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· 实验室介绍 ·

马翠, 教授、博士研究生导师, 主要从事肺动脉高压发病机制的基础研究与转化工作。马翠教授深耕肺动脉高压发病机制研究十余载, 带领团队构建“临床问题–基础研究–转化应用”的全链条科研范式, 发现部分肺动脉高压患者存在独特的基因超级增强子修饰, 由此提出了“转录因子–超级增强子–基因启动子”染色质环路互作假说。通过染色质免疫沉淀、单细胞测序与空间转录组等技术, 首次揭示内皮细胞亚群HCG20/U2AF2/EIF2AK2信号轴在肺血管重塑中的核心调控作用。团队系列成果发表于*Circ Res*、*Arterioscler Thromb Vasc Biol*以及*Hypertension*等杂志, 相关成果获评教育部自然科学成果二等奖、黑龙江省自然科学技术奖三等奖、中华医学会自然科学技术奖三等奖等多项科技奖励; 团队申报国家发明专利3项, 为肺动脉高压早期诊断和治疗药物研发提供了潜在靶点。

靶向超级增强子的肺血管稳态调控及潜在治疗策略

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摘要 超级增强子(super-enhancer, SE)是一类由多个增强子簇组成、具有强转录激活能力的顺式调控元件, 通过富集高密度转录因子、共激活因子及活性组蛋白修饰标记, 驱动关键基因的高水平表达。研究表明, SE在细胞命运决定、组织稳态维持及疾病发生发展过程中发挥关键调控作用。肺血管稳态依赖于内皮细胞与平滑肌细胞之间精细的转录调控和信号协同, 而SE能够整合机械力、代谢信号、炎症反应及缺氧等多种信号, 在肺血管相关细胞中调控关键基因表达, 参与血管功能维持与病理重构。在肺动脉高压中, SE驱动的转录调控网络在肺动脉平滑肌细胞、肺动脉内皮细胞以及成纤维细胞和免疫细胞等多种细胞类型病变中发挥关键作用。SE通过调控细胞增殖、表型转换、代谢重编程、炎症反应信号及细胞间通信等机制参与肺血管重构并促进肺动脉高压等多种肺部疾病的发生发展。与此同时, 针对SE依赖性转录程序的干预策略也不断发展, 包括靶向BET蛋白及CDK等的小分子抑制剂、CRISPR/Cas9基因编辑与表观基因组编辑技术、基于染色质三维结构的调控策略以及转录因子靶向降解技术等, 为靶向SE维持肺血管稳态的精准治疗策略提供了新的思路。该文系统综述了SE的基本特征及其在肺血管稳态中的调控作用, 以及当前针对SE的潜在治疗策略研究, 为相关疾病的机制研究和SE靶向治疗提供了参考。

关键词 超级增强子; 肺血管稳态; 肺动脉高压; 表观遗传调控; 超级增强子相关非编码RNA; 靶向治疗

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Super-Enhancer-Targeted Regulation of Pulmonary Vascular Homeostasis and Its Therapeutic Potential

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Abstract SE (super-enhancer) is a class of *cis*-regulatory elements composed of clusters of multiple enhancers that possess strong transcriptional activation capabilities. SE drives the high expression of key genes by enriching high-density transcription factors, co-activators, and active histone modification marks. Studies have shown that SE plays critical regulatory roles in cell fate determination, maintenance of tissue homeostasis, and the onset and progression of diseases. Pulmonary vascular homeostasis relies on the fine-tuned transcriptional regulation and signaling synergy between endothelial cells and vascular smooth muscle cells. SE integrates multiple signals, including mechanical forces, metabolic signals, inflammatory responses, and hypoxia, to regulate the expression of key genes in pulmonary vascular-related cells, thereby participating in the maintenance of vascular function and pathological remodeling. In pulmonary hypertension, the SE-driven transcriptional regulatory network plays a key role in the pathology of various cell types, such as pulmonary artery smooth muscle cells, pulmonary artery endothelial cells, fibroblasts, and immune cells. SE contributes to pulmonary vascular remodeling and promotes the development and progression of various pulmonary diseases, including pulmonary hypertension, by regulating processes such as cell proliferation, phenotypic transformation, metabolic reprogramming, inflammatory signaling, and intercellular communication. Meanwhile, intervention strategies targeting SE-dependent transcriptional programs are continuously evolving, including small molecule inhibitors such as those targeting BET proteins and CDKs, CRISPR/Cas9-based gene editing and epigenomic editing technologies, regulatory strategies based on the three-dimensional structure of chromatin, and transcription factor-targeted degradation technologies. These approaches offer new insights into precision therapeutic strategies aimed at maintaining pulmonary vascular homeostasis by targeting SE. This article systematically reviews the fundamental characteristics of SE, their regulatory roles in pulmonary vascular homeostasis, and current research on potential therapeutic strategies targeting SE, providing a reference for mechanistic studies of related diseases and SE-targeted therapies.

Keywords super-enhancer; pulmonary vascular homeostasis; pulmonary hypertension; epigenetic regulation; super-enhancer-associated non-coding RNA; targeted therapy

