论著·基础医学

苯并(a)芘通过NLRP3焦亡信号通路促进肺癌细胞LTEP-a-2恶性进展:基于生物信息学与细胞实验验证

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[**摘要**]　**目的**　苯并(a)芘(benzopyrene,BaP)作为最常见的多环芳烃类污染物,具有强效致癌、致畸和炎症毒性作用,既往研究发现,BaP可通过抑制人支气上皮细胞恶性转化后的铁死亡进而促进其侵袭与迁移能力,但尚不明确BaP能否调控肿瘤细胞焦亡,本研究目的是为了阐明BaP通过抑制LTEP-a-2细胞焦亡促进肺癌侵袭和迁移的作用机制。**方法**　基于比较毒理基因组学数据库(comparative toxicogenomics database,CTD)获取BaP可能的潜在基因;基于基因表达数据库(gene expression omnibus,GEO)筛选肺癌相关差异基因。对上述2组基因进行交集分析,获取候选基因集。通过STRING数据库进行蛋白-蛋白相互作用(protein-protein interaction,PPI)网络分析,利用Cytoscape软件进行拓扑属性分析,依据节点度值筛选关键核心靶基因。通过Kaplan-Meier Plotter数据库对PPI网络筛选出的候选基因进行生存分析。采用AutoDock Vina对BaP与各靶蛋白进行分子对接模拟,预测其结合构象并计算结合自由能。使用PyMOL软件进行可视化与分析,通过LigPlot+生成二维相互作用图展示与分析配体-受体间的相互作用。使用梯度浓度BaP(0、0.1、1和10 μmol/L)处理人肺癌细胞LTEP-a-2 48 h,通过CCK-8法检测细胞活力,Transwell实验分析细胞侵袭迁移能力,LDH释放实验评估细胞毒性,采用Annexin V-FITC/PI流式细胞术检测细胞凋亡;通过ELISA定量上清中IL-1β和IL-18水平,采用RT-qPCR和Western blot检测焦亡关键分子(NLRP3、ASC、Caspase-1、GSDMD、IL-1β、IL-18)表达。采用BaP联合焦亡激动剂以及焦亡抑制剂联合焦亡激动剂处理后检测细胞活力与侵袭迁移能力,分析焦亡相关指标(IL-1β/IL-18释放、焦亡关键分子表达)的变化。**结果**　体外实验表明,与对照组相比,1和10 μmol/L BaP处理能显著促进人肺癌细胞LTEP-a-2的增殖与侵袭迁移能力($P<0.01$),但未引起细胞凋亡的显著变化。生物信息学分析提示BaP相关基因显著富集于细胞焦亡通路。不同剂量BaP处理显著抑制了细胞焦亡,表现为LDH释放减少($P<0.05$),炎症因子IL-1β和IL-18的分泌下调,以及焦亡通路关键分子(NLRP3、ASC、Caspase-1、GSDMD、IL-1β、IL-18)的mRNA和蛋白表达均显著下降($P<0.05$)。与之相反,焦亡激动剂处理(与对照组相比)则诱发了明显的焦亡表型,并抑制了细胞增殖与侵袭迁移能力($P<0.05$)。而BaP或焦亡抑制剂联合焦亡激动剂处理组中,焦亡激动剂对肿瘤细胞增殖和侵袭迁移能力的抑制效应均被显著回复($P<0.01$)。生信预测及分子对接提示NLRP3和PTGS2可能是BaP调控肺癌细胞焦亡的潜在作用靶点。**结论**　BaP可通过抑制LTEP-a-2细胞NLRP3-Caspase-1-GSDMD焦亡信号通路,进而促进其侵袭和迁移。

[**关键词**]　苯并(a)芘;细胞焦亡;肺癌;侵袭和迁移
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Benzo(a)pyrene promotes malignant progression of human lung cancer LTEP-a-2 cells through the NLRP3 pyroptosis signaling pathway: Validation based on bioinformatics and cellular experiments

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[**Abstract**] **Objective** Benzo(a)pyrene (BaP), as the most common polycyclic aromatic hydrocarbon pollutant, exhibits potent carcinogenic, teratogenic, and inflammatory toxic effects. Previous studies have demonstrated that BaP promotes invasion and migration capabilities of human bronchial epithelial cells following malignant transformation by suppressing ferroptosis; however, whether BaP can regulate tumor cell pyroptosis remains unclear. This study aims to elucidate the mechanism by which BaP promotes lung cancer invasion and migration through suppressing pyroptosis in human lung cancer cell line LTEP-a-2. **Methods** Potential target genes of BaP were retrieved from the Comparative Toxicogenomics Database (CTD), and lung cancer-related differentially expressed genes (DEGs) were screened from the Gene Expression Omnibus (GEO) database. Subsequently, an intersection analysis of these 2 gene sets was performed to obtain key candidate genes. Protein-Protein Interaction (PPI) network analysis on these candidate genes was conducted using the STRING database, and topological attribute analysis was performed for topological properties with Cytoscape software to screen key hub target genes based on high node degree values. Survival analysis of these PPI-derived hub genes was performed using the Kaplan-Meier Plotter database. Molecular docking simulations between BaP and each target protein were conducted with AutoDock Vina to predict binding conformations and calculate binding free energies. Visualization and analysis of the docking results were carried out using PyMOL software, and detailed ligand-receptor interactions were visualized and analyzed using 2D interaction diagrams generated by LigPlot+. LTEP-a-2 cells were exposed to gradient concentrations of BaP (0, 0.1, 1, and 10 μmol/L) for 48 h. Subsequently, cell viability was evaluated with CCK-8 assay, invasive and migratory capabilities were assessed with Transwell assay, cytotoxicity was determined by lactate dehydrogenase (LDH) release assay, and apoptosis was detected *via* Annexin V-FITC/PI flow cytometry. The concentrations of IL-1β and IL-18 in the supernatant were determined by enzyme-linked immunosorbent assay (ELISA). RT-qPCR and Western blotting were performed to measure the expression of key pyroptosis-related molecules (NLRP3, ASC, caspase-1, GSDMD, IL-1β, and IL-18) at mRNA and protein levels. Cell viability and invasive/migratory capabilities were assessed after LTEP-a-2 cells treated with BaP combined with pyroptosis agonists, as well as pyroptosis inhibitors combined with pyroptosis agonists. Concurrently, alterations in pyroptosis-related indicators, including IL-1β/IL-18 release and expression of the aforementioned key molecules, were examined. **Results** *In vitro* experiments demonstrated that compared to the control group, exposure to 1 or 10 μmol/L BaP significantly promoted the proliferation, invasion, and migration of LTEP-a-2 cells ($P<0.01$), but did not induced obvious changes in apoptosis. Bioinformatics analysis revealed significant enrichment of BaP-related genes in the pyroptosis pathway. Treatment with different doses of BaP significantly inhibited pyroptosis, as evidenced by reduced LDH release ($P<0.05$), downregulated secretion levels of the inflammatory cytokines IL-1β and IL-18, and notable decreases in both mRNA and protein expression levels of key molecules in the pyroptosis pathway (NLRP3, ASC, caspase-1, GSDMD, IL-1β, and IL-18) ($P<0.05$). Conversely, pyroptosis agonist (compared to the control group) induced pronounced pyroptotic phenotypes and suppressed cell proliferation and invasive and migratory capacities ($P<0.05$). In the BaP or pyroptosis inhibitor combined with pyroptosis agonist treatment groups, the inhibitory

effects of the agonists on tumor cell proliferation and invasion/migration were significantly reversed ($P<0.01$). Bioinformatics prediction and molecular docking analysis indicated that NLRP3 and PTGS2 may serve as potential molecular targets for BaP-mediated regulation of pyroptosis in lung cancer cells. **Conclusion** BaP promotes the invasion and migration of LTEP-a-2 cells by inhibiting the NLRP3-caspase-1-GSDMD pyroptosis signaling pathway.

