟煤储量，传统的室内燃煤产生大量致癌物质如多芳环烃(PAHs)及 SiO_2 等[7]。上个世纪八十年代宣威市进行了大规模的改炉改灶工程，改造结束后，宣威市肺癌的死亡率仍维持在较高水平。改造后，无烟囱火塘使用率大大降低，但地炉、高灶或手提炉等的使用效果以及不同煤种燃烧后产生的烟雾物质还需要评估。比如通风炉灶比不通风炉灶、便携式炉灶和火炉具有更低的多环芳烃暴露量[8]，另一项研究通过对比有无长期接触烟煤的家庭妇女发现，前者患癌风险更高[9]。而且在宣威不同地区、不同种类的煤炭燃烧后可导致的患癌风险也不一样，如宣威市来宾镇地处宣威中心地区，该地区呈口袋状，其烟煤燃烧污染物聚集，属于肺癌高发区[6]。

同样，这些烟煤燃烧物中的颗粒物等会沉降在土壤、蔬菜、水果等食物中，绿色蔬菜、蘑菇、鲜肉等的摄入量增加与肺癌风险升高有关[10]，这可能是由于蔬菜等大面积暴露在空气中，对 PAHs 有较高的吸收能力[11]。一项在 2017 年对宣威地区进行的病例对照研究设计中发现，三十多年前的烟雾污染对患癌风险存在滞后效应，这也可以解释为什么在改炉改灶后宣威肺癌死亡率没有出现明显下降趋势[12]。

3.2. 个体易感性

易感性是由基因遗传所决定的个体患病的风险。在环境等外界因素的影响下，基因表达也起着非常重要的作用，相同的基因型可能会有不同的基因表达。在一项以宣威肺癌为基础的病例对照研究表明，端粒长度维持基因中的三个 SNPs 与肺癌风险独立相关，分别是 POT1、TERF2 和 TERT。进一步分析以上染色体端粒长度与肺癌易感性的关系发现端粒长度与肺癌风险并没有明显的相关性，但 POT1 上

rs10244817 位点与端粒长度和肺癌风险存在显著交互作用，并且在 POT1rs10244817 常见变异携带者中，端粒长度与肺癌危险性之间呈剂量－反应关系[13]。

端粒长度失调与多种癌症风险增加有关[14]，对早期非小细胞肺癌患者的肿瘤组织中基因组拷贝数变化进行分析发现在 78%的非小细胞肺癌患者组都出现了 5p15.33 区域增益，该区域的扩增标志着肺癌的易感位点[15]。一项对宣威县非吸烟男性肺腺癌患者及其相应的非肿瘤组织进行的全基因组测序研究中发现 5 号染色体上的 TERT 基因在染色体区域高度增加[16]。位于 5p15.33 的 TERT 是一种端粒酶逆转录酶[17]，端粒酶活性在大多数体细胞分化过程中受到抑制，但在肿瘤中强烈上调。端粒功能障碍是癌症发生的一个基本特征，这提示 TERT 可能参与了多种癌症的发生[18]。此外，在 1355 例云南省非小细胞肺癌患者(宣威 442 例，其他地区 913 例)中，宣威地区不常见 EGFR 突变率为 59.50%，显著高于非宣威地区[19]，另一项以临床为基础的病例对照研究表明有肺癌家族史的个体患肺癌的风险增加且一级女性亲属往往比一级男性亲属有更高的风险[20]。在宣威家族性肺癌研究发现 ANKRD20A2、ZNF812、ARHGEF5、ZNF595 和 MYO18B 在宣威家族性肺癌和肺癌组织中的突变频率高于健康人群[21]，可能是潜在的种系突变基因。但家族史通常是由研究对象自己提供的，未经独立核实[22]，因此关于宣威肺癌的家族聚集性与遗传易感性之间的关系需要进一步研究与发现。

3.3. DNA 甲基化

DNA 甲基化能够在不改变 DNA 序列的前提下，改变遗传表现[23] [24]，DNA 甲基化会受到环境暴露、饮食习惯等其他因素的共同影响，不同研究中同一基因的甲基化水平会因不同种族、肿瘤类型和环境而有差异。Zhang 等人发现了 4 个候选基因(STXBP6、BCL6B、FZD10 和 HSPB6)，与非癌肺组织相比，它们在大多数肿瘤组织中显著高甲基化并表达下调[25]。另一项对宣威地区的肺腺癌组织及其非癌组织进行的基因表达谱分析发现 UHRF1 在七个上调基因中显著升高[26]。

