四川大学学报（医学版）　2025，56（5）：1336－1343
J Sichuan Univ（Med Sci）

深地低本底辐射环境对NP69人鼻咽上皮细胞增殖迁移的抑制效应及机制*

郝智贞[1]，李　灿[2]，王　领[2]，邹宇豪[1]，文继锐[2]，吴　江[2,3,4△]，万学红[2,3,4]，刘　锋[1]，刘吉峰[1,2,3,4△]

1. 四川大学华西医院 耳鼻咽喉头颈外科（成都 610041）；2. 四川大学华西医院 深地医学研究中心（成都 610041）；
3. 锦屏深地前沿科学及暗物质四川省重点实验室（西昌 615000）；
4. 四川大学深地工程智能建造与健康运维全国重点实验室（成都 610065）

【摘要】　目的　本研究旨在探究深地低本底辐射环境对NP69人鼻咽上皮细胞生物学行为的影响及其潜在分子机制。**方法**　采用平行对照实验设计，分别于中国深地原位生命观测站（China *in situ* Deep-Underground Facility & Life Observatory, DeUFO）地表0 m（DeUFO-0 m）、埋深1 000 m（DeUFO-1 000 m）、埋深1 500 m（DeUFO-1 500 m）同步培养NP69人鼻咽上皮细胞。通过Cell Counting Kit-8（CCK-8）法和划痕实验等分别检测细胞增殖及迁移能力变化，并利用高通量转录组测序（RNA sequencing, RNA-Seq）分析差异表达基因（differentially expressed genes, DEGs）。采用基因本体（Gene Ontology, GO）和京都基因与基因组百科全书（Kyoto Encyclopedia of Genes and Genomes, KEGG）数据库对差异基因进行功能注释及通路富集分析。**结果**　CCK8显示，培养72 h后，DeUFO-0 m组的吸光度值分别为DeUFO-1 000 m组、DeUFO-1 500 m组的1.35倍和1.27倍（均$P<0.000\,1$）；培养96 h后，DeUFO-0 m组的吸光度值分别为DeUFO-1 000 m组、DeUFO-1 500 m组的1.52倍和1.41倍（均$P<0.000\,1$）。克隆形成实验显示，DeUFO-0 m组的细胞克隆数分别为DeUFO-1 000 m组、DeUFO-1 500 m组的1.59倍和1.27倍（均$P<0.001$）。划痕实验显示，DeUFO-0 m组36 h愈合率分别为DeUFO-1 000 m组、DeUFO-1 500 m组的2.22倍和4.00倍（均$P<0.000\,1$）。Transwell实验显示，DeUFO-0 m组的迁移细胞数分别为DeUFO-1 000 m组、DeUFO-1 500 m组的2.08倍和2.56倍（均$P<0.000\,1$）。转录组测序分析显示，*CELF2*、*CELF4*、*CGB8*、*GRHL2*和*DMRTA2*基因在深地不同埋深实验组中均呈现一致性上调表达。通路富集分析表明，细胞外基质（extracellular matrix, ECM）重构相关通路及基因表达调控通路在实验组中显著富集（FDR<0.05）。**结论**　深地低本底辐射环境可通过调控CELF家族基因等靶点，介导ECM重塑及转录后调控机制，进而抑制NP69人鼻咽上皮细胞的增殖与迁移活性。本研究为环境辐射剂量-细胞效应量效关系的建立提供了实验依据。

【关键词】　深地医学　低本底辐射环境　NP69人鼻咽上皮细胞　细胞增殖/迁移　转录组学

Inhibitory Effects of the Deep Underground Low Background Radiation Environment on the Proliferation and Migration of NP69 Human Nasopharyngeal Epithelial Cells and the Underlying Mechanisms

HAO Zhizhen[1], *LI Can*[2], *WANG Ling*[2], *ZOU Yuhao*[1], *WEN Jirui*[2], *WU Jiang*[2,3,4△], *WAN Xuehong*[2,3,4], *LIU Feng*[1], *LIU Jifeng*[1,2,3,4△]. 1. *Department of Otorhinolaryngology-Head and Neck Surgery, West China Hospital, Sichuan University, Chengdu 610041, China*; 2. *Deep Underground Space Medical Center, West China Hospital, Sichuan University, Chengdu 610041, China*; 3. *Jinping Deep Underground Frontier Science and Dark Matter Key Laboratory of Sichuan Province, Xichang 615000, China*; 4. *State Key Laboratory of Intelligent Construction and Healthy Operation and Maintenance of Deep Underground Engineering, Sichuan University, Chengdu 610065, China*

△ Corresponding author, WU Jiang, E-mail: jw@scu.edu.cn; LIU Jifeng, E-mail: 729122921@qq.com

[Abstract]　Objective　To investigate the effects of low background radiation environments in deep underground settings on the biological behavior of NP69 human nasopharyngeal epithelial cells (NP69 cells) and the underlying molecular mechanisms. **Methods**　A parallel control experimental design was adopted and NP69 cells were synchronously cultured in settings of three underground depths at the China *in situ* Deep-Underground Facility & Life Observatory (DeUFO)—ground level (DeUFO-0 m), 1 000 m underground (DeUFO-1 000 m), and 1 500 m underground

* 地球深部探测与矿产资源勘查国家科技重大专项（No. 2024ZD1000605、No. 2024ZD1000606）、国家自然科学基金专项项目（No. 12441517）、国家自然科学基金面上项目（No. 82371883）和四川省科技厅自然科学基金面上项目（No. 2025ZNSFSC0728）资助