[**Key words**] benzo(a)pyrene; pyroptosis; lung cancer; invasion and migration

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多环芳烃(polycyclic aromatic hydrocarbons,PAHs)作为广泛存在的环境污染物,可通过多种途径进入人体造成损伤,长时间暴露可导致肿瘤等严重后果[1]。苯并(a)芘(benzopyrene,BaP)是最常见的多环芳烃类污染物,其代谢产物因具有强效致癌、致畸和炎症毒性作用而备受关注,被世界卫生组织的国际癌症研究机构列为Ⅰ类致癌物[2]。BaP主要来源于空气污染,在工业废气、汽车尾气、香烟烟雾和厨房油烟中可以检测到较高浓度存在,其进入人体的最常见途径包括吸入、摄入和皮肤接触[3]。流行病学调查数据显示长期暴露在含有BaP的环境中肺癌的发病风险显著升高[4]。因此,深入探讨BaP促进肺癌发生发展的作用机制,对于筛选有效生物标志物应用于肺癌早期预警和防治,维护人群健康具有重要意义。

研究报道BaP促进恶性进展的关键在于它能够抑制肿瘤细胞的程序性死亡(programmed cell death,PCD),从而使细胞逃避死亡信号、持续增殖并获得更强的侵袭/转移能力[5]。PCD是由多种高度调控的死亡方式组成的复杂系统,经典的途径包括凋亡、焦亡和坏死性凋亡等多种形式[6-8]。对肿瘤细胞PCD的深入研究,不仅可以拓展对生命过程精密调控机制的认识,也为多种疾病的机制解析及靶向治疗策略的开发提供了新视角和潜在干预靶点。有研究指出,BaP可通过改变DNA甲基化、组蛋白修饰等方式整体抑制多种凋亡促进基因的转录,形成“凋亡抑制”的表观遗传环境[9]。最新报道也发现BaP通过激活Cx43/GJIC信号轴抑制小鼠肝癌细胞凋亡[10]。本课题组前期研究发现,BaP可通过抑制人支气上皮细胞恶性转化后的铁死亡进而促进其侵袭与迁移能力[11]。提示PCD可能在BaP促肺癌进展中发挥重要作用。

细胞焦亡作为一种典型的PCD,是一种免疫原性细胞死亡方式,在肿瘤进展中扮演着双重角色。一方面,细胞焦亡可直接诱导肿瘤细胞死亡,通过释放炎症因子激活抗肿瘤免疫反应,增强免疫细胞对肿瘤的清除能力[12]。而另一方面,过度焦亡可能导致慢性炎症微环境,促进肿瘤恶性进展[13]。研究发现纳米药物能通过诱导肿瘤细胞焦亡,进而发挥其抑癌作用[14],α-亚麻酸可通过激活GPR120/Caspase-1/GSDMD信号轴触发焦亡抑制卵巢癌进展[15]。但是,目前关于BaP能否调控肿瘤细胞焦亡的研究尚未见报道。本研究旨在探讨BaP是否通过调控焦亡信号通路影响肺癌细胞的侵袭和迁移能力,以揭示环境致癌物促进肺癌进展的作用机制,并为多环芳烃类污染物致肺癌的防治策略提供参考依据。

1 材料和方法

1.1 细胞

人源肺癌细胞株LTEP-a-2购自中国科学院典型培养物保藏委员会细胞库。

1.2 主要试剂与仪器

RPMI-1640培养基购自美国Gibco公司;低内毒素胎牛血清购自中国杭州四季青公司;BaP和二甲基亚砜(dimethyl sulfoxide, DMSO)均购自美国Sigma公司;脂多糖(LPS)、尼日利亚菌素(Nigericin)和MCC950均购自美国MCE公司;Transwell小室购自美国康宁公司;ELISA试剂盒购自中国爱博泰克生物科技有限公司;细胞增殖CCK-8试剂盒购自北京索莱宝科技有限公司;HRP标记的山羊抗兔和山羊抗鼠IgG、细胞LDH释放检测试剂盒、蛋白裂解液、BCA蛋白定量试剂盒以及SDS-PAGE配胶试剂盒均购自上海碧云天生物技术有限公司;细胞凋亡检测试剂盒购自美国BD公司;NLRP3抗体(鼠源)、GSDMD抗体(鼠源)、ASC抗体(兔源)、Caspase-1抗体(兔源)、IL-1β抗体(兔源)、IL-18抗体(兔源)、GAPDH抗体(兔源)均购自武汉三鹰公司;超敏ECL化学发光试剂盒购自赛默飞世尔科技有限公司;WB成像仪FUSION FX5购自中国北京五洲东方科技发展有限公司;光学显微镜购自德国Leica公司;透射电镜购自日本JEOL公司。

1.3 细胞培养和传代

用含10%胎牛血清和1%双抗的1640培养基培养LTEP-a-2细胞,培养箱条件设置为37 ℃、5% CO_2,定期更换培养基,每日观察和记录细胞状态,待细胞

密度达到80%~90%时进行传代处理。

1.4 BaP处理LTEP-a-2细胞和实验分组

取对数生长期的LTEP-a-2细胞以每孔5 000个(96孔板)或2×10^{5}个(6孔板)的密度分别接种,培养24 h后观察细胞状态与贴壁情况。BaP粉末使用二甲基亚砜(DMSO)溶解,配制成0.1、1、10 mmol/L和20 mmol/L的储备液。染毒时采用含10%胎牛血清的1640培养基进行稀释,处理各组的终浓度分别为0(对照组)、0.1、1 μmol/L和10 μmol/L。

1.5 细胞凋亡检测

采用Annexin V-FITC/PI双染细胞凋亡检测试剂盒检测细胞凋亡。具体操作如下:首先收集约1×10^5~1×10^{6}个细胞,经预冷PBS洗涤后,用适量Binding Buffer重悬。随后向细胞悬液中加入Annexin V-FITC和PI荧光染料,轻轻涡旋混匀,在室温避光条件下孵育15 min。最后,通过流式细胞仪对细胞凋亡情况进行分析。

1.6 焦亡激动剂与BaP或MCC950联合处理LTEP-a-2和实验分组

取对数生长期的LTEP-a-2细胞以每孔2×10^{5}个的密度接种于6孔板中,分为对照组、焦亡激动剂(LPS+nigericin)处理组、BaP联合焦亡激动剂(LPS+nigericin)处理组,以及焦亡抑制剂(MCC950)联合焦亡激动剂(LPS+Nigericin)组进行处理。先将Nigericin、LPS和MCC950配制成10 mmol/L储备溶液,使用时均以培养基稀释至相应工作浓度。根据预实验结果,焦亡激动剂组(LPS+Nigericin)于培养42 h后更换为含1 μg/mL LPS的无血清培养基,继续培养4 h,再加入10 μmol/L Nigericin处理2 h。BaP联合焦亡激动剂组先以10 μmol/L BaP染毒42 h,随后更换为含10 μmol/L BaP和1 μg/mL LPS的无血清培养基继续培养4 h,再加入10 μmol/L Nigericin处理2 h。MCC950联合焦亡激动剂组于培养41 h后更换为含1 μg/mL LPS的无血清培养基培养4 h,再换用含10 μmol/L MCC950的无血清培养基预处理1 h,最后加入10 μmol/L Nigericin处理2 h。对照组在各实验组换液时同步更换无血清培养基。

1.7 细胞活力测定

各组细胞处理48 h后,弃原培养基,在避光及无菌条件下,每孔加入100 μL由培养基与CCK-8试剂按9∶1比例配制的混合液。将细胞置于培养箱中孵育2 h,使用酶标仪于450 nm波长下测定各孔的光密度(*OD*)值。细胞存活率按以下公式计算:细胞存活率(%)=[(*OD*实验组-*OD*空白组)/(*OD*对照组-*OD*空白组)]×100%。