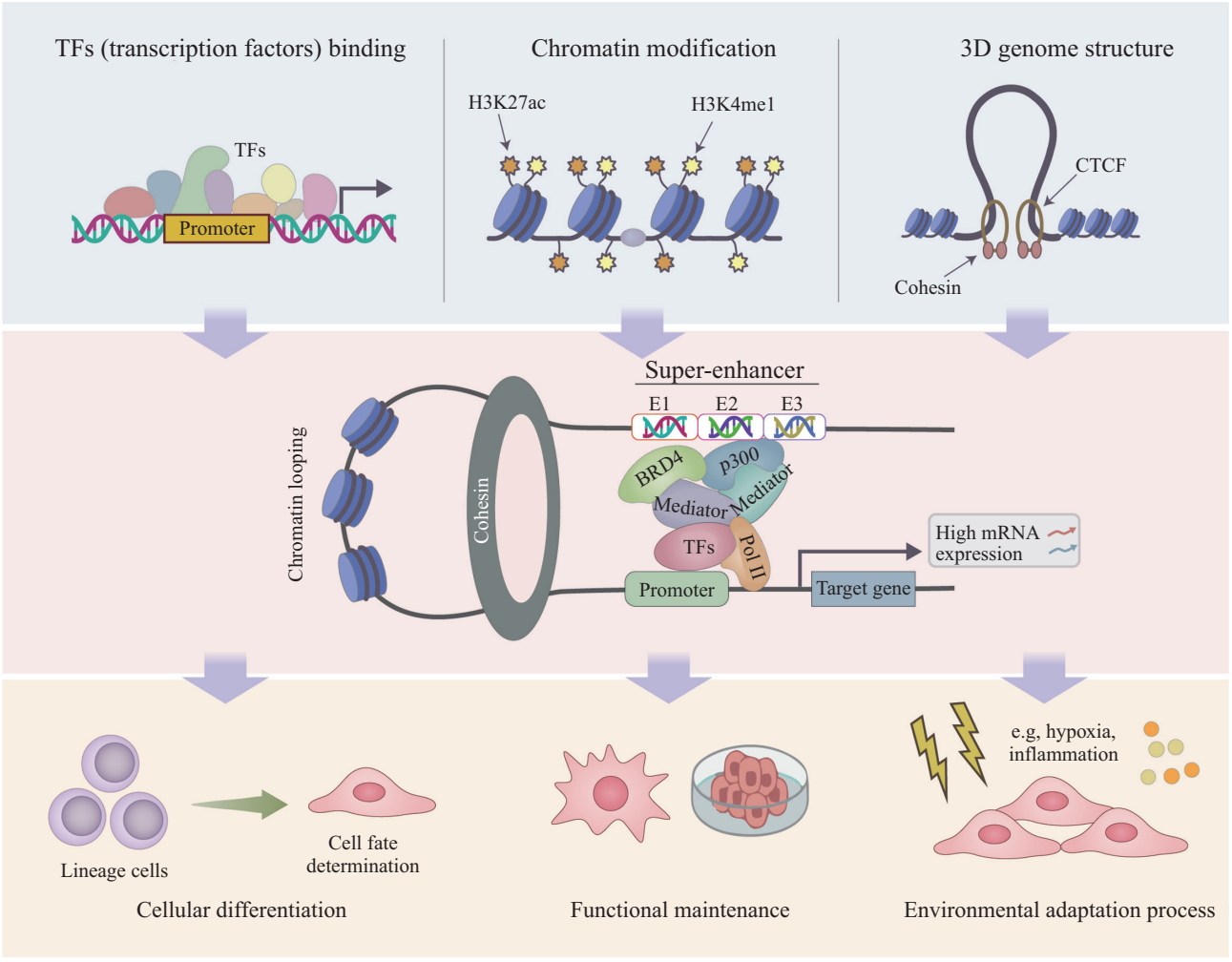
1 超级增强子概述

超级增强子(super-enhancer, SE)是一类由多个空间上相邻的典型增强子(typical-enhancer, TE)聚集形成的具有显著转录激活能力的顺式调控元件[1]。TE是一类能够结合转录因子(transcription factors, TFs)及转录辅激活因子, 通过促进靶基因启动子转录活性调控基因表达的顺式调控元件, 通常以单个增强子形式发挥作用[2]。与TE相比, SE不仅具有更大的基因组跨度和更广泛的活性组蛋白修饰区域, 还能够募集更高密度的TFs、Mediator复合物、溴结构域蛋白4(bromodomain-containing protein 4, BRD4)等转录辅激活因子, 并通过形成稳定的增强子–启动子染色质环及转录凝聚体, 建立高效的转录调控中心, 从而持续驱动细胞身份决定基因及疾病相关关键基因的高水平表达[3-4]。相比之下, TE主要调控一般功能基因, 其转录激活能力通常弱于SE[5]。SE的基因组跨度通常可达8~20 kb, 并富集组蛋白H3赖氨酸27乙酰化(histone H3 lysine 27 acetylation, H3K27ac)及组蛋白H3赖氨酸4单甲基化(histone H3 lysine 4 monomethylation, H3K4me1)等活性增强子标记[6]。通过染色质免疫共沉淀技术(chromatin immunoprecipitation, ChIP)及DNA-蛋

白互作研究技术CUT&Tag(cleavage under targets and tagmentation)等, 科研人员能够检测H3K27ac及H3K4me1等活性增强子标志及相关转录因子的富集特征, 同时可以识别并鉴定SE及其相关基因[7]。根据不同的定义策略, 科研人员可基于H3K27ac信号强度、转录因子占位或染色质互作特征对SE开展鉴定和分类。SE在不同细胞类型中呈现显著特异性, 主要调控细胞身份决定基因及疾病相关关键基因[8]。在病理状态下, 异常激活的SE可介导驱动炎症反应、细胞增殖及代谢重编程等的相关基因表达, 从而参与疾病发生发展[9](图1)。

2 血管稳态及其调控机制

血管稳态是血管系统在生理波动或病理刺激下, 通过细胞间通信、信号转导和代谢调控维持结构与功能动态平衡的过程[10], 其核心依赖于内皮细胞(endothelial cells, ECs)与血管平滑肌细胞(vascular smooth muscle cells, VSMCs)的功能协同[11-12]。近年



上: SE的形成起始于上游信号驱动的转录因子在多个相邻增强子区域的结合, 进而促进活性组蛋白修饰富集以及由CTCF和黏连蛋白复合体介导的三维(3D)基因组结构重塑, 使增强子簇在三维结构中聚集形成SE。中: 成熟的SE进一步富集转录因子(TFs)、BRD4、Mediator及RNA聚合酶II(Pol II)等转录复合体, 形成正反馈放大环路, 从而驱动靶基因的高水平表达。下: SE参与驱动的高水平基因表达在细胞谱系分化、功能维持及环境适应(如缺氧和炎症)等生物学过程中发挥关键调控作用。

Top: the formation of SE (super-enhancer) is initiated by the binding of upstream signal-driven transcription factors to multiple adjacent enhancer regions, which promotes the enrichment of active histone modifications and 3D (three-dimensional) genome reorganization mediated by CTCF and Cohesin. These processes facilitate the spatial clustering of enhancer elements, leading to the formation of SEs. Middle: mature SE further recruits and enriches transcriptional regulatory complexes, including TFs (transcription factors), BRD4, Mediator, and RNA Pol II (polymerase II), thereby establishing a positive feedback amplification loop that drives high-level expression of target genes. Bottom: SE-mediated gene expression program plays key regulatory roles in cell lineage specification, functional maintenance, and environmental adaptation (e.g., hypoxia and inflammation).

图1 SE的结构特征及其功能

Fig.1 Structural characteristics and functional roles of SE

来研究表明，机械力转导在维持血管稳态中发挥重要作用，ECs通过机械敏感离子通道Piezo1感知血流剪切力，激活内皮型一氧化氮合酶/一氧化氮(endothelial nitric oxide synthase/nitric oxide, eNOS/NO)信号通路并调控细胞骨架重排，从而维持血管舒张和抗炎表型[13]。在血管壁中层，VSMCs的表型转换是维持血管稳态的重要机制，其由收缩型向合成型转换受生长因子、线粒体动力学及自噬等因素调控，并参与动脉粥样硬化斑块稳定性的调节[14]。此外，炎症微环境和氧化应激被认为是破坏血管稳态的重要驱动因素。炎症因子可诱导ECs功能障碍，促进血小板黏附和凝血酶生成，从而促进血栓形成[15]。而线粒体活性氧(reactive oxygen species, ROS)积累导致的氧化还原失衡与血管衰老和硬化密切相关[16]。SE通过依赖信号响应性转录因子的募集、组蛋白修饰状态的动态变化及染色质空间结构重塑，整合机械力、代谢及炎症反应等多种信号，在ECs与VSMCs中调控关键基因的特异性表达，从而影响血管张力、屏障功能及血管重塑等重要生理过程[17]。系统解析SE在血管稳态调控中的作用，有助于深入理解血管疾病发生发展的分子机制，并为靶向SE的干预策略提供新的理论依据。