△ 通信作者，吴江，E-mail: jw@scu.edu.cn；刘吉峰，E-mail: 729122921@qq.com

出版日期：2025-09-20

(DeUFO-1 500 m). Changes in cell proliferation and migration capabilities were assessed using the Cell Counting Kit-8 (CCK-8) assay and scratch assay, respectively. High-throughput RNA sequencing (RNA-Seq) was performed to identify differentially expressed genes (DEGs). Functional annotation and pathway enrichment analysis of the DEGs were performed using the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases. **Results** CCK-8 assay revealed that, after 72 h of culture, the absorbance value of the DeUFO-0 m group was 1.35 times and 1.27 times those of the those of the DeUFO-1 000 m and DeUFO-1 500 m groups, respectively (both P < 0.000 1). After 96 h of culture, the absorbance value of the DeUFO-0 m group was 1.52 times and 1.41 times those of the DeUFO-1 000 m and DeUFO-1 500 m groups, respectively (both P < 0.000 1). Colony formation assays revealed that the number of cell colonies in the DeUFO-0 m group was 1.59 times and 1.27 times those in the DeUFO-1 000 m group and DeUFO-1 500 m group, respectively (both P < 0.001). The scratch assay revealed that the 36-hour wound healing rate of the DeUFO-0 m group was 2.22 times and 4.00 times those of the DeUFO-1 000 m group and DeUFO-1 500 m group, respectively (both P < 0.000 1). Transwell assays revealed that the number of migrating cells in the DeUFO-0 m group was 2.08 times and 2.56 times those in the DeUFO-1 000 m group and DeUFO-1 500 m group, respectively (both P < 0.000 1). Transcriptome sequencing analysis revealed consistent upregulation of *CELF2*, *CELF4*, *CGB8*, *GRHL2*, and *DMRTA2* genes in the DeUFO-1 000 m and DeUFO-1 500 m groups. Pathway enrichment analysis indicated significant enrichment of extracellular matrix (ECM) remodeling-associated pathways and gene expression regulation pathways in the experimental groups (false discovery rate [FDR] < 0.05). **Conclusion** The low background radiation environment in deep underground settings suppresses the proliferation and migration activities of NP69 cells by mediating ECM remodeling and post-transcriptional regulatory mechanisms through the regulation of target genes such as the CELF family. This study provides experimental evidence for establishing a dose-response relationship between environmental radiation and cellular effects.

[Key words] Deep underground medicine　Low background radiation environment　NP69 human nasopharyngeal epithelial cells　Cell proliferation/migration　Transcriptomics

人类不可避免地暴露于一定水平的本底辐射，其主要辐射来源包括宇宙射线和建筑材料所含的放射性元素等。我国居民年均所受的天然辐射本底水平估算的有效剂量当量约为2.3 mSv[1]。自射线被发现100多年以来，辐射剂量与生物学效应的关系始终是学术界的研究难点，其健康风险的确切剂量-效应关系迄今尚未完全阐明。

目前，基于流行病学研究建立的线性非阈值(linear no-threshold, LNT)模型在辐射防护领域占据主导地位。该理论假设认为，任何剂量的辐射都可能增加健康风险，且患癌风险与辐射剂量呈正相关关系，不存在安全阈值[2]。然而，越来越多的研究证据对该模型提了出质疑。研究表明，超过1 000 mSv的高剂量辐射与低于100 mSv的低剂量辐射产生的生物学效应存在显著差异。高剂量辐射确实会显著增加患癌的风险，而低剂量辐射致癌效应仍存在争议[3-4]。更有研究发现，低剂量辐射还可激活机体的修复防御系统，从而对后续高剂量辐射或其他致癌因素产生保护作用[5-6]。现有研究所涉及的低剂量辐射的剂量仍显著高于本底辐射，对于低本底辐射的生物学效应认知仍然有限。深地环境因其对宇宙射线的天然屏蔽作用，形成了独特的低本底辐射环境[7]。这一特殊环境为探索本底辐射对生命的影响提供了理想的研究平台，有助于阐明辐射剂量-生物学效应的内在规律及其分子机制。

作为连接人体与外界环境的关键界面，鼻咽上皮细胞因其持续暴露于环境辐射的特性，成为研究辐射生物学效应的理想靶细胞模型[8]。本研究团队前期利用中国锦屏地下实验室(China Jinping Underground Laboratory, CJPL)特殊隧道环境条件，搭建了以低本底辐射环境为特征、不同埋深的中国深地原位生命观测站(China *in situ* Deep-Underground Facility & Life Observatory, DeUFO)，通过系统性比较地表常规本底辐射与深地低本底辐射环境下培养的NP69人鼻咽上皮细胞在表型特征和转录组学层面的差异，深入探究细胞对低剂量辐射的分子响应机制。这一研究不仅可为验证和优化现行辐射防护理论(如线性无阈模型)在低剂量区的适用性提供关键实验证据，更能为环境辐射本底波动对人体健康的潜在影响提供科学依据[9-10]。

1　材料与方法

1.1　主要材料和设备

NP69人鼻咽上皮细胞株、NP69SV40T细胞专用培养基(武汉普诺赛生命科技有限公司)，0.05%胰蛋白酶(Gibco)，4%多聚甲醛通用型组织固定液、PBS缓冲液(Biosharp)，Trizol(南京诺唯赞生物科技股份有限公司)，

Cell Counting Kit-8细胞计数试剂、结晶紫染色液(上海碧云天生物技术有限公司)。超低温保存箱(海尔生物医疗),电热恒温水浴锅(上海精密仪器仪表有限公司),二氧化碳培养箱(Esco Lifesciences Group),净化工作台(天津市泰斯特仪器有限公司),低速离心机(安徽中科中佳科学仪器有限公司),正置显微镜(Leica Microsystems),多功能酶标仪(赛默飞世尔科技公司)。

1.2 方法

1.2.1 辐射剂量选择

本研究在前期环境辐射本底实测和计算的基础上,选择3个辐射剂量进行实验,即地表0 m(DeUFO-0 m,辐射剂量率为125.48 nGy/h)、埋深1 000 m组(DeUFO-1 000 m,辐射剂量率为 80.57 nGy/h)、埋深1 500 m组(DeUFO-1 500 m,辐射剂量率为90.82 nGy/h)。取NP69人鼻咽上皮细胞于DeUFO 0 m实验室复苏,在NP69SV40T细胞专用培养基中培养,于37 ℃、体积分数5%CO_2的恒温孵箱里继续培养1周后(期间进行正常传代)将细胞分为DeUFO-0 m组、DeUFO-1 000 m组、DeUFO-1 500 m组,分别置于对应实验室(期间进行正常传代),培养1个月后完成后续实验。