1.8 Transwell侵袭及迁移实验

使用胰蛋白酶消化各处理组细胞后计数,将3×10^{4}个细胞接种于Transwell小室中(细胞侵袭实验:预先在小室中铺基质胶;细胞迁移实验:不铺基质胶),培养24 h后固定、染色并拍照,分析各组LTEP-a-2细胞侵袭和迁移能力的变化。

1.9 细胞形态学观察

各组细胞处理48 h后,通过光学显微镜和透射电子显微镜观察细胞焦亡小体的形态变化[16-17]。

1.10 LDH释放实验

将LTEP-a-2细胞接种于96孔板中,分组处理48 h后,按说明书方法收集细胞培养上清液,经500 ×*g*离心5 min去除细胞碎片。采用乳酸脱氢酶(LDH)释放测定试剂盒检测细胞毒性。

1.11 酶联免疫吸附测定(ELISA)

收集各组细胞上清液,并于1 000 ×*g*、4 ℃条件下离心10 min。随后,按照制造商说明书,使用ELISA试剂盒对IL-1β和IL-18的浓度进行定量分析。利用多功能酶标仪在450 nm波长下测定光密度(*OD*)值,测定时间为5 min,并据此计算细胞因子的最终浓度。

1.12 定量实时荧光定量PCR(RT-qPCR)

采用Trizol法从各组细胞中提取总RNA,随后使用RevertAid First Strand cDNA Synthesis Kit进行逆转录反应合成cDNA。利用TB Green Advantage® qPCR预混液进行实时荧光定量PCR实验,并通过$2^{-\Delta\Delta Ct}$方法对所得数据进行数据分析。

1.13 Western blot蛋白印迹实验

使用RIPA裂解物提取各组蛋白质,并用超声波破碎机均质化。高速离心后,收集上清液,用BCA法定量。通过SDS-PAGE电泳分离一定量的30 μg蛋白溶液,转移到聚偏二氟乙烯(PVDF)膜上,在脱脂牛奶中封闭并与抗NLRP3抗体、抗ASC抗体、抗Caspase-1抗体、抗GSDMD抗体、抗IL-1β抗体、抗IL-18抗体、抗GAPDH抗体在4 ℃下过夜。最后,与适当的二抗孵育后,通过ECL化学发光法检测靶蛋白条带,并使用Image J软件对蛋白条带进行量化。

1.14 生物信息学分析BaP可能作用的相关通路

本研究首先从GEO数据库(数据集号:GSE32863)下载肺癌微阵列数据,对原始表达矩阵进行log2转换。随后,利用limma包的removeBatchEffect函数消除批次效应,并基于limma的线性模型筛选肺癌组织与癌旁正常组织间的差异表达基因(differentially expressed genes, DEGs)。接着,在比较毒理基因组学数据库(comparative toxicogenomics database, CTD)中检索BaP的潜在作用靶基因,并通过Venny 2.1.0(https://bioinfogp.cnb.csic.es/tools/venny/)

在线工具将DEGs与BaP靶基因进行交叉比对,获得交集基因。随后,使用clusterProfiler包的bitr函数将交集基因映射为Entrez ID。针对生物过程(biological process,BP),利用enrichGO函数进行GO富集分析,多重假设检验校正采用Benjamini-Hochberg方法,显著性阈值设定为$P<0.05$且校正后Q值<0.2。最后,利用dotplot可视化富集结果,展示显著性最高的前8个GO条目,并将结果图像保存用于后续展示。

1.15 构建蛋白质-蛋白质相互作用(protein-protein interaction,PPI)网络及鉴定核心目标基因

利用STRING平台对交集基因进行PPI网络分析,并完成网络图谱的可视化。随后,将PPI网络数据导入Cytoscape软件(版本3.10.2),进行拓扑属性分析。依据节点度值筛选关键核心靶基因。

1.16 生存预后分析

为验证候选基因的临床意义,我们通过Kaplan-Meier Plotter数据库(涵盖TCGA、GEO等大型肺癌队列)对PPI网络筛选出的枢纽基因进行生存分析。

1.17 分子对接及可视化分析

为系统评估BaP与关键靶蛋白的相互作用,本研究采用分子对接方法进行分析。关键靶蛋白的三维结构均来源于蛋白质数据库(protein data bank,PDB)。BaP的三维结构及其立体化学信息取自PubChem数据库(CID:2336)。在对接前,使用PyMOL软件对靶蛋白结构进行预处理,包括去除原始配体及溶剂分子。随后,利用AutoDockTools的结构优化模块为蛋白质添加氢原子,分配Gasteiger电荷,并进行能量最小化处理以优化结构。最终,采用AutoDock Vina(v1.1.x)执行盲对接模拟,获取BaP与各靶蛋白的结合模式及结合自由能。

分子对接获得的结合模式三维结构结果,使用PyMOL(PyMOL 3.0.3)进行可视化与分析。配体-受体间的相互作用细节,则通过LigPlot+(v2.3.1)生成二维相互作用图进行展示与分析。

1.18 统计学分析

所有数据使用SPSS 23.0或GraphPad Prism 8.0软件进行分析。两组间比较采用t检验评估统计学显著性差异;多组间比较则使用单因素方差分析。$P<0.05$视为差异具有统计学意义。

2 结果

2.1 BaP染毒增强LTEP-a-2细胞活力、侵袭和迁移能力

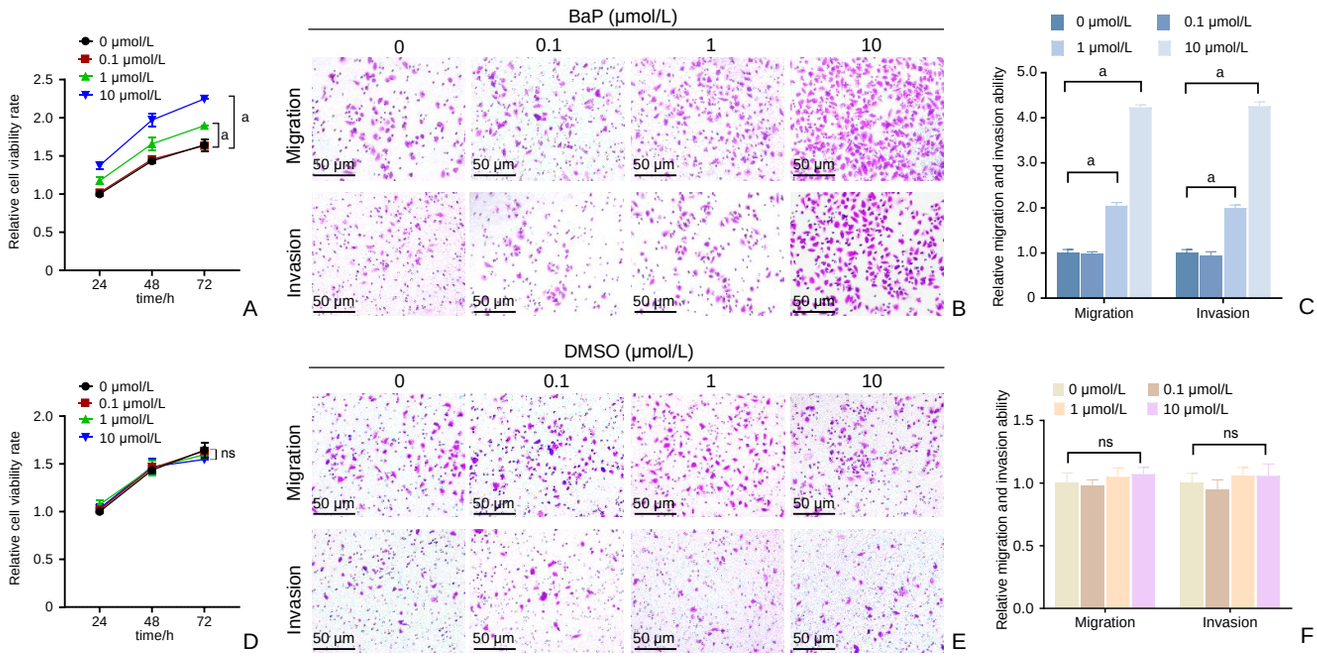
为探究BaP对LTEP-a-2细胞活力、侵袭和迁移能力的影响,我们首先通过CCK-8法检测梯度浓度BaP处理LTEP-a-2细胞24、48和72 h后的细胞活力变化。结果发现,在同一时间节点,与对照组相比,0.1 μmol/L BaP处理组的细胞活力未见显著变化,而在1和10 μmol/L BaP处理后细胞活力明显升高,当BaP终浓度为10 μmol/L时,细胞活力增强最显著($P<0.01$,图1A)。Transwell实验结果显示,0.1 μmol/L BaP处理对细胞侵袭和迁移能力无显著影响;但在1和10 μmol/L BaP处理条件下,细胞的侵袭和迁移能力明显增强,10 μmol/L BaP组增强最显著($P<0.01$,图1B、C)。为排除溶剂干扰,以等效浓度DMSO处理细胞,其增殖、侵袭及迁移能力均未出现明显变化(图1D~F)。以上结果表明浓度为10 μmol/L的BaP暴露可显著增强LTEP-a-2细胞的增殖、侵袭和迁移能力。