3 SE与肺血管稳态

在生理条件下，肺血管稳态依赖于精细调控的转录程序，以维持血管张力、内皮屏障完整性及细胞静息状态[18]。作为一类关键的顺式调控元件，SE可通过富集转录共激活因子(如BRD4)，参与炎症反应相关基因转录程序的调控，从而在肺血管ECs和VSMCs中维持炎症反应与细胞增殖之间的动态平衡[19]。此外，ECs中的机械敏感性SE可响应血流剪切力变化，调控与氧化应激及代谢重编程相关基因的转录活性，从而影响血管内皮功能及适应性稳态[20]。然而，在缺氧、炎症反应及血流动力学改变等因素的刺激下，SE的活性和分布可发生动态重编程，导致稳态转录网络失衡，并伴随促增殖、炎症及代谢重编程相关基因的异常表达，从而破坏肺血管结构与功能稳态[21]。从机制层面看，SE是整合缺氧、机械力及炎症反应等上游环境信号的重要转录调控枢纽[9,22]。上述刺激可通过核因子κB(nuclear factor κB, NF-κB)等信号轴重塑增强子景观，影响SE的形成与活性，最终构建上游信号-SE重编程–靶基因表达异常的调控轴[23]。

3.1 肺动脉平滑肌细胞

肺动脉平滑肌细胞(pulmonary artery smooth muscle cells, PASMCs)是维持肺血管张力与血管结构稳定的关键细胞类型，其异常增殖、凋亡抵抗及表型转换可直接驱动肺血管重构，并参与多种肺血管疾病，尤其是肺动脉高压(pulmonary hypertension, PH)的发生发展[24]。

3.1.1 SE调控PASMCs增殖和代谢重编程

PASMCs的病理性增殖和代谢重编程是PH的核心病理特征[25]。随着表观遗传调控研究的深入，越来越多的证据表明，SE在PASMCs异常增殖及代谢重编程过程中发挥重要的上游调控作用。例如，在缺氧诱导的PH进程中，核小体组装蛋白1样蛋白4(nucleosome assembly protein 1 like 4, NAP1L4)发生核转位并增强己糖激酶II(hexokinase II, HK II)的编码基因*HK2*启动子区SE活性，从而显著上调*HK2*的转录，促进PASMCs增殖与糖酵解，最终加速肺血管重构并促进PH的发展[26]。此外，也有证据表明，SE通过招募转录因子叉头盒J3(forkhead box J3, FOXJ3)参与调控Glu/Asp富集羧基末端结构域CREB结合蛋白/p300互作转录激活因子2[(CREB-binding protein, CBP)/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 2, CITED2]持续高表达，从而限制缺氧条件下PASMCs的异常增殖并延缓PH的进展[21]。SE相关的长链非编码RNA(long non-coding RNA, lncRNA)在PASMCs代谢调控中同样发挥重要作用。研究表明，在缺氧条件下，CCAAT/增强子结合蛋白β(CCAAT/enhancer-binding protein β, CEBPB)可被招募至lncRNA LINC01013的启动子区域并协同SE将其激活，参与调控其转录及表达上调。LINC01013进一步诱导电压依赖性阴离子通道1(voltage-dependent anion channel 1, VDAC1)寡聚化并引发线粒体功能失调，包括氧化应激作用增强和糖酵解水平升高，进而参与调控PASMCs增殖及炎症，最终加速PH的进展[27]。近期研究发现，在缺氧诱导的PASMCs中，SE相关LINC00599表达显著上调。LINC00599依赖N^6-甲基腺苷(N^6-methyladenosine, m^6A)修饰，与GTP酶激活蛋白SH3结构域结合蛋白1(GTPase-activating protein SH3 domain-binding protein 1, G3BP1)及细胞骨架蛋白肌球蛋白重链9(myosin heavy chain 9,

MYH9)形成液–液相分离结构, 这一过程与PASMCs增殖及血管重塑相关。敲低LINC00599可显著缓解PH相关病理改变, 进一步提示SE在PASMCs病理激活过程中具有潜在的治疗靶点价值[28]。

3.1.2 SE调控PASMCs程序性细胞死亡及炎症反应 进一步研究发现, SE可通过调控多种程序性细胞死亡形式(如焦亡及泛凋亡), 参与PASMCs炎性病变及功能重编程。例如, SE可通过形成特异性染色质环结构, 招募转录因子叉头盒P3(forkhead box P3, FOXP3)至UNC5B-AS1的启动子区域, 进一步抑制其转录。UNC5B-AS1表达的下调进一步通过影响组蛋白H3K18乳酸化, 介导PASMCs炎性表型转换和肺血管重塑, 最终参与PH的发生发展[29]。此外, 在缺氧诱导的PH模型中, 环状RNA肌球蛋白重链8(circular RNA myosin heavy chain 8, circ-MYH8)通过招募组蛋白赖氨酸乙酰转移酶7(lysine acetyltransferase 7, KAT7)增强Fos样蛋白2(Fos-like antigen 2, *FOSL2*)位点的H3K27ac修饰并激活其相关SE, 该过程使*FOSL2*转录活性增强, 从而诱导PASMCs发生泛凋亡, 最终加剧肺血管重构并推动PH进展[30]。另一项研究表明, 在缺氧条件下, SE参与调控PASMCs中环状RNA Lrch3(circular RNA leucine-rich repeats and calponin homology domain containing 3, circ-Lrch3)的表达, 并在其宿主基因*LRCH3*位点形成R环(R-loop)结构。抑制SE活性可破坏R-loop结构稳定性, 进而增强炎性小体信号并促进细胞焦亡, 最终加重肺血管重构并推动PH的进展[31]。值得注意的是, SE的激活并非单向促进炎症反应。在缺氧等病理刺激下, SE高度活化并富集H3K27ac修饰, 与配对样同源盒转录因子1(paired like homeodomain 1, PITX1)协同作用, 驱动双特异性磷酸酶4(dual-specificity phosphatase 4, *DUSP4*)的转录上调。*DUSP4*通过抑制丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路减轻程序性细胞死亡, 在一定程度上限制PASMCs的病理性重塑并延缓PH的进展[32]。

上述研究表明, SE对PH进程的调控具有情境依赖性, 其功能差异主要取决于所调控的靶基因类型及细胞状态, 而非SE本身结构特征的差异(表1)。

3.1.3 SE调控PASMCs自噬与表型转换 PASMCs的过度自噬也是肺血管重塑的重要因素之一[33]。除上述程序性细胞死亡调控外, PASMCs的自噬水平同样受到SE的直接影响。研究表明, 在缺氧条件下, PASMCs内SE被激活并参与调控环状RNA钙调蛋白4(circular RNA calmodulin 4, circ-CALM4)的异常上调。circ-CALM4通过招募转录因子嘌呤富集元件结合蛋白B(purine-rich element binding protein B, Purb), 显著提升自噬相关蛋白Beclin 1编码基因*BECN1*的转录水平, 进而激活PASMCs自噬, 促进肺血管重构并推动PH的发生发展[34]。此外, 在PH相关病理条件下, PASMCs的表型转换也受到SE相关非编码RNA的调控。SE驱动的UNC5B-AS1通过调控乳酰化修饰介导的炎症反应信号, 促进PASMCs增殖及炎症激活, 并下调收缩表型标志物钙调蛋白结合蛋白1(calponin 1, CNN1)和平滑肌蛋白22α(smooth