1.2.2 细胞增殖检测

将各组NP69人鼻咽上皮细胞以1×10^3/孔的密度接种于96孔板中,连续观察96 h,在24、48、72、96 h更换含CCK-8试剂的培养基(体积分数为10%),避光孵育2 h后在酶标仪450 nm处检测吸光度,并绘制生长曲线。

1.2.3 克隆形成实验

将各组NP69人鼻咽上皮细胞以1×10^3/孔的密度接种于6孔板,常规培养7 d后经PBS漂洗、4%多聚甲醛固定15 min、0.5%结晶紫染色30 min,计数直径>50 μm的细胞克隆,计算克隆数占接种细胞数的百分比作为克隆形成率。

1.2.4 Transwell迁移实验

向24孔板加入500 μL含体积分数10% FBS的培养基,然后将Transwell小室置于24孔板中。取100 μL不含血清的细胞悬液(密度为3×10^3/100 mL)加入Transwell小室上层,之后将24孔板置于CO_2培养箱静置培养24 h。取出小室,弃培养基,PBS漂洗3次后,甲醇固定10 min、0.5%结晶紫染色30 min、PBS漂洗3次,棉签擦去小室上层未迁移细胞,自然晾干,光学显微镜下随机选取5个独立视野,对迁移到小室下层的细胞进行计数。

1.2.5 划痕实验

取各组NP69人鼻咽上皮细胞以3.5×10^5/孔密度接种于6孔板,培养至100%融合,用200 μL无菌枪头制造垂直划痕,PBS清洗后更换无血清培养基。在12、24、36 h使用Image J软件计算划痕面积,采用(初始划痕面积−t时刻划痕面积)/初始划痕面积计算细胞迁移率。

1.2.6 转录组学测序分析

收集各组细胞后,使用Trizol试剂提取总RNA(RNA完整性指数>8.0);构建cDNA文库(NEBNext® Ultra™ Kit),在Illumina Novaseq 6000测序平台上进行150 bp双端测序;使用FastQC/Trimmomatic进行原始数据质量评估,通过HISAT2比对至GRCh38基因组(Ensembl v108),Stringtie重构转录本、RSEM计算FPKM值,DESeq2筛选差异基因($|\log_2 FC|>1$且$q<0.05$)。对差异基因通过clusterProfiler完成基因本体(Gene Ontology, GO)富集分析,其次开展通路注释,包括京都基因与基因组百科全书(Kyoto Encyclopedia of Genes and Genomes, KEGG)、Reactome及WikiPathways,最后基于STRING数据库构建蛋白质互作网络(protein-protein interaction, PPI)。

1.2.7 统计学方法

所有数据以$\bar{x}\pm s$表示,采用GraphPad Prism 9.5进行统计分析。经正态性检验及方差齐性检验后,多组间比较使用单因素ANOVA结合Bonferroni法事后检验,$P<0.05$为差异有统计学意义。

2 结果

2.1 深地低本底辐射环境抑制NP69人鼻咽上皮细胞增殖

生长曲线结果如图1A所示,培养24 h后,DeUFO-0 m组、DeUFO-1 000 m组及DeUFO-1 500 m组的吸光度值分别为0.308、0.292和0.297,无明显差异($P>0.05$);培养48 h后,DeUFO-0 m组、DeUFO-1 000 m组和DeUFO-1 500 m组的吸光度值分别为0.415、0.358和0.363,无明显差异($P>0.05$)培养72 h后,DeUFO-0 m组吸光度值为0.661,分别是DeUFO-1 000 m组(0.487)、DeUFO-1 500 m组(0.519)吸光度值的1.36倍和1.27倍(均$P<0.000\,1$);培养96 h后,DeUFO-0 m组吸光度值为1.054,分别是DeUFO-1 000 m组(0.698)、DeUFO-1 500 m组(0.744)吸光度值的1.51倍和1.42倍(均$P<0.000\,1$)。克隆形成实验结果见图1B,DeUFO-0 m组细胞克隆数(261个)分别为DeUFO-1 000 m组(165个)、DeUFO-1 500 m组(207个)的1.58倍和1.26倍(均$P<0.001$)。以上结果表明,深地低本底辐射环境可显著抑制NP69人鼻咽上皮细胞的增殖与克隆形成能力。

2.2 深地低本底辐射环境抑制NP69人鼻咽上皮细胞迁移

结果显示(图2A、2B),划痕后12 h,DeUFO-0 m组的细胞迁移率为35.46%,分别是DeUFO-1 000 m组(21.43%)、

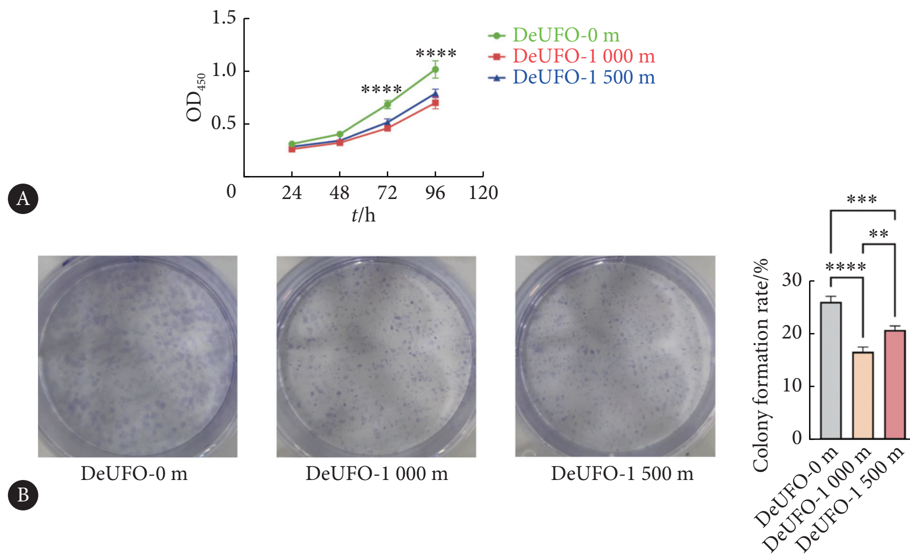


图 1　地表实验室及深地实验室培养的NP69人鼻咽上皮细胞的增殖能力比较

Fig 1　Comparison of the proliferative capacity of NP69 cells cultured in ground-level and deep underground laboratories

A, Growth curve of NP69; B, colony formation assay of NP69. $n = 3$. $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.000\,1$.

