中国细胞生物学学报 Chinese Journal of Cell Biology 2025, 47(11): 2940–2949
DOI: 10.11844/cjcb.2025.11.0020
CSTR: 32200.14.cjcb.2025.11.0020

· 综述 ·

核旁斑调控DNA损伤应答的机制及其在癌症发生发展中的作用

张雨欣[1] 陈雯[1] 梁启惠[1] 丁胜勇[2] 吴海萃[3]*
([1]山东中医药大学第一临床医学院, 济南 250014; [2]山东中医药大学附属医院药学部, 济南 250014;
[3]山东中医药大学附属医院生殖与遗传科, 济南 250011)

摘要 DNA是遗传信息的来源, 保持其完整性对于细胞功能的维持至关重要。DNA损伤应答(DNA damage response, DDR)是细胞进化形成的一种复杂而精细的生物学机制, 用来识别、清除或修复内源性和外源性因素导致的DNA损伤, 确保基因组的完整性和功能性。作为一种细胞核内的重要亚核体, 核旁斑(paraspeckles)是由长链非编码RNA和几种RNA结合蛋白通过液–液相分离(liquid-liquid phase separation, LLPS)动态组装形成的核内无膜细胞器, 在细胞的稳态维持及功能修复中发挥着重要的作用。研究发现核旁斑参与DDR过程, 在DNA损伤的感知、信号转导及修复阶段均有重要影响, 且与癌症的发生发展密切相关, 其可介导p53的激活调控DDR效率, 也可介导细胞周期停滞及激活DNA损伤修复通路修复DNA损伤, 其异常聚集与化疗耐药及放疗抗性密切相关。该文系统综述了核旁斑在调控DDR中的分子机制, 探讨了其在癌症发生发展中的作用, 并展望了靶向核旁斑调控在癌症治疗中的潜在应用前景。

关键词 核旁斑; DNA损伤应答; *NEAT1*; 癌症

Mechanism of Paraspeckles in Regulating DNA Damage Response and Its Role in Carcinogenesis and Cancer Development

ZHANG Yuxin[1], CHEN Wen[1], LIANG Qihui[1], DING Shengyong[2], WU Haicui[3]*
([1]*First Clinical College of Shandong University of Traditional Chinese Medicine, Jinan 250014, China*;
[2]*Pharmacy Department of Shandong University of Traditional Chinese Medicine Affiliated Hospital, Jinan 250014, China*;
[3]*Reproductive and Genetic Department of Shandong University of Traditional Chinese Medicine Affiliated Hospital, Jinan 250011, China*)

Abstract DNA serves as the source of genetic information, and maintaining its integrity is crucial for the maintenance of cellular functions. DDR (DNA damage response) is a complex and sophisticated biological mechanism evolved by cells to eliminate or repair DNA damage caused by endogenous and exogenous factors, ensuring the integrity and functionality of the genome. As an important sub-nuclear structure within the cell nucleus, paraspeckles are membrane-less nuclear organelles dynamically assembled through liquid-liquid phase separation of long non-coding RNAs and several RNA-binding proteins, playing a significant role in the maintenance of cellular

收稿日期: 2025-05-06 接受日期: 2025-08-06
国家自然科学基金(批准号: 82274573)、山东省泰山学者工程项目(批准号: tsqn202103182)和山东省自然科学基金(批准号: ZR2021MH255)资助的课题
*通信作者。Tel: 0531-68616659, E-mail: haicui_w@163.com
Received: May 6, 2025 Accepted: August 6, 2025
This work was supported by the National Natural Science Foundation of China (Grant No.82274573), the Shandong Province's Taishan Scholar Project (Grant No.tsqn202103182), and the Natural Science Foundation of Shandong Province (Grant No.ZR2021MH255)
*Corresponding author. Tel: +86-531-68616659, E-mail: haicui_w@163.com