表1 SE调控PASMCs功能及PH进展的代表性研究

Table 1 Representative studies on SE-mediated regulation of PASMC functions and PH progression

SE相关分子 SE-related molecules	靶基因/下游通路 Target genes/downstream pathways	主要生物学效应 Major biological effects	对PH影响 Impacts on PH
NAP1L4	HK II	Glycolysis ↑ Proliferation ↑	Promotes PH
LINC01013	VDAC1	Mitochondrial damage Glycolysis ↑	Promotes PH
LINC00599	G3BP1/MYH9	Formation of LLPS Proliferation ↑	Promotes PH
circ-MYH8	Inflammatory phenotypic switching	Panoptosis ↑	Promotes PH
UNC5B-AS1	H3K18la	Inflammatory phenotypic switching	Attenuates PH
FOXJ3	CITED2	Inhibition of proliferation	Attenuates PH
circ-Lrch3	Pyroptosis regulation	Pyroptosis inhibition	Attenuates PH
PITX1	*DUSP4*	MAPK inhibition	Attenuates PH

↑: 上调。

↑: upregulated.

muscle protein 22α, SM22α)的表达, 上调炎症/合成表型标志物骨桥蛋白(osteopontin, OPN)和Krüppel样因子4(Krüppel-like factor 4, KLF4)的表达, 从而驱动PASMCs向炎症性合成表型转换并参与肺血管重构[29]。

3.1.4 SE介导细胞间通信 除调控PASMCs自身代谢和增殖等生物学过程外, SE还可通过介导肺血管细胞间通信影响肺血管稳态。研究发现, 缺氧导致SE异常激活与PASMCs中多配体蛋白聚糖4(syndecan-4, SDC4)的持续高表达相关。SDC4通过促进肺动脉内皮细胞(pulmonary artery endothelial cells, PAECs)与PASMCs之间的细胞间通信, 介导PASMC在缺氧条件下的增殖和迁移, 进一步推动肺血管重塑和PH发展[35]。类似地, PASMCs在缺氧处理后, MIR100HG受SE的影响表达上调, 其通过与无义转录本调控因子1(regulator of nonsense transcripts 1, UPF1)相互作用调节核因子2相关因子2(nuclear factor erythroid 2-related factor 2, *NRF2*) mRNA的稳定性, 参与调控氧化损伤和炎症因子的释放, 进而促进PASMCs与巨噬细胞互作, 招募巨噬细胞向肺血管募集, 推动肺血管炎性微环境形成及PH进展[36]。

上述研究表明, SE在PASMCs中主要通过调控代谢重编程、炎症反应、自噬及表型转换等过程, 驱动其异常增殖和功能重编程, 从而参与调控肺血管重构。这为深入理解PH的发病机制及开发新的治疗策略提供了重要理论依据。

3.2 肺动脉内皮细胞

肺动脉内皮细胞(PAECs)是感知血流动力学变化、氧张力波动及炎症刺激的重要细胞类型, 其功能障碍被认为是肺血管重构和PH发生的早期事件之一[37]。研究表明, 除传统转录因子和信号通路外, 表观遗传调控在PAECs病理重塑中的作用逐渐受到关注[38-39]。其中, SE通过重塑增强子景观并协同表观遗传修饰调控关键基因表达, 进而参与肺血管重塑, 这一调控模式已在多组学研究中得到进一步验证。Reyes等[40]通过整合PH患者来源PAECs的RNA测序(RNA sequencing, RNA-Seq)、染色质免疫共沉淀测序(chromatin immunoprecipitation sequencing, ChIP-Seq)检测组蛋白修饰(H3K27ac、H3K4me1、H3K4me3)水平, 发现在疾病状态下PAECs的活性增强子景观发生显著重塑, 其中部分增强子区域进一步扩展并获得SE特征, 从而驱动异常的基因调控网络并参与PH的发生发展。

3.2.1 SE驱动的circRNA 在缺氧等病理刺激下, SE活性改变可调控非编码RNA介导的ECs功能异常。例如, 在缺氧条件下PAECs中角蛋白4(keratin 4, *Krt4*)基因座相关的SE被显著激活并富集H3K27ac修饰, 通过招募转录因子CCAAT/增强子结合蛋白α(CCAAT/enhancer-binding protein α, CEBPA)促进环状RNA circ-Krt4的转录。功能学研究表明, SE依赖性高表达的circ-Krt4可通过与富嘌呤序列结合蛋白A(purine-rich element binding protein A, Pura)相互作用参与调控内皮–间充质转化(endothelial-to-mesenchymal transition, EndMT)。同时, SE通过结合线粒体甘油激酶(glycerol kinase, GLPK)扰乱线粒体稳态并加剧线粒体呼吸异常及氧化应激损伤, 从而导致PAEC增殖和迁移, 最终促进肺血管重构并推动PH进展[41]。

3.2.2 SE驱动的lncRNA SE还可通过调控lncRNA参与PAECs功能障碍。近期研究发现, SE驱动的lncRNA HLA复合体第20组基因(HLA complex group 20, HCG20)在缺氧PAECs中显著上调。机制研究显示, HCG20能够直接结合可变剪接因子U2小核RNA辅助因子2(U2 small nuclear RNA auxiliary factor 2, U2AF2), 促进下游真核翻译起始因子2α激酶2(eukaryotic translation initiation factor 2α kinase 2, *EIF2AK2*)基因的异常剪接, 从而诱导PAECs焦亡及EndMT。同时, 过表达的HCG20还可通过内皮来源外泌体释放并被邻近的PASMCs摄取, 进而促进其增殖。在多种PH小鼠及大鼠模型中, 特异性干预ECs HCG20表达能够显著抑制肺血管重塑, 并逆转PH表型[42]。

上述研究表明, SE通过重塑PAECs的增强子景观并调控circRNA及lncRNA等非编码RNA调控网络, 介导PAECs炎症反应、细胞程序性死亡及EndMT等多种病理过程, 从而在肺血管重构及PH发生发展中发挥重要调控作用。

3.3 其他细胞

肺血管稳态的维持依赖于肺部微环境多种细胞类型之间高度协调的转录调控与细胞间互作, 包括成纤维细胞、免疫细胞等[43]。在这一背景下, 系统梳理不同细胞群体中SE介导的转录调控机制, 有助于从多细胞整体网络层面深化对肺血管稳态失衡及肺血管疾病发生发展的认识。