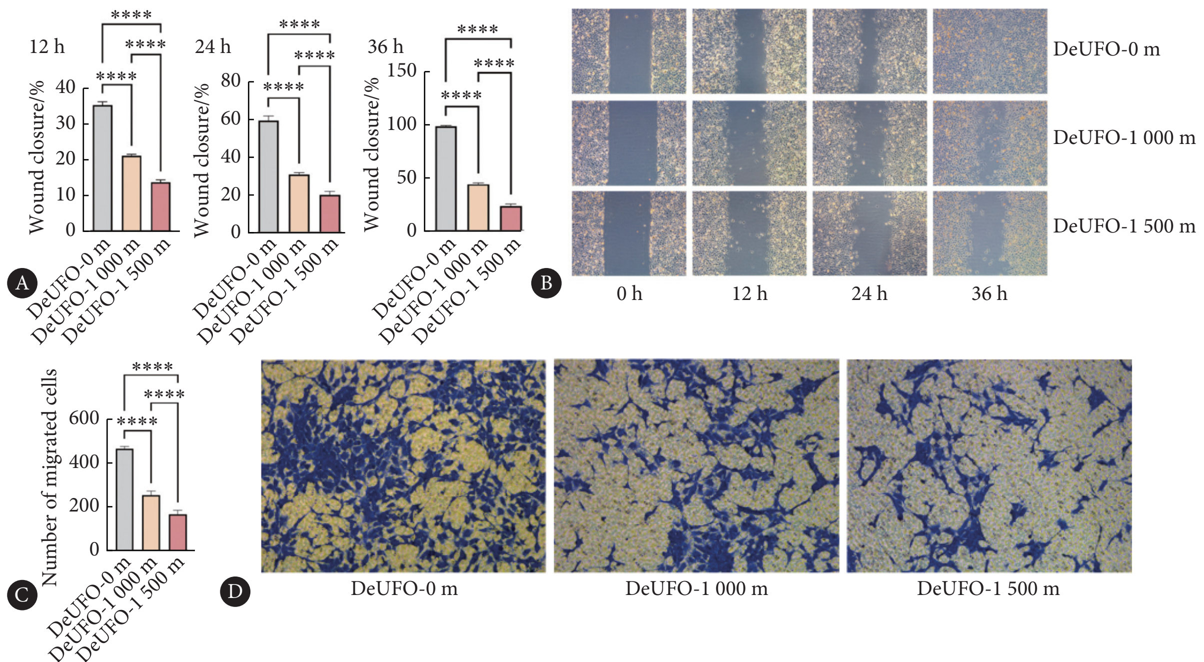


图 2　地表实验室及深地实验室培养的NP69人鼻咽上皮细胞的迁移能力比较

Fig 2　Comparison of the migration capacity of NP69 cells cultured in ground-level and deep underground laboratories

A, Scratch assay of NP69; B, photographs of the scratch assay of NP69 (original magnification ×100); C, transwell migration assay of NP69; D, photographs of transwell migration assay of NP69 (original magnification × 100). $n = 3$. $^{****}P < 0.000\,1$.

DeUFO-1500 m组(14.63%)的1.67倍和2.44倍(均P<0.0001); 划痕后24 h, DeUFO-0 m组的细胞迁移率为59.69%, 分别是DeUFO-1000 m组(31.12%)、DeUFO-1500 m组(20.66%)的1.92倍和2.89倍(均P<0.0001)。划痕后36 h, DeUFO-0 m组的细胞迁移率为100%, 分别是DeUFO-1000 m组(44.63%)、DeUFO-1500 m组(24.77%)的2.22倍和4.00倍(均P<0.0001)。

Transwell实验进一步显示(图2C、2D), DeUFO-0 m组的细胞迁移数量高于各DeUFO-1000 m组和DeUFO 1500 m组, 其迁移细胞数分别约为DeUFO-1000 m组的2.08倍和DeUFO-1500 m组的2.56倍(P<0.0001)。以上结果表明, 深地低本底辐射环境能够显著抑制NP69人鼻咽

上皮细胞的迁移能力。

2.3 不同辐射环境对NP69人鼻咽上皮细胞基因表达的影响

样本基因FPKM值的箱线图分析显示，各组样本基因表达的整体分布具有良好的一致性(图3A)，表明实验操作和测序过程稳定可靠。差异基因火山图和热图显示，与DeUFO-0 m组相比较，DeUFO-1 000 m组和DeUFO-1 500 m组部分基因表达存在显著差异。在DeUFO-1 000 m组中，透明质酸结合蛋白2(hyaluronan binding protein 2, *HABP2*)、α1-微球蛋白/胆胰蛋白酶抑制剂前体(alpha-1-microglobulin/bikunin precursor, *AMBP*)、溶菌酶G2(lysozyme g2, *LYG2*)、钠电压门控通道α亚基9(sodium voltage-gated channel alpha subunit 9, *SCN9A*)的表达分别为DeUFO-0 m组的3/500、7/1 000、3/250和1/250(均P<0.05)，而Wnt家族成员7A(wnt family member 7a, *WNT7A*)、CUGBP Elav样家族成员2(cugbp elav-like family member 2, *CELF2*)、CUGBP Elav样家族成员4(cugbp elav-like family member 4, *CELF4*)、绒毛膜促性腺激素β亚基8(chorionic gonadotropin subunit beta 8, *CGB8*)、粒状头样2(grainyhead like 2, *GRHL2*)、双性和Mab-3相关转录因子A2(doublesex- and mab-3-related transcription factor A2, *DMRTA2*)的表达分别为DeUFO-0 m组的244.9、408.1、402.5、830.6、244.8和361.9倍(图3E, 均P<0.05)。在DeUFO-1 500 m组中，含FXYD域离子传输调节因子2(FXYD domain containing ion transport regulator 2, *FXYD2*)、溶质载体家族14成员1(solute carrier family 14 member 1, *SLC14A1*)、乙醛脱氢酶家族3成员A1(aldehyde dehydrogenase 3 family member a1, *ALDH3*)、微精原蛋白(microseminoprotein, *MSMP*)的表达分别为DeUFO-0 m组的2/125、3/500、3/1 000和9/1 000(均P<0.05)，而BEN结构域蛋白5(BEN domain-containing protein 5, *BEND5*)、*CELF2*、*CELF4*、*CGB8*、*GRHL2*、*DMRTA2*的表达分别为DeUFO-0 m组的396.1、204.7、168.1、292.6、167.4和211.1倍(图3F, 均P<0.05)。其中，*CELF2*、*CELF4*、*CGB8*、*GRHL2*、*DMRTA2*在DeUFO-1 000 m组和DeUFO-1 500 m 组均呈现表达上调，这些基