2.2 BaP对LTEP-a-2细胞凋亡无显著影响但抑制LTEP-a-2细胞焦亡发生

为探究BaP影响肺癌细胞进展的潜在分子途径,我们首先利用CTD数据库筛选可能与BaP相互作用的基因,并基于GEO数据库的GSE32863数据集进行差异表达分析。通过Venn交叉分析获得交集基因后,进一步对这些基因进行GO富集分析(图2A)。结果显示,BaP相关基因显著富集于细胞凋亡和焦亡相关信号通路(图2B)。随后,采用流式细胞术检测不同处理组细胞的凋亡水平,并通过光学显微镜和透射电子显微镜观察各组细胞焦亡形态学特征。结果显示,BaP以不同剂量处理后细胞凋亡水平无显著变化(图2C、D)。但是与对照组相比,焦亡激动剂(LPS+nigericin)处理组细胞中出现大量焦亡小泡;而且BaP联合焦亡激动剂(LPS+nigericin)及焦亡抑制剂MCC950联合焦亡激动剂(LPS+nigericin)处理组均显著逆转了这一现象(图2E)。以上结果表明,BaP可抑制LTEP-a-2细胞焦亡发生。

2.3 BaP抑制LTEP-a-2细胞焦亡关键分子的表达

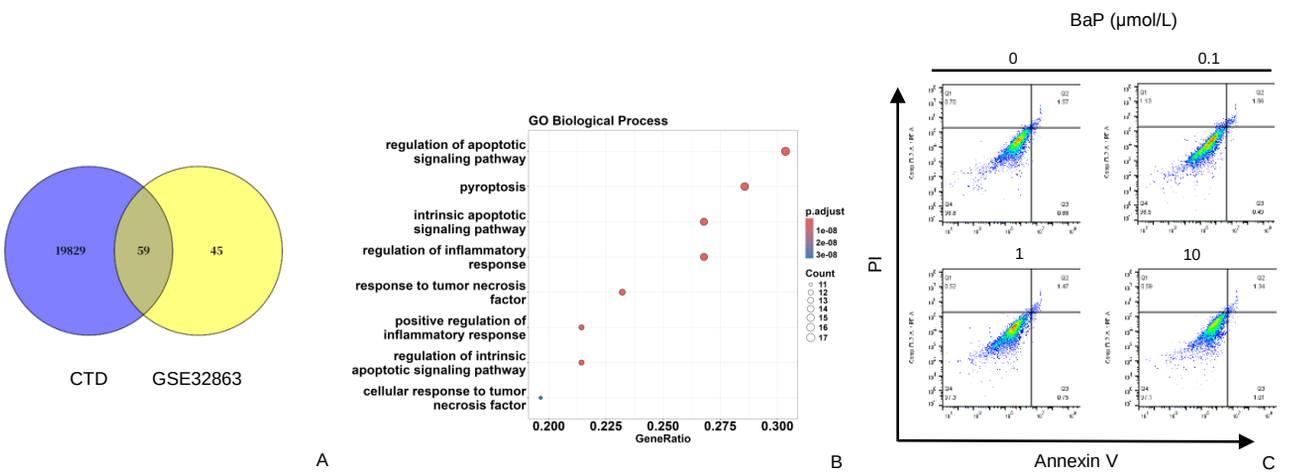
BaP染毒后各组LDH释放实验结果显示,随着BaP浓度(0~10 μmol/L)升高,LDH释放呈现逐渐下降趋势,其中10 μmol/L处理组下降最显著($P<0.01$,图3A)。通过ELISA检测细胞释放的IL-18和IL-1β水平,结果显示,这两种细胞因子的释放水平与BaP染毒呈现剂量依赖下降趋势,在10 μmol/L BaP处理组中下降最显著($P<0.05$,图3B、C)。此外,RT-qPCR和Western blot检测各处理组焦亡相关分子的表达水平,与未处理组相比,不同浓度(0.1~10 μmol/L)的BaP染毒后,NLRP3、ASC、Caspase-1和GSDMD在mRNA和蛋白水平均出现下调,在10 μmol/L染毒组中相关分子表达最低($P<0.05$,图3D~F)。以上结果进一步证实BaP暴露可抑制LTEP-a-2细胞焦亡相关信号通路。



A and D: Changes in LTEP-a-2 cells viability after exposure to different concentrations of BaP (A) and DMSO (D); B, C and E, F: Changes in the invasive and migratory capacities of LTEP-a-2 cells after exposure to different concentrations of BaP (B and C) and DMSO (E and F). Scale bar indicates 50 μm. BaP: benzo(a)pyrene; ns: not significant. a: $P<0.01$

图1 不同浓度的BaP染毒LTEP-a-2细胞活力、侵袭能力和迁移能力变化

Figure 1 Changes in cell viability and invasive and migratory capacities of LTEP-a-2 cells exposed to different concentrations of BaP

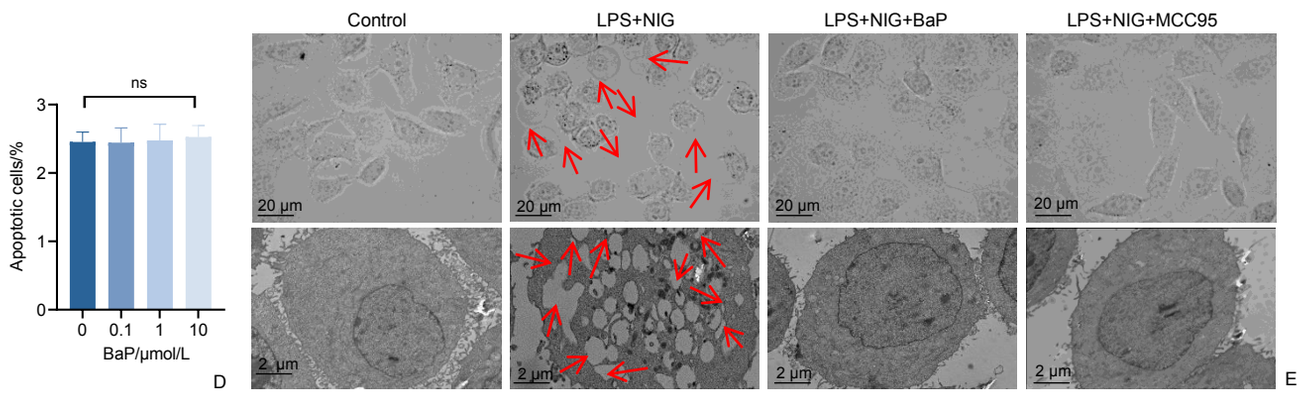


A: Venn diagram illustrating the overlap between predicted BaP target genes (from CTD) and differentially expressed genes identified in the GSE32863 dataset; B: Bar chart depicting the top significantly enriched Gene Ontology (GO) biological processes (BP) terms for the overlapping genes identified in panel A; C and D: Quantification of apoptosis levels in LTEP-a-2 cells treated with different concentrations of BaP, as measured by Annexin V/PI flow cytometry. Data are presented as mean±SD (n=3);