homeostasis and functional repair. Research has revealed that paraspeckles are involved in the DDR process, exerting important influences on the stages of DNA damage sensing, signal transduction, and repair, and are closely associated with carcinogenesis and cancer development. They can mediate the activation of p53 to regulate the efficiency of DDR, mediate cell cycle arrest and activate the DNA damage repair pathway to repair DNA damage. Their abnormal aggregation is closely related to chemotherapy resistance and radiotherapy resistance. This article systematically reviews the molecular mechanism of paraspeckles in regulating DDR, explores their role in carcinogenesis and cancer development, and prospects the potential application of targeted paraspeckle regulation in cancer treatment.

Keywords paraspeckles; DNA damage response; *NEAT1*; cancer

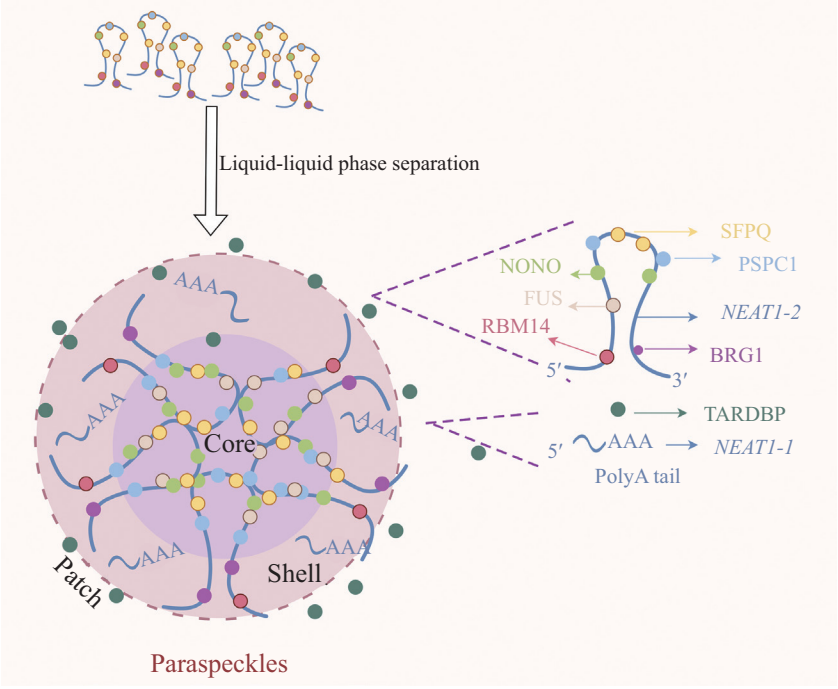
真核细胞核内高度有序的亚结构域在基因完整性保持调控和应激适应中发挥核心作用。核旁斑是一类由长链非编码RNA(LncRNA)-*NEAT1*(nuclear enriched abundant transcript 1)及其多种RNA结合蛋白(如PSPC1、NONO、SFPQ等)动态组装形成的核内无膜细胞器[1]。自2002年被发现以来, 核旁斑被证实参与细胞功能重构、转录调控、RNA选择性剪接及病毒防御等多种生物学过程[2-3]。由于其独特的液–液相分离(liquid-liquid phase separation, LLPS)组装特性, 核旁斑能够响应外界刺激(如缺氧、热休克)快速重构, 通过滞留含有腺苷–肌苷富集元件的mRNA, 调控靶基因的转录后表达[4-5], 在细胞稳态维持及功能修复等过程中发挥着重要的作用。