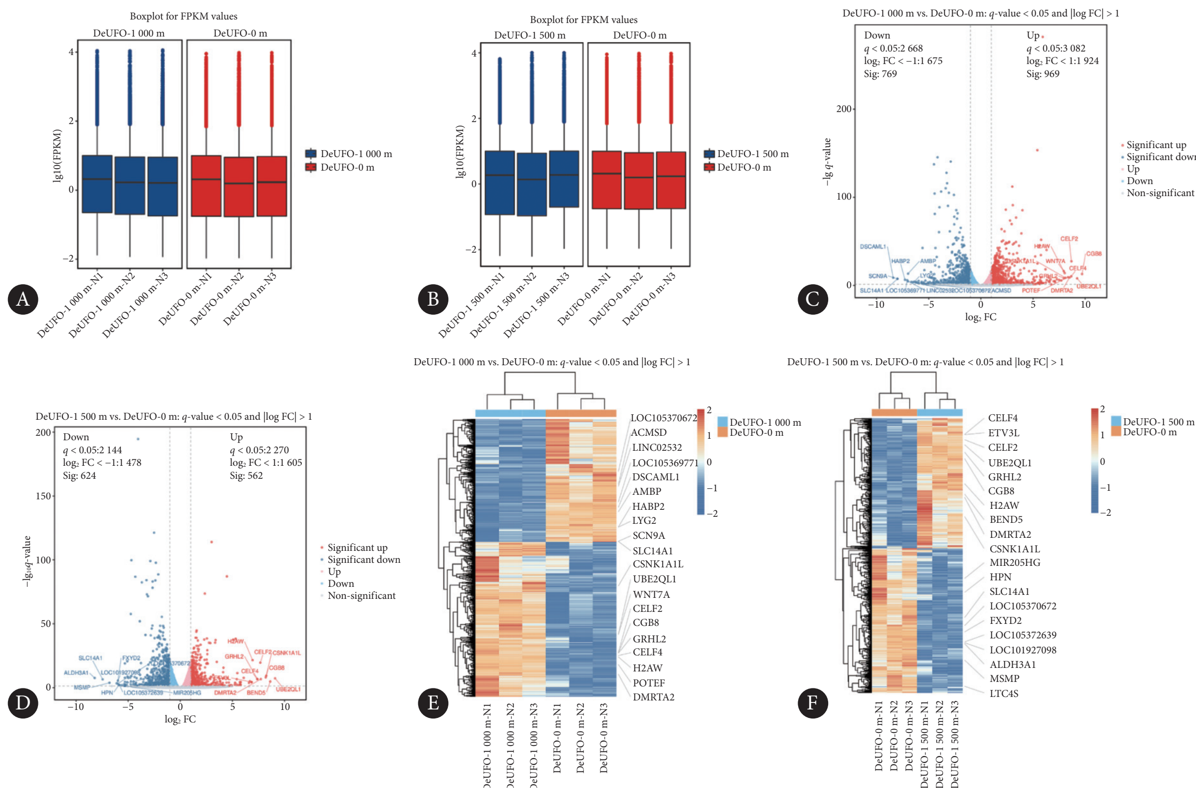


图 3 深地低本底辐射环境下NP69人鼻咽上皮细胞的差异表达基因

Fig 3 Differentially expressed genes in NP69 cells under low background radiation environment in deep underground laboratories

A and B, FPKM value boxplots of DeUFO-1 000 m group vs. DeUFO-0 m group (A) and DeUFO-1 500 m group vs. DeUFO-0 m group (B). C and D, Volcano plots for differential expression of DeUFO-1 000 m group vs. DeUFO-0 m group (C) and DeUFO-1 500 m group vs. DeUFO-0 m (D), with gray dots representing non-significant genes and red/blue dots representing significantly upregulated/downregulated genes. E and F, Hierarchical clustering heatmaps of differentially expressed genes of DeUFO-1 000 m group vs. DeUFO-0 m group (E) and DeUFO-1 500 m group vs. DeUFO-0 m group (F), with red representing relatively highly expressed protein-coding genes and blue representing relatively lowly expressed protein-coding genes.

因主要参与基因表达调控(*CELF2*、*CELF4*)、细胞外基质重塑(*HABP2*)、细胞分化调控(*GRHL2*、*DMRTA2*)等相关通路。

2.4　深地低本底辐射环境下NP69人鼻咽上皮细胞的差异信号通路

GO分析结果显示, DeUFO-1 000 m 组中显著富集细胞外基质组织(GO:0030198)、细胞黏附(GO:0007155)、细胞表面(GO:0009986)等信号通路, DeUFO-1 500 m组除上述通路外, 还显著富集DNA复制(GO:0006260)等信号通路; KEGG分析结果显示, DeUFO-1 000 m组中显著富集运动蛋白、ABC转运体等信号通路, DeUFO-1 500 m组中显著富集DNA复制、细胞周期、细胞外基质-受体相互作用等信号通路; Reactome分析结果显示, DeUFO-1 000 m组中显著富集细胞外基质、细胞周期等信号通路, DeUFO-1 500 m组中显著富集G_1/S期特异性转录、同源修复等信号通路; WikiPathways分析结果显示, DeUFO-1 000 m组中显著富集氧化损伤、上皮间质转化等信号通路, DeUFO-1 500 m组中显著富集DNA复制、DNA放射性损伤等信号通路(图4)。跨数据库分析一致显示, 细胞外基质重塑及基因表达调控等相关通路在DeUFO-1 000 m组及DeUFO-1 500 m组均显著富集, 进一步证实了深地低本底辐射环境对基因表达调控过程的影响。