图2 BaP抑制LTEP-a-2细胞的焦亡

Figure 2 BaP inhibits pyroptosis in LTEP-a-2 cells

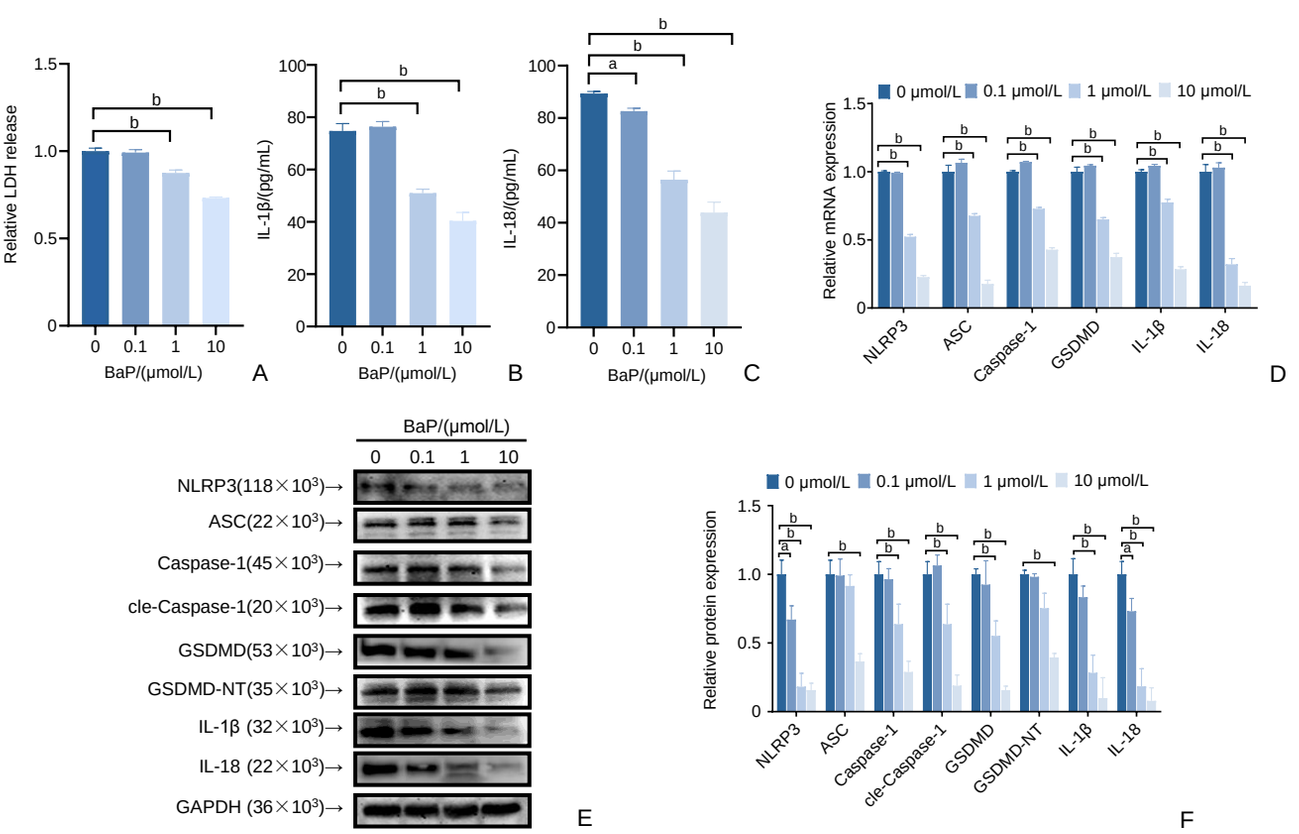
(图2D~E续下页)



C and D: Quantification of apoptosis levels in LTEP-a-2 cells treated with different concentrations of BaP, as measured by Annexin V/PI flow cytometry. Data are presented as mean±SD (n=3); E: Representative light microscopy (scale bar =20 μm) and transmission electron microscopy (TEM; scale bar=2 μm) images of LTEP-a-2 cells from the following experimental groups: Control, pyroptosis agonist (LPS+Nigericin), BaP+Pyroptosis agonist (LPS+Nigericin) and MCC950+Pyroptosis agonist (LPS+Nigericin). BaP: benzo(a)pyrene; ns: not significant

续图2 BaP抑制LTEP-a-2细胞的焦亡

Figure 2(Continued) BaP inhibits pyroptosis in LTEP-a-2 cells



A: LDH release in LTEP-a-2 cells after exposure to different concentrations of BaP; B and C: Changes in IL-1β and IL-18 in LTEP-a-2 cell culture medium after exposure to different concentrations of BaP detected by ELISA; D and E: mRNA (D) and Protein (E) levels of apoptosis-related molecules in LTEP-a-2 cells after exposure to different concentrations of BaP; F: Relative protein expression levels of pyroptosis-related molecules NLRP3, ASC, Caspase-1, GSDMD, IL-1β, and IL-18 in LTEP-a-2 cells after exposure to different concentrations of BaP. BaP: benzo(a)pyrene; LDH: lactate dehydrogenase. a: P<0.05, b: P<0.01

图3 BaP抑制LTEP-a-2细胞焦亡关键分子的表达

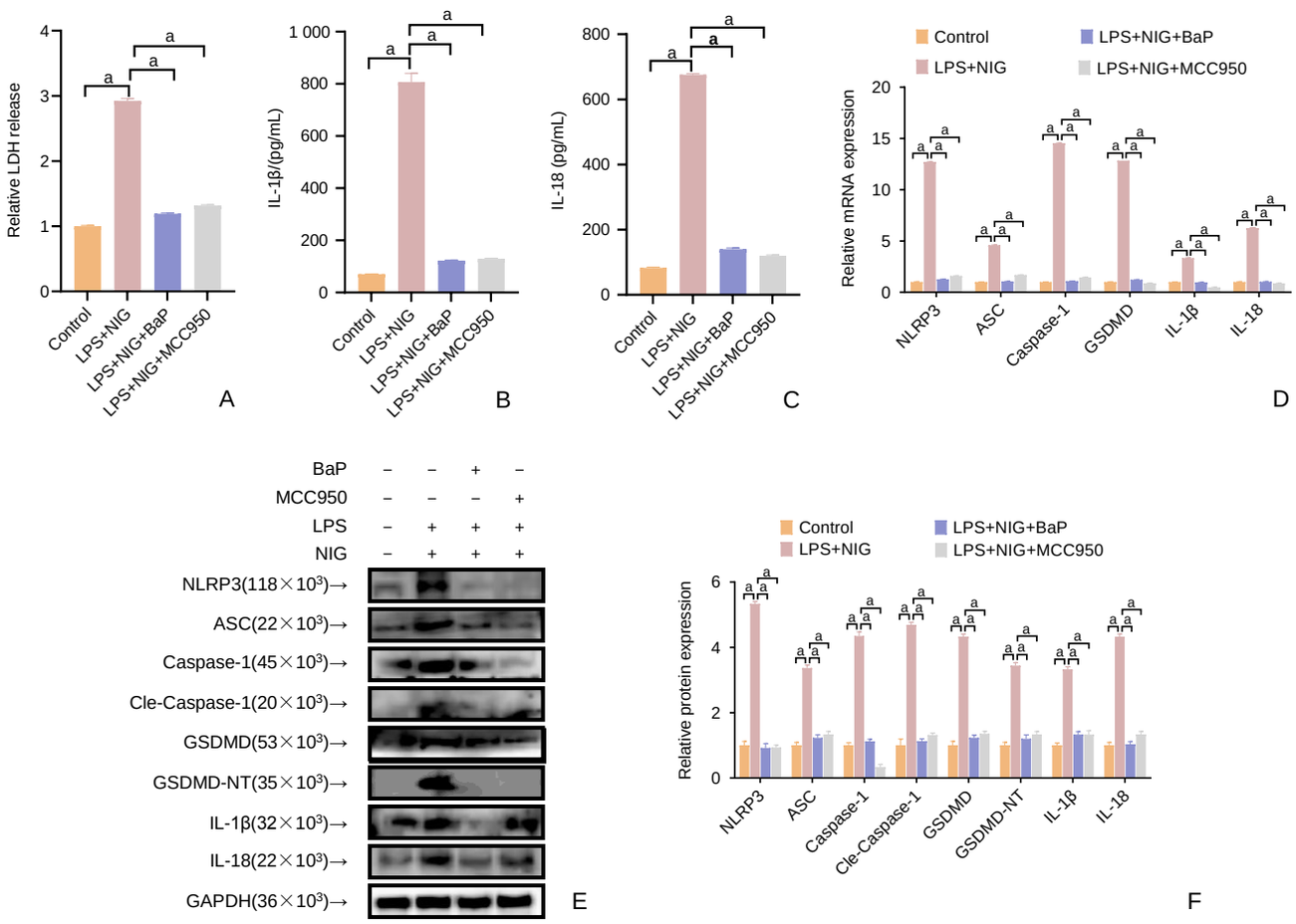
Figure 3 BaP inhibits the expression of key pyroptosis-associated molecules in LTEP-a-2 cells