3.3.1 肺成纤维细胞 成纤维细胞作为一种重要的间充质细胞, 主要通过调节细胞外基质(extracellular matrix, ECM)的更新与重塑, 在伤口愈合和组织再生过程中发挥作用[44]。然而, 在病理条件下, 成纤维细胞向肌成纤维细胞异常分化被认为是肺纤维化(pulmonary fibrosis, PF)发生发展的核心机制之一[45]。研究人员基于H3K27ac ChIP-Seq对PF组织样本进行分析, 发现SE能够靶向并参与调控一类病理性成纤维细胞相关基因的高水平转录, 从而维持成纤维细胞的持续异常激活状态。这一过程不仅促进ECM过度沉积及增强细胞迁移能力, 还通过放大旁分泌信号进一步加剧肺组织结构重塑及PF进展[46]。此外, SE还可通过调控关键转录因子表达维持成纤维细胞的致病性表型。研究表明, 在肺成纤维细胞中, SE与转录因子叉头盒L1(forkhead box L1, *FOXL1*)的高水平表达相关, 直接调控多种与ECM重塑及细胞增殖相关的下游分子, 包括骨形态发生蛋白(bone morphogenetic protein, BMP)、血小板源性生长因子受体α(platelet-derived growth factor receptor α, PDGFRα)以及TAZ/YAP(transcriptional co-activator with PDZ-binding motif/Yes-associated protein)信号通路相关分子等。当*FOXL1*被沉默时, 上述功能基因的转录水平显著下降, 提示SE通过调控*FOXL1*的表达维持成纤维细胞的功能活性, 并可能通过重塑血管周围微环境间接参与肺血管稳态失衡及特发性PF的发生发展[47]。

3.3.2 肺泡巨噬细胞 肺泡巨噬细胞作为肺组织中重要的免疫调控细胞, 其极化状态可显著影响肺血管周围炎症反应、细胞因子释放水平及血管通透性[48]。在慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)等慢性肺部炎症状态下, 极化的肺泡巨噬细胞伴随大量SE激活, 并显著富集于促炎及组织破坏相关基因位点。机制研究表明, 这些SE能够募集BRD4等转录共激活因子, 参与调控基质金属蛋白酶12(matrix metalloproteinase 12, *MMP12*)、白细胞介素-1β(interleukin 1β, *IL1B*)等致病基因的持续高表达, 从而放大局部炎症反应并促进肺泡结构破坏[49]。

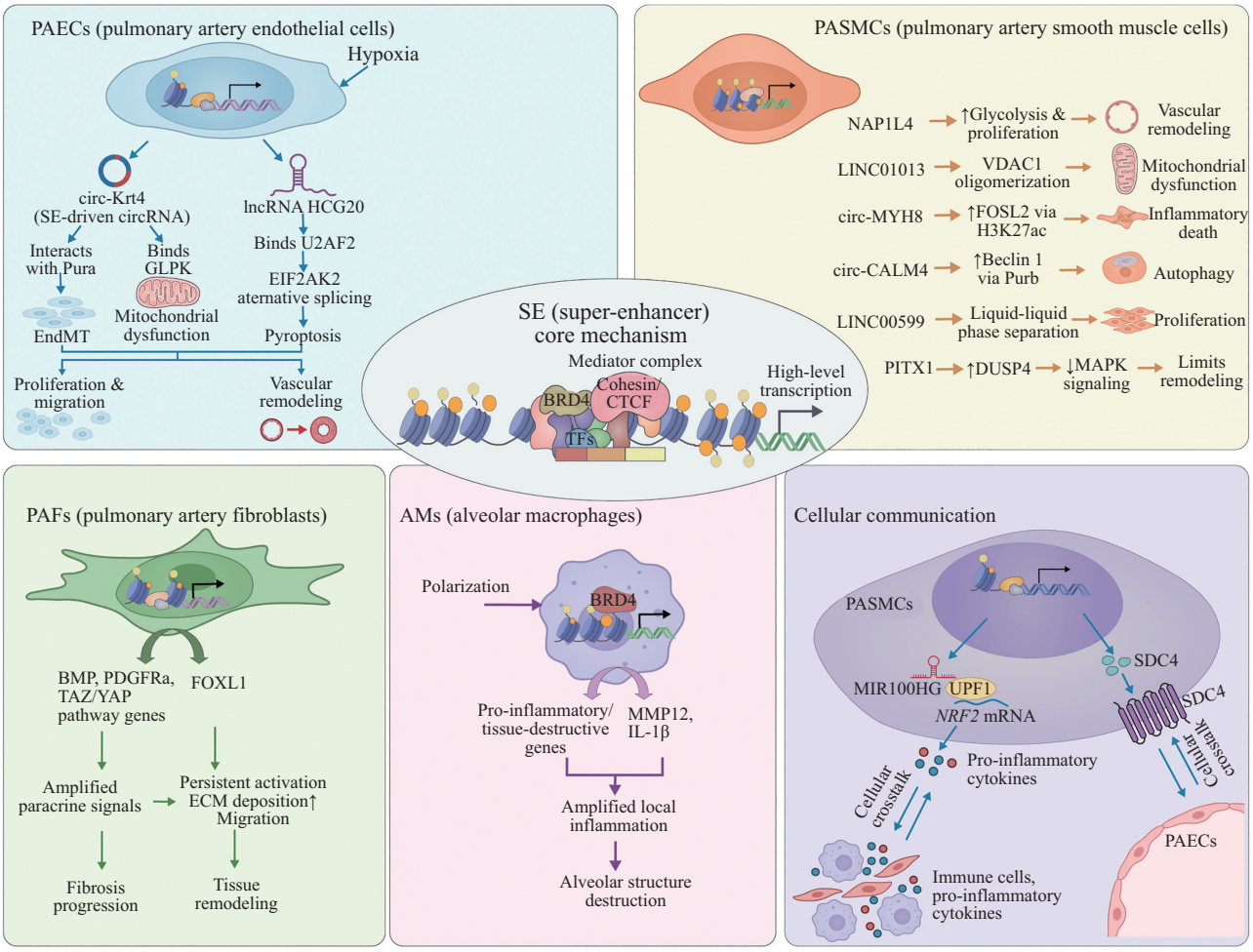
综上所述, SE在肺血管系统中的调控作用呈现出若干共性机制: 一是通过重塑代谢相关基因的增强子活性, 驱动细胞代谢重编程; 二是通过激活炎症反应相关基因及信号通路, 放大炎症反应; 三是通过调控程序性细胞死亡(包括凋亡、焦亡及泛凋亡等)、自噬及表型转换相关过程, 介导细胞功能重编程; 四是通过驱动非编码RNA表达, 构建多层次转录调控网络; 五是通过影响细胞间通信, 协调不同细胞类型间的功能互作。上述机制共同构成了SE参与肺血管稳态调控及疾病发生发展的核心分子基础。基于上述机制, SE在不同肺部相关细胞类型中, 协调关键转录因子并调控相关基因的表达, 既参与维持各细胞的正常功能特性, 也可能在病理条件下通过细胞间通信影响肺血管稳态(图2)。