DDR(DNA damage response)是细胞对抗基因组威胁的核心防御机制, 其通过ATM(ataxia telangiectasia-mutated gene)/ATR(ataxia telangiectasia and Rad3-related)激酶级联反应激活细胞周期检查点、协调修复通路并决定细胞命运(修复、衰老或凋亡)[6]。近年来, 随着DDR机制的深入研究, 核旁斑参与维持基因组稳定性的关键作用逐渐被证实: DNA双链断裂(DNA double-strand break, DSB)、复制压力等多种损伤信号可导致ATM、ATR等蛋白被激活并通过磷酸化作用激活p53, p53的激活刺激*NEAT1*的上调, 从而通过多价蛋白-RNA相互作用网络驱动LLPS, 形成动态的功能性无膜区——核旁斑, 提示其可能作为DDR信号网络的动态调控枢纽[7-8]。传统研究多聚焦于蛋白质修饰(如磷酸化、泛素化)对DDR的调控, 近年来研究表明, 以核旁斑为代表的RNA-蛋白质复合物可参与这一过程。这些发现不仅挑战了“DDR仅由蛋白质主导”的传统模式, 也为解析RNA分子在基因组稳定性中的调控网络提供了新视角。

1 核旁斑的结构简述

核旁斑是由*NEAT1*和多种RNA结合蛋白相互作用共同形成的[9]。*NEAT1*对于核旁斑的完整性是至关重要的, 敲低*NEAT1* RNA可以导致核旁斑结构的丢失[10-11]。而*NEAT1*存在两种不同的异构体, *NEAT1-1*和*NEAT1-2*, 虽然这两种亚型使用相同的启动子, 但它们的加工过程是不同的, *NEAT1-2*异构体是核旁斑形成所必需的支架[12]。在核旁斑的组装过程中, *NEAT1-2* RNA首先作为骨架起始组装, 并优先结合核旁斑核心组分NONO蛋白和SFPQ蛋白以形成稳定的*NEAT1*-RNP中间产物(NONO/SFPQ/*NEAT1-2*核糖核蛋白颗粒), 随后招募其他富含朊蛋白样无序结构域蛋白质到*NEAT1*基因附近介导核旁斑的完整组装[13], 形成一个以*NEAT1-2*中间区域为核心, *NEAT1-2*和*NEAT1-1*的5′和3′端为边缘的壳球状结构[14], 如图1所示。通常情况下, 大部分核旁斑呈球状, 一小部分会融合产生香肠状结构; 当*NEAT1-2*的表达量增多时, 两个或多个球状核旁斑会合并形成细长状核旁斑[15]。

核旁斑中包含40余种RNA结合蛋白, 根据每种蛋白质耗竭时导致核旁斑的破坏程度分为三类。第I类蛋白质: 对维持核旁斑的结构不可或缺, 缺乏此类蛋白质核旁斑将无法形成。根据是否影响*NEAT1-2*的表达量, 第I类蛋白质可以分为Ia和Ib两个亚类, 其中, Ia类蛋白质是生成和稳定*NEAT1-2*的必需蛋白, 如NONO、SFPQ等; Ib类蛋白质缺失不影响*NEAT1-2*的表达量。第II类蛋白质: 此类蛋白质的缺失可造成核旁斑的大量减少, 如TARDBP。第III类蛋白质: 影响核旁斑的数量。根据是否影响*NEAT1-1*的表达量, 第III类蛋白质又可分为IIIa和IIIb两个亚类。其中, IIIa类蛋白质的缺失可造成*NEAT1-1*的表达量减少; 而IIIb类蛋白质则不影响



核旁斑是核内无膜细胞器, 是以液–液相分离(liquid-liquid phase separation, LLPS)动态组装形成的, 以*NEAT1-2*中间区域为核心, *NEAT1-2*和*NEAT1-1*的5′和3′端为边缘的壳球状结构, 核旁斑蛋白根据它们在核旁斑中的位置可分为三组: 核心组、贴片组和壳组, 每个核旁斑蛋白都以有序的方式分布在不同的位置。

Paraspeckles are membrane-less organelles within the nucleus, which are dynamically assembled through liquid-liquid phase separation. They have a shell-globular structure with the middle region of *NEAT1-2* as the core and the 5′ and 3′ ends of *NEAT1-2* and *NEAT1-1* as the periphery. Paraspeckle proteins can be classified into three groups according to their positions within paraspeckles: the core group, the patch group, and the shell group. Each paraspeckle protein is distributed in an orderly manner at different positions.