2.4 焦亡激动剂单独或联合BaP、MCC950处理对LTEP-a-2细胞焦亡的影响

LDH释放实验结果显示,与对照组相比,焦亡激动剂组的LDH释放水平显著升高,而BaP联合焦亡激动剂组及MCC950联合焦亡激动剂组的LDH释放水平均显著降低(P<0.01,图4A)。通过ELISA检测细胞因子释放水平发现,焦亡激动剂组中IL-1β和IL-18的释放显著上升,而BaP联合焦亡激动剂组及MCC950联合焦亡激动剂组的IL-1β和IL-18水平均较诱导组显著下降(P<0.01,图4B、C)。RT-qPCR和Western blot实验结果显示,焦亡激动剂处理后,NLRP3、ASC、Caspase-1和GSDMD在mRNA和蛋白水平均显著上调;而BaP或MCC950与焦亡激动剂联合处理则显著抑制了这些分子的表达(P<0.01,图4D~F)。以上结果表明,BaP能够有效抑制LTEP-a-2细胞的焦亡过程及NLRP3/Caspase-1/GSDMD信号通路。

2.5 焦亡激动剂单独或联合BaP、MCC950处理对LTEP-a-2细胞活力、侵袭和迁移能力的影响

CCK-8实验结果显示,相较于对照组,焦亡诱导剂(LPS+Nigericin)处理显著抑制了细胞活力(P<0.01,图5A)。然而,在焦亡诱导剂基础上联合BaP或MCC950处理,均能显著恢复细胞活力(P<0.01,图5A)。Transwell实验进一步证实,焦亡诱导剂处理显著降低了细胞的迁移与侵袭能力(P<0.01,图5B、C);该抑制效应同样被BaP或MCC950联合处理显著逆转(P<0.01,图5B、C)。为明确细胞焦亡对LTEP-a-2细胞恶性表型的影响,我们设置了以下处理组:空白对照(BaP 0 μmol/L)、DMSO对照(10 μmol/L)、单独BaP



A: LDH release in each group of cells; B and C: Changes in IL-1β (B) and IL-18 (C) in the culture medium of each group of cells; D and E: mRNA (D) and protein (E) levels of pyroptosis-related molecules in each group; F: Relative protein expression of pyroptosis-related molecules NLRP3, ASC, Caspase-1, GSDMD, IL-1β, and IL-18 in each group of cells. BaP: benzo(a)pyrene; LDH: lactate dehydrogenase. a: P<0.01

图4 BaP通过NLRP3/Caspase-1/GSDMD通路调控细胞焦亡

Figure 4 BaP regulates pyroptosis via the NLRP3/Caspase-1/GSDMD pathway

(10 μmol/L)以及BaP(10 μmol/L)联合焦亡诱导剂(LPS+Nigericin)。通过CCK-8和Transwell实验检测发现,BaP能显著逆转焦亡诱导剂对细胞增殖、侵袭和迁移能力的抑制作用(图5D~F)。上述结果表明,BaP可通过抑制LTEP-a-2细胞焦亡进而促进其增殖、侵袭和迁移能力。

2.6　整合PPI网络与生存分析鉴定BaP促进肺癌的关键靶点

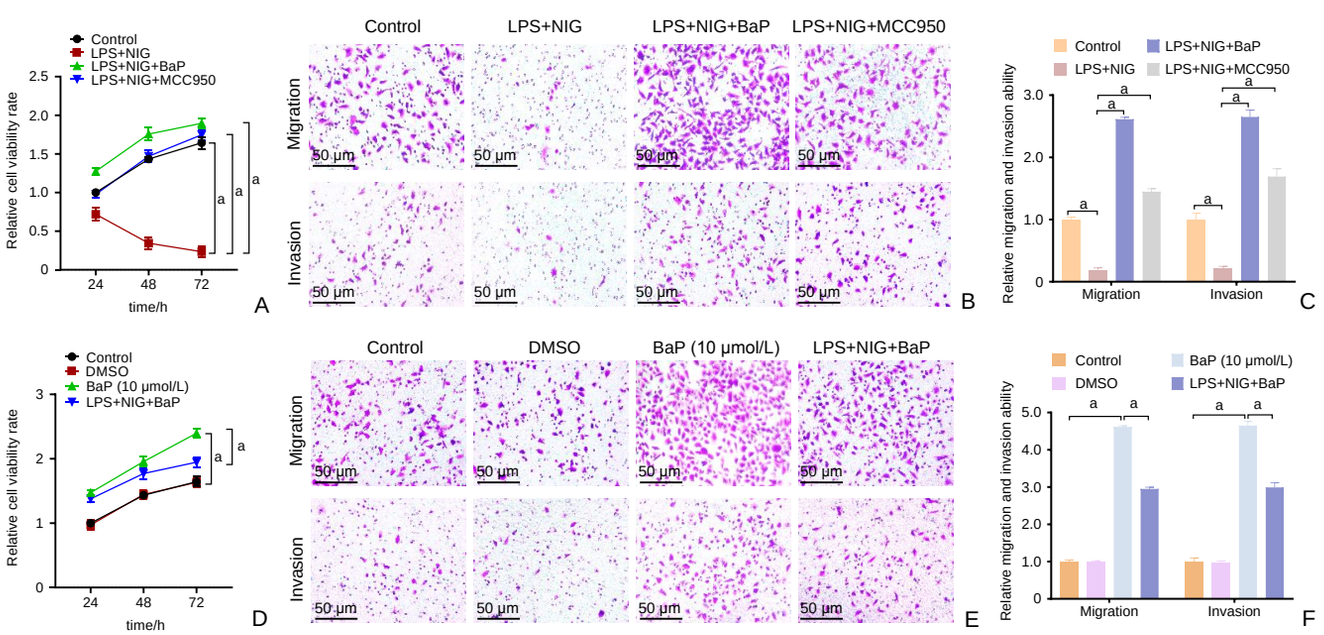
为识别BaP促进肺癌进展的关键靶点,我们首先在STRING数据库中对差异表达基因进行PPI网络分析(图6A)。随后,利用Cytoscape软件对PPI网络进行拓扑属性分析,并依据节点度值筛选关键核心基因(图6B)。结果表明,TP53、Caspase-3、HIF1A、AKT1、PTGS2、IL1B、NLRP3和Caspase-1可能是BaP的潜在作用靶点。为评估这些基因在肺癌中的临床意义,我们在Kaplan-Meier Plotter公共数据库进行了生存分析(图6C~J),结果显示NLRP3、PTGS2和Caspase-1的高表达与肺癌患者总生存期的延长显著相关。结果提示NLRP3、PTGS2和CASP1可能是BaP促进肺癌进展的潜在作用靶点。