4 靶向SE的潜在治疗策略

4.1 靶向SE驱动转录程序的小分子化合物

4.1.1 BET家族靶向抑制剂 近年来, 靶向SE驱动转录程序的小分子抑制剂治疗策略已成为抗肿瘤及表观遗传研究领域的重要研究方向[50]。溴结构域和额外末端(bromodomain and extra-terminal, BET)蛋白家族, 特别是BRD4, 能够通过其溴结构域识别活化的组蛋白乙酰化标记, 如H3K27ac, 并优先富集于基因组SE区域。BRD4可促进RNA聚合酶II的募集并促进转录延伸, 从而维持SE驱动的致癌基因高表达[51]。因此, 靶向BRD4的小分子抑制剂在多种肿瘤模型中展现出显著的治疗潜力。例如, BET抑制剂JQ1能够下调SE调控的肿瘤干性相关基因的表达, 包括肿瘤蛋白P63(tumor protein P63, *TP63*)、MET原癌基因(MET proto-oncogene, *MET*)和Fos样蛋白1(Fos like 1, *FOSL1*), 从而抑制头颈部鳞状细胞癌的肿瘤侵袭、生长和转移[52]。另一种BET抑制剂OTX015能够破坏溴结构域蛋白2(bromodomain-containing protein 2, BRD2)、溴结构域蛋白3(bromodomain-containing protein 3, BRD3)和BRD4与染色质的结合, 抑制由SE驱动的MYC原癌基因(MYC proto-oncogene, *MYC*)及其下游转录, 并在急性白血病细胞中诱导细胞周期阻滞和凋亡[53], 进一步凸显靶向SE依赖性转录程序的治疗潜力。

4.1.2 CDK家族靶向抑制剂 除BET家族外, 与转录调控过程密切相关的细胞周期蛋白依赖性激酶(cyclin-dependent kinases, CDKs)在维持SE驱动的基因高水平转录输出方面也发挥关键作用[54]。在嵌合抗原受体T细胞(chimeric antigen receptor T-cell, CAR-T)治疗诱导的细胞因子释放综合征(cytokine release syndrome, CRS)模型中, CDK7抑制剂THZ1



SE在多种肺部相关细胞类型中通过调控关键基因及非编码RNA的异常表达, 参与肺血管稳态的维持及病理重塑过程。在PASMCs中, SE通过调控代谢重编程、炎症反应、自噬及表型转换, 参与调控细胞异常增殖和血管重构; 在PAECs中, SE通过驱动circRNA及lncRNA表达, 介导内皮功能障碍、炎症反应及EndMT; 在成纤维细胞中, SE促进肌成纤维细胞分化及ECM沉积; 在肺泡巨噬细胞中, SE通过激活炎症相关基因放大局部炎症反应。不同细胞类型之间还可通过非编码RNA、炎症因子及膜受体相关信号通路介导细胞间通信, 促进PASMCs、PAECs及免疫细胞之间的相互作用, 共同驱动肺血管微环境失衡和肺血管重构。

SE regulates the abnormal expression of key genes and non-coding RNAs across multiple lung-related cell types, contributing to pulmonary vascular homeostasis and pathological remodeling. In PASMCs, SE regulates metabolic reprogramming, inflammation, autophagy, and phenotypic switching, participate in the regulation of abnormal proliferation and vascular remodeling. In PAECs, SE drives circRNA and lncRNA expression, leading to endothelial dysfunction, inflammation, and EndMT. In fibroblasts, SE promotes myofibroblast differentiation and ECM deposition. In alveolar macrophages, SE amplifies local inflammatory responses by activating inflammation-related genes. Intercellular communication mediated by non-coding RNAs, inflammatory mediators, and membrane receptor-associated signaling pathways promotes crosstalk among PASMCs, PAECs, and immune cells, collectively driving pulmonary vascular microenvironment imbalance and vascular remodeling.

图2　SE在肺血管稳态及肺血管疾病中的多细胞调控作用

Fig.2　Multicellular regulatory roles of SE in pulmonary vascular homeostasis and disease

能够显著降低与SE相关的炎症反应基因[如信号转导与转录激活因子1(signal transducer and activator of transcription 1, *STAT1*)和*IL1B*]的表达水平, 同时抑制RNA聚合酶II在Ser5和Ser7位点的磷酸化, 从而缓解炎症反应[55]。类似地, 在前列腺癌中, CDK9抑制剂CDKI-73可降低RNA聚合酶II Ser2位点的磷酸化水平, 从而协同抑制雄激素受体(androgen receptor, AR)、MYC和BRD4等多条致癌相关信号通路, 并抑制SE相关基因表达, 在患者来源的类器官和异种移植模型中表现出显著的抗增殖作用[56]。

4.1.3　组蛋白乙酰化干预　在表观遗传调控层面, p300和CBP是关键的组蛋白乙酰转移酶, 可在增强子和SE区域促进H3K27ac修饰, 从而维持其活性并驱动靶基因的高水平转录[57]。选择性CBP/p300催化抑制剂A-485在雌激素受体阳性乳腺癌中表现出显著抑制作用。具体而言, A-485处理可显著降低

*MYC*和细胞周期蛋白D1(cyclin D1, *CCND1*)等致癌基因上游SE区域的H3K27ac富集水平, 从而抑制SE依赖性转录[58]。这表明, 通过药物阻断CBP/p300-H3K27ac轴这一策略能够有效干扰由SE驱动的致病性转录程序。此外, 组蛋白去乙酰化酶(histone deacetylases, HDACs)也参与调控SE相关乙酰化标记及染色质开放状态[59]。在胶质母细胞瘤模型中, 使用HDAC抑制剂如Panobinostat和Romidepsin处理后可显著重塑肿瘤特异性SE的H3K27ac景观, 并伴随SE相关基因位点RNA聚合酶II占据率降低, 从而干扰SE驱动的致癌转录程序[60]。

值得注意的是, 尽管上述小分子抑制剂的研究主要集中于肿瘤领域, 但靶向BET蛋白等SE相关调控因子的策略在肺动脉高压模型中已被证实具有一定疗效。例如, 研究表明, 临床可用的BET抑制剂RVX208在多中心前临床研究中可显著改善肺血管重构, 并逆转血流动力学异常以及PAECs和PASMCs的异常增殖、抗凋亡及炎症表型, 进一步支持其在肺血管疾病中的潜在应用价值[61-62]。

4.2 靶向SE的基因编辑与表观基因组编辑策略

4.2.1 CRISPR/Cas9技术 随着CRISPR/Cas9基因组编辑技术的发展, 研究人员可通过直接删除基因组中的SE序列, 在疾病模型中解析其转录调控功能[63]。例如, 在多种肿瘤模型中, CRISPR/Cas9介导删除Ephrin A型受体2(Ephrin type-A receptor 2, *EphA2*)相关SE可显著降低*EphA2*的表达水平。这一干预在体外和体内模型中均明显抑制了肿瘤细胞的增殖和迁移, 证明了靶向SE具有重要的功能意义[64]。类似地, 在卵巢癌研究中, 多组学分析鉴定出一组异常激活的SE, 这些SE主要调控核心致癌基因, 如配对盒基因8(paired box 8, *PAX8*)和*EphA2*。利用CRISPR/Cas9破坏这些SE可显著降低靶基因表达并抑制肿瘤细胞增殖[65]。总体而言, 这些研究从遗传学层面为利用CRISPR/Cas9靶向SE提供了有力证据, 这一手段既可作为功能研究工具, 也具有潜在的治疗应用价值。