图1　核旁斑结构示意图(由Figdraw绘制)

Fig.1　Schematic diagram of the paraspeckles structure (by Figdraw)

*NEAT1-1*的表达量[15-16]。

NONO、SFPQ和PSPC1是当前研究较多的几种RNA结合蛋白, 它们同属于DBHS蛋白家族, 可互相作用形成同源或异源二聚体发挥作用。DBHS家族均包含保守的DBHS核心区域, 这些区域由参与RNA和DNA相互作用的串联RNA识别基序RRMs(RRM1、RRM2)、参与DBHS二聚化的NonA/核旁斑域(NonA-paraspeckle domain, NOPS)和促进二聚化和寡聚化的C末端卷曲螺旋结构域组成, 它们的整体结构在蛋白水平的一致性>70%[17-19], 而DBHS区域两侧的N-端和C-端是低复杂度区域, 这些区域在核旁斑形成过程中驱动LLPS。

2　DNA损伤应答及其过程

核旁斑的LLPS特性及其RNA-蛋白质复合物结构, 为其动态响应DNA损伤信号提供了分子基础。当DNA损伤信号产生时, 核旁斑能够灵敏地接收这些信号, 并触发其内部关键蛋白、RNA分子的定位、募集或释放发生改变, 从而实现与DDR机制在时空上的紧密协调。

DNA是遗传的基本单位, 其完整性对细胞功能至关重要。受内外环境变化影响, 人体细胞面临多种内源性和外源性因素造成的DNA损伤[20-21]: 外源性因素即环境因素, 如紫外线[22]、电离辐射[23-24]、毒性化学物质[25-26]; 内源性因素包括细胞内代谢活动的产物, 如氧化呼吸产生的活性氧(reactive oxygen species, ROS)[27-28]。内源性和外源性因素都可能导致DNA的结构和功能发生异常, 干扰DNA复制或转录过程进而损害细胞功能[21]。

为维持基因组稳定性, 细胞演化出复杂的DDR机制, 涵盖损伤感知、信号转导、细胞周期检查点阻滞及损伤修复过程。DDR首先检测到损伤信号, 如ATM(双链断裂)、ATR(单链断裂)、PARP(单链断裂)识别损伤并激活下游信号, 通过激酶级联反应, ATM/ATR磷酸化下游靶蛋白CHK1(checkpoint kinase 1)/CHK2(checkpoint kinase 2), 放大损伤信号,

然后抑制细胞周期从G_1到S(G_1/S检查点)、DNA复制(S内检查点)或G_2到有丝分裂(G_2/M检查点)的进展, 阻滞细胞周期进程, 然后进行损伤修复[29]。

DNA损伤形式包括碱基改变(错配、损伤)、单链断裂(single strand break, SSB)、DSB、加合物损伤(DNA adduct damage)、链间交联(interstrand cross-link, ICL)等[30], DSB是危害性最大的DNA损伤类型。如果这些损伤不被修复或损伤超出修复能力时, 它们可能导致突变, 染色体畸变, 最终导致疾病的发生。

DNA损伤修复是DDR信号的下游效应通路, 是维护基因组稳定性的核心执行环节[21]。对于不同类型的DNA损伤, 细胞能够通过相应的DNA修复机制进行修复。DNA复制过程中发生的碱基错配能够通过错配修复(mismatch repair, MMR)机制得到校对; 碱基切除修复(base excision repair, BER)机制针对单碱基化学修饰或微小损伤进行精准清除; 大范围DNA损伤则可通过核苷酸切除修复(nucleotide excision repair, NER)机制被去除; DNA单链断裂修复过程与碱基切除修复过程重叠, 共享核心修复元件[31]; 同源重组(homologous recombination, HR)与非同源末端连接(non-homologous end joining, NHEJ)是修复DSB的两种机制[32]。HR发生在细胞周期的S期和G_2期, 利用姐妹染色体作为修复模板, 因而更加精准。NHEJ通过直接连接DSB末端实现快速修复, 虽不依赖模板但可维持复制期外基因组完整性[33-34]。一些特定的病变也可以通过直接化学逆转和链间交联修复(ICL repair)来去除[35]。