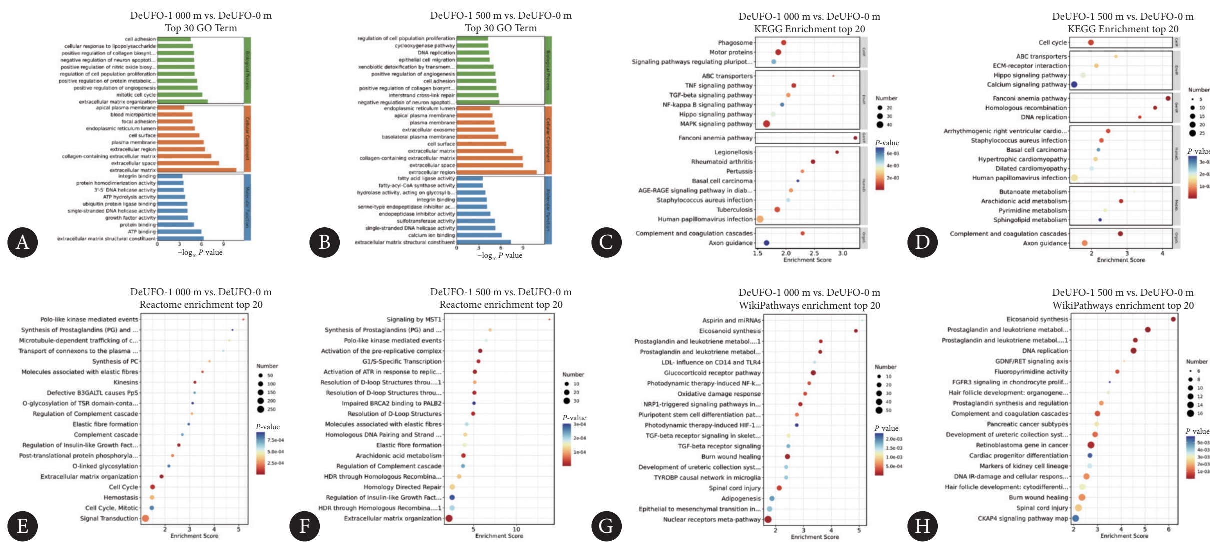


图 4　深地低本底辐射环境下NP69人鼻咽上皮细胞的差异信号通路

Fig 4　Differential signaling pathways in NP69 cells under low background radiation environment in deep underground laboratories

A and B, GO enrichment analysis of DeUFO-1 000 m group vs. DeUFO-0 m group (A) and DeUFO-1 500 m group vs. DeUFO-0 m group (B), with the *Y*-axis showing GO terms and the *X*-axis showing —lg (*P*-value). C and D, KEGG enrichment analysis of DeUFO-1 000 m group vs. DeUFO-0 m (C) and DeUFO-1 500 m group vs. DeUFO-0 m group (D), with the *X*-axis showing enrichment scores, the bubble size indicating the number of differentially expressed genes, and the color gradient (blue-white-yellow-red) representing the significance level (*P*-value decreases with color transition). E and F, Reactome enrichment analysis of DeUFO-1 000 m group vs. DeUFO-0 m group (E) and DeUFO-1 500 m group vs. DeUFO-0 m group (F). G and H, WikiPathways enrichment analysis of DeUFO-1 000 m group vs. DeUFO-0 m group (G) and DeUFO-1 500 m group vs. DeUFO-0 m group (H).

2.5　深地低本底辐射环境下NP69人鼻咽上皮细胞的差异基因互作关系

在深地低本底辐射环境中, NP69人鼻咽上皮细胞的基因互作关系发生了明显变化。DeUFO-1 000 m 组的互作基因主要包括编码微管蛋白的*TUBB*家族基因以及*MCM5*等DNA复制相关基因; 而DeUFO-1 500 m组的互作基因则主要包括*RRM1*、*RRM2*等DNA合成与修复基因以及*MCM5*等DNA复制相关基因(图5)。这些差异基因互作关系与基因表达调控过程及细胞外基质紧密相连, 进一步揭示了深地低本底辐射环境对NP69人鼻咽上皮细胞生物学行为的潜在影响机制。

3　讨论

关于深地低本底辐射生物学效应的研究可追溯至1987年法国PLANEL团队的开创性工作, 该研究首次发现在200 m岩层覆盖的地下实验室中, 草履虫增殖活性受到显著抑制, 且当额外添加5 cm厚的铅屏蔽层时, 抑制效果更加明显[10]。随后, 多个实验室也相继在细菌、昆虫及哺乳动物细胞中观察到类似生物学效应[11-16]。本研究前期实测并计算了深地实验室埋深环境的辐射本底, 结果发现伽马、缪子和中子等总辐射剂量低于地面实验室, 且深地实验室的中子和缪子通量可以忽略不计。DeUFO-