4.2.2 CRISPRi技术 与不可逆的基因组删除相比, CRISPR干扰技术(CRISPR interference, CRISPRi)通过将失活型Cas9(dead Cas9, dCas9)与Krüppel相关盒结构域(Krüppel-associated box, KRAB)抑制结构域融合, 在不改变DNA序列的情况下对目标位点进行表观遗传抑制, 实现对SE活性的可逆调控[66]。在鼻咽癌研究中, CRISPRi抑制SRY相关HMG盒转录因子2(SRY-box transcription factor 2, *SOX2*)相关SE表达后, SE区域H3K27ac富集水平显著降低, 同时削弱增强子与启动子之间的染色质相互作用, 从而降低*SOX2*表达水平并削弱肿瘤细胞增殖及致瘤能力[67]。此外, 在主动脉血管ECs中, CRISPRi抑制*FOXP1*相关SE会削弱*FOXP1*依赖的转录激活能力并加速ECs衰老, 进一步说明SE驱动转录程序可以在不改变基因组序列的情况下被调控[68]。这些研究为在疾病背景下通过表观遗传靶向干预SE提供了实验依据。

尽管上述策略为实现SE的精准调控提供了重要技术基础, 但目前在肺血管疾病背景下的相关研究仍主要停留在机制探索阶段。

4.3 基于染色质空间结构的干预策略

研究证据表明, SE的功能在很大程度上依赖于其周围的三维染色质结构[69]。这一特性为从空间层面干预SE驱动的转录程序提供了新的研究思路。

4.3.1 Mediator复合体 转录介导子复合体Mediator作为连接增强子与启动子的核心转录共激活因子, 在SE区域高度富集, 并通过促进RNA聚合酶II组装以及介导增强子–启动子之间的相互作用来维持强效的转录输出[70]。研究表明, 利用dTAG系统急性降解Mediator后, 多个强效SE与其靶基因启动子之间的相互作用频率显著降低, 同时SE依赖基因的表达水平明显下调[71]。这些结果提示, 抑制Mediator功能能够有效干扰SE驱动的异常转录程序, 并可能具有潜在的治疗价值。在结直肠癌细胞中, siRNA敲低Mediator激酶模块的亚基(如MED12或MED13/MED13L)可显著降低多种肿瘤获得性SE驱动基因的mRNA水平, 并抑制肿瘤细胞增殖[72]。这些研究进一步支持了将功能性干扰Mediator亚基以选择性抑制SE依赖性转录作为抗肿瘤策略的可行性。

4.3.2 Cohesin/CTCF 由黏连蛋白复合体(Cohesin)和CCCTC结合因子(CCCTC-binding factor, CTCF)介导的染色质环结构在限制SE调控范围及其靶基因选择性方面发挥关键作用。SE通常位于拓扑关联结构域(topologically associating domains, TADs)内, 并通过Cohesin依赖的染色质环结构与靶基因启动子形成稳定的空间接触[73]。在小鼠胚胎干细胞中, 对PR/SET结构域蛋白14(PR/SET domain-

containing protein 14, *Prdm14*)相关SE周围染色质结构的分析表明, 该SE通过Cohesin/CTCF介导的环挤压(loop extrusion)机制维持与*Prdm14*启动子的空间邻近性。此外, 该SE还影响邻近基因溶质载体有机阴离子转运蛋白家族成员5A1(solute carrier organic anion transporter family member 5A1, *Slco5a1*)的表达, 进一步证明了Cohesin/CTCF介导的三维染色质拓扑结构在SE调控网络中的功能作用[74]。目前研究从不同层面证实, 干预Cohesin/CTCF可影响SE驱动的靶基因转录。首先, 针对CTCF的研究表明, CRISPR/Cas9介导的CTCF位点删除或CTCF降解会显著破坏Cohesin锚定的染色质环结构, 导致增强子–启动子接触频率下降。CTCF缺失后约90%的Cohesin依赖性环结构消失, 同时增强子–启动子相互作用强度下降20%~30%, 并伴随部分增强子依赖性基因表达下调[75]。其次, 在Cohesin层面, 其核心亚基RAD21的降解不仅导致染色质环结构大规模丧失, 还使CBP/p300依赖的增强子靶基因表达下调, 提示Cohesin在维持SE驱动转录中的关键作用[76]。

尽管针对染色质空间结构的有效干预在肺血管疾病中的研究仍较为有限, 但其在调控SE功能方面的潜在作用值得进一步探索。

4.4 靶向转录因子的干预策略

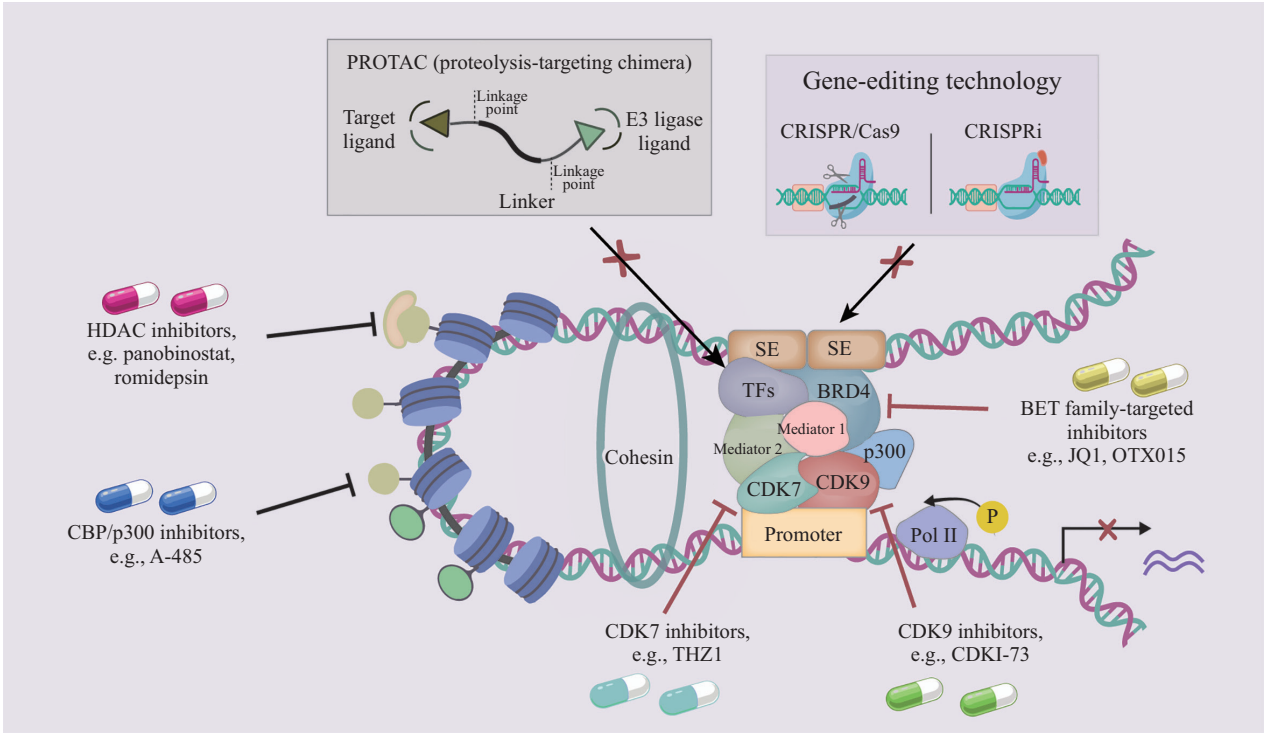
SE通常富集并依赖一组核心转录因子(core transcription factors, core TFs)及其协同辅因子, 以维持高度活跃的转录状态[77]。例如, 在胃癌模型中, SE可驱动core TFs核受体亚家族3C组成员1(nuclear receptor subfamily 3 group C member 1, *NR3C1*)的高表达, 从而激活下游致病转录程序并促进肿瘤细胞对化疗药物的耐受。药理学干预抑制SE活性或靶向*NR3C1*, 可显著重塑SE依赖的转录网络, 逆转5-氟尿嘧啶耐药并抑制肿瘤进展, 显示出良好的治疗潜力[78]。在葡萄膜黑色素瘤中, SE通过驱动小眼畸形相关转录因子(microphthalmia-associated transcription factor, *MITF*)和转录因子AP-2α(transcription factor AP-2α, *TFAP2A*)的高表达, 构建核心转录调控网络, 从而介导基因转录失调及代谢重编程并促进肿瘤进展。进一步研究发现, 干预这些core TFs的表达或活性可显著抑制SE依赖的转录并进一步限制肿瘤细胞生长, 提示靶向SE相关转录因子网络具有潜在的治疗价值[79]。