3 核旁斑缓解DNA损伤的机制

核旁斑被认为是响应细胞DNA损伤应答过程和细胞凋亡的关键调节因子(图2)[36]。

3.1 核旁斑介导p53的激活缓解DNA损伤

TP53(编码p53蛋白)是重要的抑癌因子之一, 50%以上的人类肿瘤与*TP53*基因突变有关[37], 作为一种能够激活多种靶基因表达的转录因子, 在调节细胞周期、细胞凋亡、基因组稳定性、细胞代谢、肿瘤微环境和自噬等方面发挥着关键作用。当细胞暴露于内外应激信号, 包括DNA损伤、缺氧时, p53信号通路激活, 从而激活细胞周期阻滞、DNA修复、衰老和凋亡等转录程序[38-39]。

p53被证明直接或间接地介导DDR的激活, 可以通过转录依赖性和非依赖性机制调节几乎所有的DNA修复过程[40]。*NEAT1*作为核旁斑的重要组成成分, 已有研究确定并验证其为p53靶点, 这些研究还指出*NEAT1*耗尽时, 细胞的DDR效率受损[41-42]。BLUME等[43]报道了慢性淋巴细胞白血病(chronic lymphocytic leukemia, CLL)原代细胞中DNA损伤后, *NEAT1*在功能性p53存在下被诱导, 但在携带p53突变的CLL中不被诱导, 并且其诱导与DNA损伤后的细胞死亡密切相关。在人乳腺癌细胞中, 用p53诱导剂处理会诱导*NEAT1*表达, 与形成的核旁斑增加有关[44], 同时通过γ-H2AX免疫荧光证实, *NEAT1*敲除后DNA损伤焦点数量增加, DDR信号转导被诱导, 以及KAP1磷酸化部分增加[8]。