2.7　BaP潜在作用靶点的分子对接验证

为验证BaP与NLRP3、PTGS2及CASP1的结合能力,我们从PDB数据库下载了NLRP3(ID:7PZC)、PTGS2(ID:5F19)和Caspase-1(ID:8WRA)的蛋白结构,并将它们与BaP进行了盲对接。对接结果显示,NLRP3-BaP和PTGS2-BaP的结合能均低于-7 kJ/mol(对接阈值),表明结合较强;而Caspase-1-BaP的结合能为-6.5 kJ/mol,相对较弱(图7A~C)。这些结果表明,BaP可能主要通过作用于NLRP3和PTGS2,进而影响肺癌细胞焦亡水平。

3　讨论

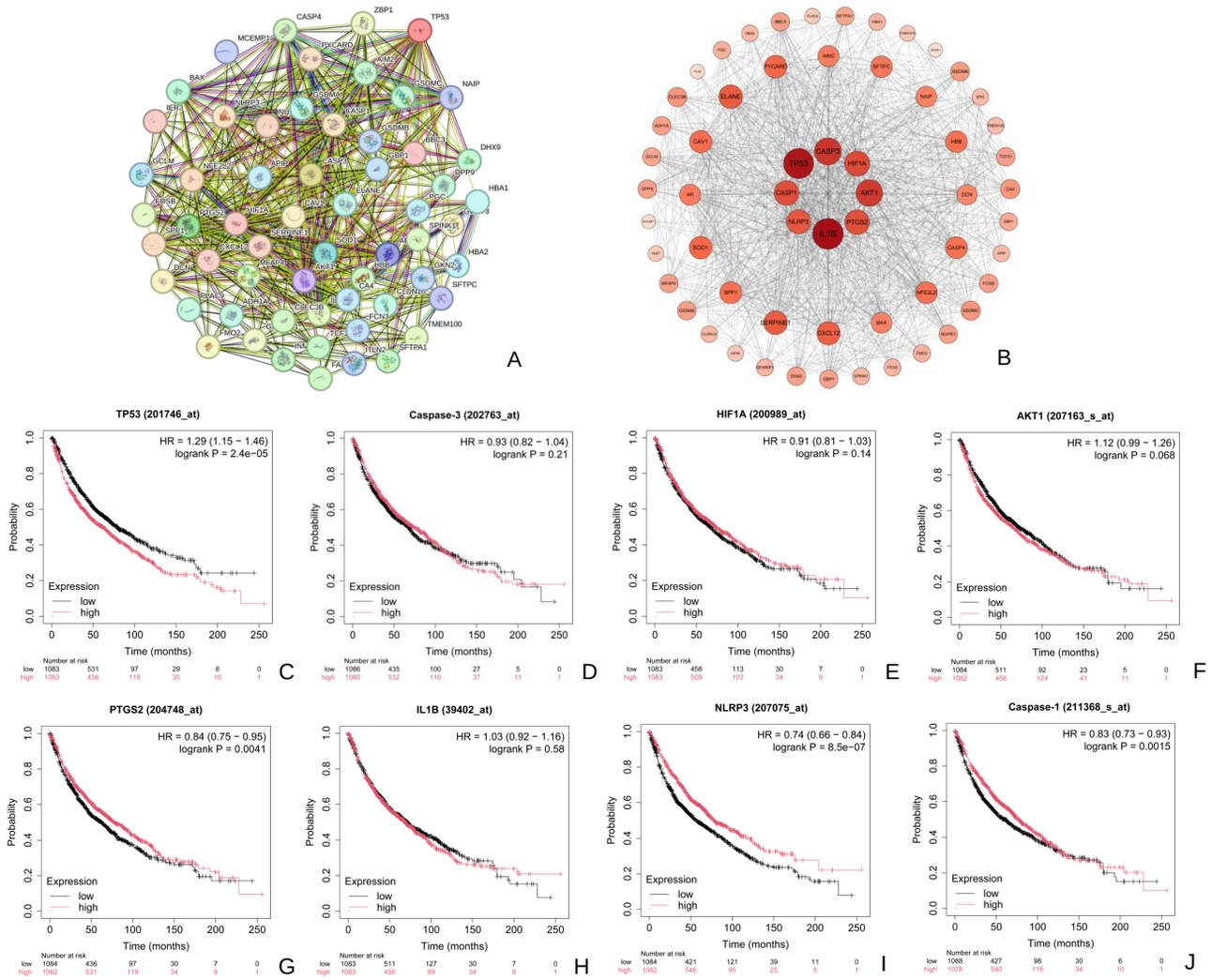
PAHs是由2个或多个融合的芳环组成的有机化合物,具有多种异构体和同系物,广泛存在于环境中[18-19]。PAHs具有致癌、致突变和遗传毒性,对人类健康构成巨大威胁[20]。BaP作为典型的多环芳烃类污染物,广泛存在于人类生产生活中,已成为肿瘤发生发展的独立危险因素[21]。根据最新全球数据显示,肺癌发病率在不同性别中均位居恶性肿瘤第二位,而死亡率仍位居榜首[22]。近年来肺癌的防治研究取得了较大的进展,尽管患者的远期生存率有所提升,但是



A to C: Changes in cell viability (A) and migratory capacity (B and C) of LTEP-a-2 cells in the control, pyroptosis agonist, BaP+pyroptosis agonist, and MCC950+pyroptosis agonist groups. Scale bar=50 μm; D to F: Changes in in cell viability (D), and migratory and invasive capacities (E and F) of LTEP-a-2 cells in the control, DMSO-treated group, BaP-treated group, and BaP combined with pyroptosis agonist group. Scale bar=50 μm. BaP: benzo(a)pyrene. a: $P<0.01$

图5　BaP通过抑制LTEP-a-2细胞焦亡促进其生长、侵袭和迁移

Figure 5　BaP promotes the growth, invasion, and migration of LTEP-a-2 cells by inhibiting pyroptosis