UHRF1 可编码含有 PHD 和环指结构域 1 (UHRF1)的泛素样蛋白[27]，作为表观遗传调控的关键因子它可以连接 DNA 甲基化和染色质修饰[28]。UHRF1 在调节免疫系统和肿瘤发生发展中起着重要作用[29]。UHRF1 在胸腺中高表达，其通过表观遗传沉默调节早期生长反应 1 (EGR1)的表达，此外 UHRF1 与 EGR1 位点 CpG 启动子区域的 DNA 甲基转移酶 1(DNMT1)相互作用，可影响染色质修饰[30]。Tu 等人发现 UHRF1 主要影响肺腺癌的生存和发展以及并与肺腺癌的不良预后有关，在肺腺癌中 UHRF1 的过表达可诱导 UHRF1 关键基因的低甲基化，并通过激活细胞周期途径来促进肺腺癌患者的生存期[31]。由于干扰 DNA 甲基化是癌症临床治疗的重要途径，有研究发现细胞周期调节的蛋白质甲基转移酶 SET8 可通过甲基化介导的泛素依赖的降解来控制 UHRF1 的蛋白质稳定性，从而防止 DNA 过度甲基化，结果提示靶向 UHRF1 的化合物有望成为癌症治疗的靶点[32]。

3.4. 非编码 RNA

近年来越来越多的研究集中在宣威人群中非编码小分子 RNA(miRNAs)、长链非编码 RNA(LncRNAs)及其信号通路在肺癌发病机制中的作用。MiRNAs 是一种长度为 18-24 个核苷酸的的非编码小 RNA [33]，miRNAs 一般通过控制 mRNA 的稳定性、降解和基因翻译来调节基因的表达[34]。MiRNAs 可特异性识别并与靶 mRNA 3′端非翻译区(UTR)上的互补位点结合从而导致转录后基因沉默[33]。许多研究集中对宣威肺癌组织及其配对组织中 miRNAs 差异表达进行分析并得到了不同的结果[35]。

与正常组织及细胞相比，宣威肺癌中 miR-135b-3p、miR-485-5p、miR-135b-5p、miR-9-5p、miR-369-3p、miR-134-5p、miR-224-5p、miR-501-5p、miR-96-5p、miR-938 均表达上调[35]，而 miR-144 [36]、miR-144-5p、miR-598-3p、miR218 [37]、miR-34a [38]表达下调[39]。miR-135b-3p [40]、miR-485-5p [41]、miR-135b-5p

[34] [42]、miR-9-5p [43]、miR-501-5p [44]、miR-96-5p [45]、miR-938 [46]已在不同癌症中如三阴乳腺癌[47]、胃癌[34] [48]、宫颈癌[49]、大肠癌[50]等中发现其过表达可促进细胞增殖、迁移和侵袭；其中 miR-938 过表达可促进肺腺癌细胞增殖[51]，miR-134-5p 可促进早期肺腺癌转移和化疗耐药[52]，miR-501-5p 在宣威肺癌中与患者年龄、TNM 分期、血清 CEA 水平显著相关[53]。有研究表明 miR-302b-3p 可通过下调 N-乙酰氨基葡萄糖转移酶(GCNT3)来降低非小细胞肺癌细胞的增殖、侵袭和转移[54]。

LncRNAs 和 mRNAs 共表达网络分析确定差异表达的 lncRNAs 和 mRNAs 之间显著相关[55] [56]。在宣威肺癌中显著上调的 lncRNAs 有：SGOL1-AS1，SNHG4，PVT1 及显著下调的 lncRNAs：FENDRR，H19，PWRN1 [56]，对宣威肺癌的全基因组关联分析显示 KLF 在宣威肺癌中显著低表达可能降低患者的总体生存率且 FENDDR 与 KLF 的低表达可能会导致细胞周期过度激活从而加速宣威肺癌进展[55]。许多研究表明在非小细胞癌中 FENDRR 表达显著下调，FENDRR 可通过调节细胞的迁移、侵袭和转移而抑制肿瘤的进展[57] [58]。此外 lncRNA CAR10 的过度表达与空气污染有关，研究表明烟煤燃烧致癌物二苯并[a, h]蒽通过增加转录因子 FoxF2 的表达上调 CAR10 的表达，从而促进肺癌细胞增殖[59]。

4. 小结

肺癌的发生发展是一个极其复杂的过程，宣威地区肺癌是否有特殊的发病机制还需大量体内外的生物学实验来探究。从宣威地区独特的环境因素到人群个体易感性、DNA 甲基化、非编码 RNA 等多方面的探索为揭示宣威肺癌高发的原因提供了基础。综上，宣威肺癌是环境因素和遗传因素长期共同作用的结果，为进一步探究和了解宣威肺癌发生的复杂机制，积极探索宣威肺癌发生的环境因素与遗传因素的交互作用对研究宣威肺癌是重要且必须的。

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