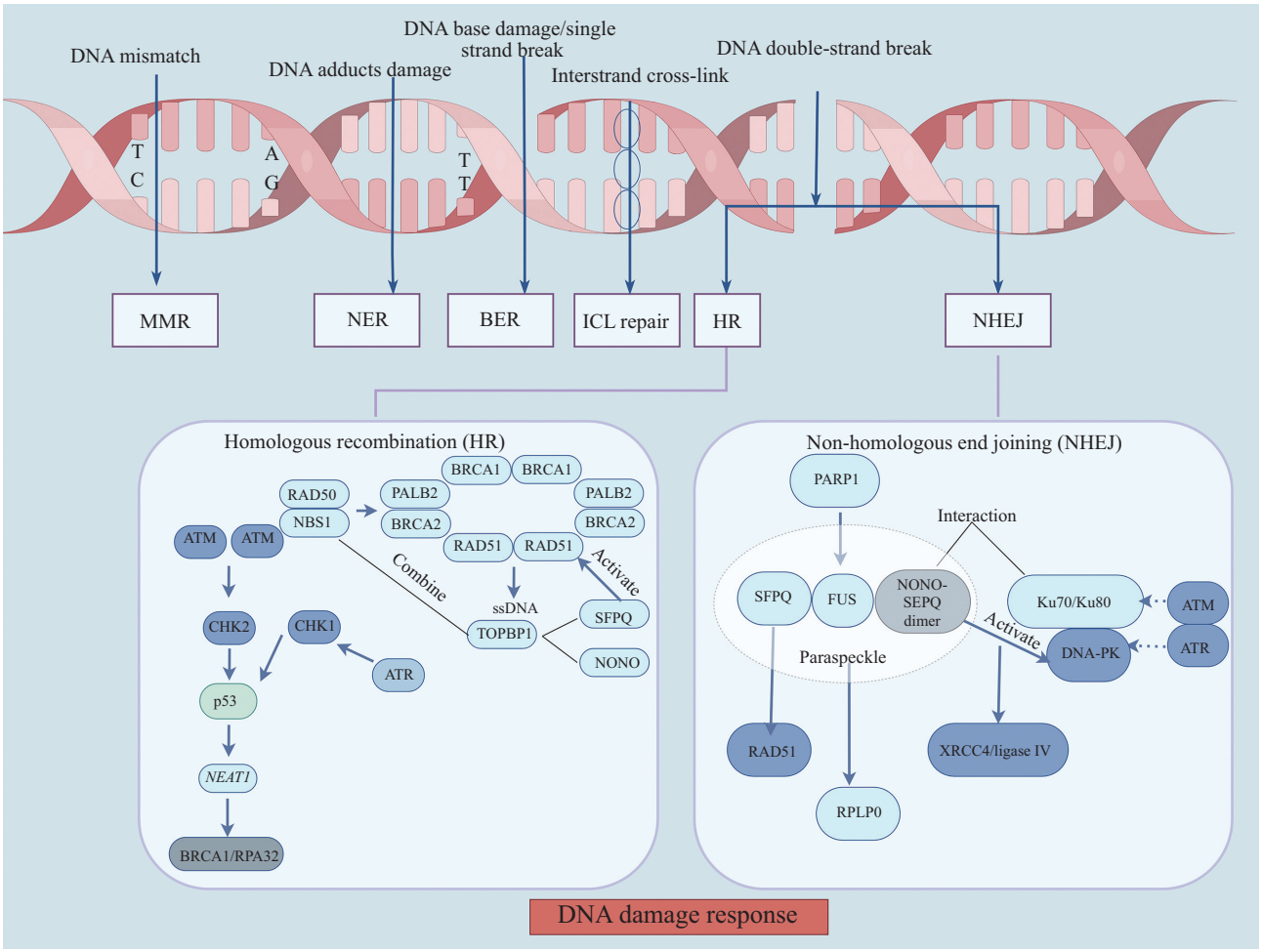
在p53缺失或突变的部分前列腺癌中, *NEAT1*通过CDC5L-AGRN通路促进DDR, 帮助肿瘤细胞逃避p53介导的凋亡, 从而支持肿瘤细胞增殖[45]。在p53野生型结直肠癌细胞中, PDT(光动力疗法)抑制c-Myc/*NEAT1*轴并促进miR-124/iASPP/p53反馈环, 其放大PDT功能, 诱导癌细胞凋亡。在p53突变型结直肠癌细胞中, c-Myc/*NEAT1*轴的表达上调, 反馈环不能被激活, 导致诱导凋亡失败, 从而导致PDT耐受[46]。

3.2 核旁斑介导细胞周期停滞缓解DNA损伤

细胞周期检查点是细胞周期调控的关键机制, 通过监测细胞内外环境及DNA完整性, 确保细胞周期各阶段(G_1、S、G_2、M)的顺利进行[6]。当机体DNA遭到损伤时, 检查点会被激活从而暂停细胞周期, 提供修复时间; 若损伤无法修复, 则触发细胞凋亡或衰老, 防止错误遗传到子代细胞。S期内检查点用于阻止DNA受损细胞的S期DNA合成, G_2/M DNA损伤检查点的激活阻止受损细胞有丝分裂进入[47]。