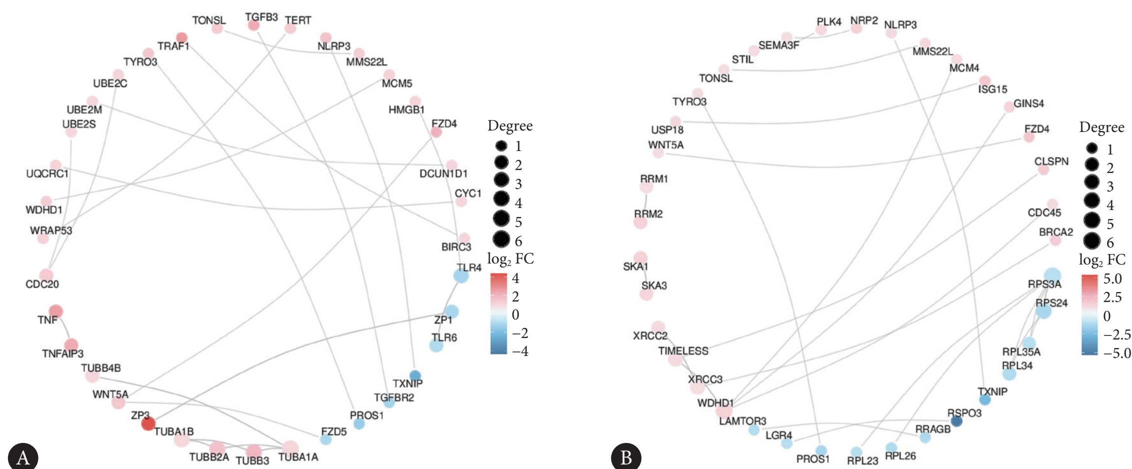


图 5 深地低本底辐射环境下NP69人鼻咽上皮细胞的差异基因互作关系

Fig 5 Interaction network of differentially expressed genes in NP69 cells under low background radiation environment in deep underground laboratories

A, DeUFO-1 000 m group vs. DeUFO-0 m group, B, DeUFO-1 500 m group vs. DeUFO-0 m group. Red represents upregulated differentially expressed genes, while blue represents downregulated differentially expressed genes; the more genes are associated, the larger the gene locus.

1 500 m实验室的氡剂量则略高于DeUFO-1 000 m实验室，主要是由于实验通风和岩层特性的影响，与岩石埋深关系不大。本研究还系统评估了深地低本底辐射环境对NP69人鼻咽上皮细胞生物学效应的影响。研究发现，深地低本底辐射环境能显著抑制细胞的增殖和迁移能力，该研究结果与既往深地实验室的生物学研究结论一致。这些跨物种研究证据共同揭示了低本底辐射作为一种特殊环境因子，其核心生物学效应表现为细胞增殖能力下降和应激防御功能适应性改变。

基因表达调控网络在细胞生物学行为和环境应激响应中发挥着核心作用。基因表达是一个高度精细的多级调控过程，涉及表观遗传修饰、转录调控、mRNA加工、蛋白质翻译及翻译后修饰等多个关键环节。这些环节共同构成了一个复杂的动态平衡系统，在维持细胞稳态和应对环境变化中起着决定性作用。既往研究表明，深地低本底辐射环境能够显著影响基因表达的不同层面[11-13]。CASTILLO等[15, 17]在耐辐射球菌UWO298模型中发现，深地环境可干扰包括蛋白质转运折叠、蛋白水解、基因转录和DNA复制在内的多个基因表达关键步骤。

本研究通过高通量转录组学分析，系统揭示了深地低本底辐射环境对NP69人鼻咽上皮细胞基因表达谱的影响，其中*CELF2*、*CELF4*、*GRHL2*、*DMRTA2*、*CGB8*基因在DeUFO-1 000 m和DeUFO-1 500 m组中发生一致性上调表达。*CELF2*、*CELF4*均为RNA结合蛋白，调控mRNA剪接、翻译及稳定性[18]。*GRHL2*为上皮发育关键转录因子，在维持细胞黏附/屏障功能中发挥作用[19]。*DMRTA2*基因编码的蛋白质含有两个DNA结合结构域，可作为转录因子发挥功能，参与基因表达的调控[20]。*CGB8*基因是绒毛膜促性腺激素β亚基基因家族中的一个成员，与细胞的增殖和分化密切相关[21]。此外，通路富集分析进一步证实，细胞外基质重塑、基因表达调控(特别是转录及转录后水平)、DNA复制与修复、细胞周期调控等信号通路在深地实验室组中均差异表达。

以上结果提示，细胞通过多层次的基因表达重编程来适应深地环境。一方面增强基因组稳定性维护机制(如DNA修复)，另一方面下调增殖相关通路(如细胞周期)。这种适应性重塑虽然保障了细胞在极端环境中的存活，却可能因资源再分配而导致增殖和迁移等功能性抑制。这一发现为理解低本底辐射的生物学效应提供了新的分子视角，也为后续研究环境辐射与细胞稳态的关系奠定了重要基础。

* * *

作者贡献声明 郝智贞负责数据审编、正式分析、调查研究、验证、可视化、初稿写作和审读与编辑写作，李灿和王领负责调查研究、研究方法、监督指导、验证和可视化，邹宇豪负责调查研究、研究方法、监督指导、验证、可视化和审读与编辑写作，文继锐负责论文构思、数据审编、正式分析、调查研究、研究方法、研究项目管理、监督指导、验证、可视化、初稿写作和审读与编辑写作，刘锋负责论文构思、研究项目管理、提供资源、监督指导和审读与编辑写作，吴江、万学红和刘吉峰负责论文构思、经费获取、研究方法、研究项目管理、提供资源、监督指导和审读与编辑写作。所有作者已经同意将文章提交本刊，且对将要发表的版本进行最终定稿，并同意对工作的所有方面负责。

Author Contribution HAO Zhizhen is responsible for data curation, formal analysis, investigation, validation, visualization, writing--original draft, and writing--review and editing. LI Can and WANG Ling are responsible for investigation, methodology, supervision, validation, and visualization. ZOU Yuhao is responsible for investigation, methodology, supervision, validation, visualization, and writing--review and editing. WEN

Jirui is responsible for conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing--original draft, and writing--review and editing. LIU Feng is responsible for conceptualization, project administration, resources, supervision, and writing--review and editing. WU Jiang, WAN Xuehong, and LIU Jifeng are responsible for conceptualization, funding acquisition, methodology, project administration, resources, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突　所有作者均声明不存在利益冲突

Declaration of Conflicting Interests　All authors declare no competing interests.

参　考　文　献

[1] 潘自强, 郭明强, 崔广志, 等. 中国天然辐射本底水平和居民剂量估算. 辐射防护, 1992(4): 251-259.
PAN Z, GUO M, CUI G, *et al*. Estimation of natural radiation background levels and public dose in china. Radiat Prot, 1992(4): 251-259.

[2] LINDELL B, SOWBY D. The 1958 UNSCEAR report. J Radiol Prot, 2008, 28: 277-282. doi: 10.1088/0952-4746/28/3/R01.