近年来, 蛋白降解靶向嵌合体(proteolysis-targeting chimera, PROTAC)技术为靶向以往被认为“不可成药”的转录因子提供了新的药理学干预策略[80]。PROTAC通过诱导泛素–蛋白酶体系统介导的降解, 可靶向SE相关core TFs或其关键辅因子, 在蛋白水平实现持续而高效的抑制。例如, 在骨肉瘤模型中, 靶向BRD4的PROTAC分子GNE-987通过诱导BRD4降解, 降低SE区域H3K27ac的富集水平, 并下调SE依赖的致癌基因表达。这一干预显著抑制了肿瘤细胞增殖并促进了细胞凋亡, 证明了该策略在破坏SE驱动致病转录程序方面的有效性[81]。此外, 另一项研究利用BRD4靶向PROTAC观察到SE相关相分离转录凝聚体中BRD4的解聚[82]。这一发现提示, PROTAC不仅能够降解关键蛋白, 还可能通过破坏SE相关转录凝聚体的结构来动态调控其功能, 从而进一步削弱SE驱动的转录活性。总体而言, PROTAC介导的靶向降解策略能够有效下调SE相关转录因子及其功能复合物, 从而系统性削弱SE驱动的致病转录网络活性, 凸显了该策略在未来精准治疗中的重要潜力。然而, 目前该类策略在肺血管疾病中的应用研究仍相对有限, 但其靶向SE核心转录调控网络的特性提示其具有潜在的转化价值。

综上, 靶向SE的干预策略可通过小分子抑制剂、表观遗传调控、基因编辑及染色质空间结构调控等多种方式干扰其驱动的异常转录程序。尽管相关研究主要集中于肿瘤领域, 但已有证据表明该类策略在肺动脉高压模型中可改善肺血管重构并可以减少炎症反应, 提示其潜在应用价值(图3)。

5 总结与展望

随着表观遗传学和三维基因组学研究的快速发展, SE作为驱动细胞特异性转录程序的重要调控元件, 其在血管稳态及疾病发生发展中的关键作用逐渐被揭示。大量研究表明, SE通过整合缺氧、机械力及炎症反应等上游信号, 并依赖转录因子募集、组蛋白修饰及染色质空间结构重塑, 构建环境刺激-SE重编程–靶基因表达改变的调控轴, 在PASMCs、PAECs以及成纤维细胞和免疫细胞等多种血管相关细胞中形成细胞特异性的转录调控网络, 从而维持血管结构与功能的动态平衡。在病理条件下, 如缺氧、炎症反应或氧化应激等刺激可导致SE景观重塑, 驱动关键致病基因及非编码RNA异常表达, 进而调控肺血管重构、炎症反应及代谢重编程等病理过程, 最



从转录调控、小分子抑制、基因/表观遗传编辑及染色质空间结构等多个层面干预SE活性, 从而抑制其驱动的异常基因转录。

SE activity can be modulated at multiple levels, including transcriptional regulation, small-molecule inhibition, genetic/epigenetic editing, and chromatin spatial organization, thereby suppressing SE-driven aberrant gene transcription.

图3 靶向SE的潜在治疗策略

Fig.3 Potential therapeutic strategies targeting SE

终破坏肺血管稳态并推动PH等疾病的进展。

与此同时, 针对SE驱动转录程序的干预策略正在不断发展。从药理学角度看, 小分子抑制剂如BET抑制剂、CDK抑制剂及CBP/p300抑制剂能够通过干扰SE相关转录复合体或改变表观遗传修饰, 有效抑制SE依赖性致病基因表达。基因编辑和表观基因组编辑技术(如CRISPR/Cas9和CRISPRi)则为直接调控SE活性提供了精准工具。此外, 基于三维染色质结构的干预策略以及转录因子靶向降解技术(如PROTAC)等方法, 也为靶向SE相关调控网络提供了新的治疗思路。这些多层次策略的出现, 使得从不同层面调控SE功能成为可能, 并为开发肺血管病变新型精准治疗手段奠定了基础。

尽管当前研究已取得重要进展, 但SE在肺血管稳态中的调控机制仍存在诸多亟待解决的问题。首先, 不同细胞类型之间SE调控网络的协同关系仍有待系统解析, 特别是在多细胞互作和微环境调控层面。其次, SE相关非编码RNA(如增强子RNA、长链非编码RNA和环状RNA)在肺血管疾病中的具体功能及其分子机制仍需进一步研究。此外, 如何在保证特异性和安全性的前提下实现SE靶向干预的临床转化, 也是未来研究的重要方向。

随着单细胞组学、空间转录组学及三维基因组学等技术的不断发展, 科研人员未来有望更加精确地描绘不同细胞类型中的SE调控图谱, 并深入解析其在肺血管稳态维持及疾病发生发展中的动态变化。同时, 结合新型药物递送系统及基因编辑技术, 靶向SE相关转录网络的精准干预策略有望为PH及其他肺血管疾病的治疗提供新的突破。因此, 进一步系统研究SE在肺血管系统中的功能及其调控机制, 不仅具有重要的基础研究意义, 也具有广阔的临床应用前景。

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