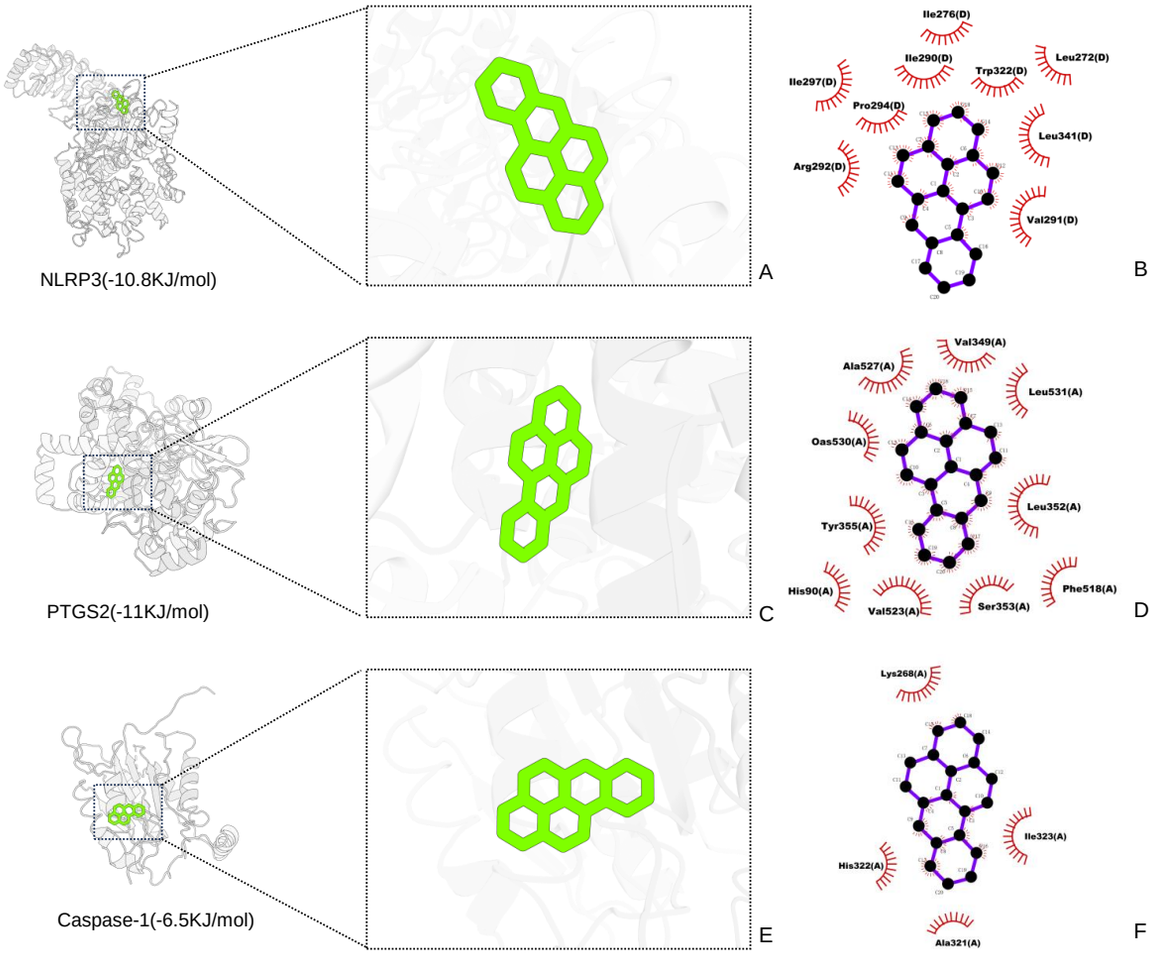
A: protein-protein interaction (PPI) network of differentially expressed genes constructed using STRING; B: Topological analysis of PPI network in Cytoscape with node degree centrality mapping; C to J: Kaplan-Meier survival curves demonstrating the association between expression levels of candidate genes (TP53, Caspase-3, HIF1A, AKT1, PTGS2, IL1B, NLRP3, Caspase-1) and clinical outcomes in lung cancer patients. BaP: benzo(a)pyrene

图6 基于生物信息学方法筛选BaP潜在靶点

Figure 6 Screening of potential targets for BaP using integrated bioinformatics

其复发和转移依然很严重,总体治疗效果仍不理想。流行病学数据显示BaP暴露水平与肺癌发病风险之间呈显著正相关[23],但是其具体机制有待进一步研究明确。本研究通过实验证实,环境浓度BaP暴露可通过抑制NLRP3介导的细胞焦亡显著增强肺癌生长、侵袭及迁移能力,导致肺癌恶性进展。

肿瘤的恶性进展不仅依赖于细胞“能动性”的增强,同样取决于其死亡“逃逸”能力[24]。细胞死亡可分为意外性细胞死亡和PCD两大类。不同的PCD类型在触发机制、信号通路和形态特征方面存在显著差异,分别在维持组织稳态、应对内外源应激以及肿瘤的发生与发展过程中发挥关键作用[25-26]。值得注意的是,BaP对PCD的调控呈现显著的剂量依赖性。研究发现在肝细胞中,50 μmol/L BaP可激活ROS/NF-κB/NLRP3通路促进焦亡导致肝脏损伤[27]。但本研究发现,环境相关剂量(0.1~10 μmol/L)的BaP可显著抑制肺癌细胞NLRP3炎症小体的组装及其下游Caspase-1/GSDMD介导的焦亡进程。这表明BaP对细胞死亡的调控存在剂量依赖性。这一发现证实,BaP不仅通过经典促生长通路(如EGFR/Akt)驱动肿瘤发展[28],还能通过抑制细胞焦亡来削弱癌细胞的自我清除能力,从而为肿瘤细胞提供了一条新的死亡逃逸途



A to F: 3D structural model and 2D binding schematic of the NLRP3-BaP complex (A and B), the PTGS2-BaP complex (C and D), and the Caspase-1-BaP complex (E and F). BaP: benzo(a)pyrene

图7 基于分子对接的BaP靶蛋白相互作用验证

Figure 7 Validation of BaP binding to target proteins by molecular docking

径,该机制可能与经典的促增殖信号协同作用,共同推动肺癌的进展。

细胞焦亡的发生涉及多种途径,最典型的是炎症小体途径。典型炎症小体是一种蛋白质复合物,根据结构特征大致可分为两类:核苷酸结合结构域样受体(NLR)家族和黑色素瘤2(AIM2)[29]。其中NLR家族因其独特的炎症小体组装能力,是焦亡的核心调控者。尽管NLR家族多个成员(如NLRP1、NLRP3和NLRC4)均可参与焦亡调控[30],但NLRP3对多种危险信号尤其是环境致癌物具有独特的敏感性,而且可在肿瘤微环境中的关键作用,是NLR家族中链接细胞焦亡的重要节点[16, 31]。本研究结果显示BaP可显著增强肺癌细胞活力、侵袭及迁移能力,这与前期研究结论一致[11]。同时在此基础上首次发现BaP可显著抑制NLRP3的激活,从而抑制Caspase-1和GSDMD等焦亡效应分子的表达,进一步证实这条信号通路可能成为肺癌治疗的重要靶点。此外,我们通过生物信息学分析发现PTGS2和NLRP3可能是BaP的潜在作用靶点。未来的研究应深入探讨BaP通过调控PTGS2/NLRP3信号通路发挥作用的具体分子机制。本研究所采用的BaP染毒浓度(0.1~10 μmol/L)旨在模拟人体长期低剂量暴露下的靶器官内累积浓度。BaP作为一种高脂溶性的持久性污染物,可在生物体内(尤其是肺组织)显著蓄积[32-33]。因此,长期的环境暴露(如通过空气与饮食)会导致其在靶器官中的浓度持续累积[34],最终形成远高于单次或短期暴露的稳态负荷。本研究的浓度梯度设置基于此原理:0.1 μmol/L与基于生物标志物推算的特定人群体内暴露当量浓度相近,代表一种基础累积水平;而10 μmol/L则用于模拟并探究在更高长期蓄积负荷下可能引发的生物学效

应,从而为评估BaP的长期健康风险提供实验依据。这提示我们必须高度警惕BaP可能对肿瘤患者等重点人群造成的巨大危害,并采取有力措施加强防范。未来需要大力治理环境中的BaP污染,可从源头管理、减少排放、妥善处理废弃物和加强监管等方面入手,通过技术升级、政策约束和公众意识提升,系统性降低其环境和健康风险。

综上所述,BaP可能通过调控PTGS2与NLRP3等关键分子,抑制肺癌细胞中NLRP3炎症小体的激活,进而阻碍下游Caspase-1的活化与GSDMD-NT的生成。NLRP3/Caspase-1/GSDMD轴可能是BaP促进肺癌细胞增殖、侵袭和迁移重要信号通路。需要指出的是,本研究主要从肿瘤进展视角揭示了BaP的促恶性机制。然而,BaP作为明确的肺癌起始因子,其在肿瘤发生早期的效应(如诱导DNA损伤、引发基因毒性应激及慢性炎症启动)同样不可或缺。因此,未来的研究应贯通"肿瘤起始"与"肿瘤进展"两大阶段,深入揭示BaP暴露触发的早期分子事件如何通过程序化的调控网络,影响后期(如焦亡抑制等)促进肿瘤进展的关键机制,最终为制定更具针对性的环境致癌风险防控策略提供坚实且完整的理论依据。

利益冲突 本文所有作者声明不存在利益冲突

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