[3] MORCIANO P, CIPRESSA F, PORRAZZO A, *et al*. Fruit flies provide new insights in low-radiation background biology at the INFN underground gran sasso national laboratory (LNGS). Radiat Res, 2018, 190: 217-225. doi: 10.1667/RR15083.1.

[4] WADSWORTH J, COCKELL C S, MURPHY A S, *et al*. There's plenty of room at the bottom: low radiation as a biological extreme. Front Astron Space Sci, 2020, 7: 50. doi: 10.3389/fspas.2020.00050.

[5] DOBRZYNSKI L, FORNALSKI K W, FEINENDEGEN L E. Cancer mortality among people living in areas with various levels of natural background radiation. Dose Response, 2015, 13: 1559325815592391. doi: 10.1177/1559325815592391.

[6] LEHRER S, ROSENZWEIG K E. Lung cancer hormesis in high impact states where nuclear testing occurred. Clin Lung Cancer, 2015, 16: 152-155. doi: 10.1016/j.cllc.2014.09.010.

[7] LAMPE N, BRETON V, SARRAMIA D, *et al*. Understanding low radiation background biology through controlled evolution experiments. Evol Appl, 2017, 10: 658-666. doi: 10.1111/eva.12491.

[8] DENG L, YIN Q, LIU S, *et al*. MicroRNA-613 enhances nasopharyngeal carcinoma cell radiosensitivity via the DNA methyltransferase 3B/tissue inhibitor of matrix metalloproteinase-3/signal transducer and activator of transcription-1/forkhead box o-1 axis. Dis Markers, 2022, 2022: 5699275. doi: 10.1155/2022/5699275.

[9] 谢和平, 刘吉峰, 高明忠, 等. 深地医学研究进展及构想. 四川大学学报(医学版), 2018, 49 (2): 163-168.
XIE H P, LIU J F, GAO M Z, *et al*. The research advancement and conception of the deep-underground medicine. J Sichuan Univ (Med Sci), 2018, 49 (2): 163-168.

[10] 白亚宁, 孙晓茹, 文巧, 等. 极端环境对人类睡眠的影响. 四川大学学报(医学版), 2024, 55 (4): 1034-1043. doi: 10.12182/20240760402.
BAI Y N, SUN X R, WEN Q, *et al*. Effects of extreme environments on human sleep. J Sichuan Univ (Med Sci), 2024, 55 (4): 1034-1043. doi: 10.12182/20240760402.

[11] LIU Y, GAO Y, CHENG J, *et al*. Transcriptome analysis of well-differentiated laryngeal squamous cell carcinoma cells in below-background environment. Ann Transl Med, 2022, 10: 824. doi: 10.21037/atm-22-2997.

[12] LIU J, MA T, GAO M, *et al*. Proteomic characterization of proliferation inhibition of well-differentiated laryngeal squamous cell carcinoma cells under below-background radiation in a deep underground environment. Front Public Health, 2020, 8: 584964. doi: 10.3389/fpubh.2020.584964.

[13] LIU J, MA T, GAO M, *et al*. Proteomics provides insights into the inhibition of Chinese hamster V79 cell proliferation in the deep underground environment. Sci Rep, 2020, 10: 14921. doi: 10.1038/s41598-020-71154-z.

[14] MORCIANO P, IORIO R, IOVINO D, *et al*. Effects of reduced natural background radiation on *Drosophila melanogaster* growth and development as revealed by the FLYINGLOW program. J Cell Physiol, 2018, 233: 23-29. doi: 10.1002/jcp.25889.

[15] CASTILLO H, SCHODERBEK D, DULAL S, *et al*. Stress induction in the bacteria *Shewanella oneidensis* and *Deinococcus radiodurans* in response to below-background ionizing radiation. Int J Radiat Biol, 2015, 91: 749-756. doi: 10.3109/09553002.2015.1062571.

[16] SMITH G B, GROF Y, NAVARRETTE A, *et al*. Exploring biological effects of low level radiation from the other side of background. Health Phys, 2011, 100: 263-265. doi: 10.1097/hp.0b013e318208cd44.

[17] CASTILLO H, SMITH G B. Below-background ionizing radiation as an environmental cue for bacteria. Frontiers in Microbiology, 2017, 8. doi: 10.3389/fmicb.2017.00177.

[18] PENG S, CAI X, CHEN J, *et al*. The role of CELF family in neurodevelopment and neurodevelopmental disorders. Neurobiol Dis, 2024, 197: 106525. doi: 10.1016/j.nbd.2024.106525.

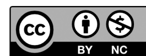
[19] FORRESTER-GAUNTLETT B, PETERS L, OBACK B. Grainyhead-like 2 is required for morphological integrity of mouse embryonic stem cells and orderly formation of inner ear-like organoids. Front Cell Dev Biol, 2023, 11: 1112069. doi: 10.3389/fcell.2023.1112069.

[20] SHEN X, ANIRUDHAN J, FATIMA A, *et al*. Evidence that dmrta2 acts through repression of pax6 in cortical patterning and identification of a mutation impairing DNA recognition associated with microcephaly in human. eNeuro, 2025, 12 (6): ENEURO. 0377-24.2025. doi: 10.1523/ENEURO.0377-24.2025.

[21] NAGIRNAJA L, VENCLOVAS C, RULL K, *et al*. Structural and functional analysis of rare missense mutations in human chorionic gonadotrophin beta-subunit. Mol Hum Reprod, 2012, 18: 379-390. doi: 10.1093/molehr/gas018.

（2025－06－23收稿, 2025－08－23修回）

编辑　何学令



开放获取　本文使用遵循知识共享署名—非商业性使用4.0国际许可协议（CC BY-NC 4.0），详细信息请访问https://creativecommons.org/licenses/by-nc/4.0/。

OPEN ACCESS　This article is licensed for use under Creative Commons Attribution-NonCommercial 4.0 International license (CC BY-NC 4.0). For more information, visit https://creativecommons.org/licenses/by-nc/4.0/.

© 2025《四川大学学报(医学版)》编辑部

Editorial Office of *Journal of Sichuan University (Medical Sciences)*