ROBERTS等[48]首先观察到NONO在DDR中的作用。在G_2/M阻滞期间纯化后, NONO被磷酸化; 此外, SFPQ也已证明在G_2/M期阻滞期间被过度磷酸化。这些研究表明, NONO和SFPQ磷酸化与细胞周期停滞有关[49]。ALFANO等[50]报道了暴露于紫外线辐射下的NONO沉默细胞仍然能够合成DNA, 并显示出CHK1磷酸化受损, 从而导致紫外线照射下的S期内检查点激活缺陷。

PSPC1与NONO高度相似, 并且是DBHS成员, 尚未报道为DSB修复的关键成分。然而, 过表达PSPC1可以挽救NONO的敲低[51]。这可能表明



DSBs发生后, 首先被核心激酶ATM、DNA依赖性蛋白激酶催化亚基(DNA-PKcs)感知, 它们磷酸化组蛋白H2AX的S139位点(形成γ-H2AX)。随后招募MRN(MRE11、RAD50和NBS1)复合物及MDC1(mediator of DNA damage checkpoint protein 1)等信号转导因子, 放大DNA损伤信号, 进而促进DNA修复因子的募集。在HR修复通路中, MRN复合物启动DSB末端的修切(end-resection), 暴露出单链DNA(ssDNA)。ssDNA随即被复制蛋白A(RPA)结合覆盖, 后在BRCA2协助下, RAD51被募集并置换RPA, 形成RAD51核蛋白丝。此核蛋白丝检索同源序列, 并促进断裂DNA与同源模板间形成连接分子, 最终完成HR修复。*NEAT1*作为p53的靶标, 其下调可导致BRCA1和RPA32表达水平降低, 从而调节DDR过程; NONO和SFPQ可直接与TOPBP1相互作用, 然后与NBS1结合, 定位于DNA损伤位点。在NHEJ通路中, NONO/SFPQ可产生一种异二聚体, 该异二聚体可以与Ku70/Ku80相互作用, 促进DNA底物的结合, Ku-DNA复合物招募DNA-PKcs, DNA-PKcs与Ku70/Ku80共同组成具有激酶活性的DNA-PK全酶复合物。DNA-PKcs被激活后发生自身磷酸化, 从而启动NHEJ通路, 随后募集XRCC4/DNA连接酶IV(ligase IV)复合物完成末端连接。SFPQ激活RAD51, PARP1募集FUS, 核旁斑募集RPLP0, 定位于DNA损伤部位。

After DSBs occur, they are first sensed by the core kinases ATM and DNA-dependent protein kinase catalytic subunit (DNA-PKcs), which phosphorylate the S139 site of histone H2AX (forming γ-H2AX). Subsequently, the MRN (MRE11, RAD50, and NBS1) complex and signal transduction factors such as MDC1 (mediator of DNA damage checkpoint protein 1) are recruited to amplify the DNA damage signal and promote the recruitment of DNA repair factors. In the HR repair pathway, the MRN complex initiates end-resection at the DSB ends, exposing ssDNA (single-stranded DNA). The ssDNA is then bound and covered by RPA (replication protein A), and with the assistance of BRCA2, RAD51 is recruited and replaces RPA to form RAD51 nucleoprotein filaments. These nucleoprotein filaments search for homologous sequences and promote the formation of connection molecules between the broken DNA and the homologous template, ultimately completing HR repair. *NEAT1*, as a target of p53, its downregulation can lead to decreased expression of BRCA1 and RPA32, thereby regulating the DDR process; NONO and SFPQ can directly interact with TOPBP1 and then bind to NBS1, localizing at the DNA damage site. In the NHEJ pathway, NONO/SFPQ can form a heterodimer, which can interact with Ku70/Ku80 to promote the binding of DNA substrates. The Ku-DNA complex recruits DNA-PKcs, and DNA-PKcs, together with Ku70/Ku80, form the DNA-PK holoenzyme complex with kinase activity. After activation, DNA-PKcs undergoes autophosphorylation, thereby initiating the NHEJ pathway, and subsequently recruits the XRCC4/DNA ligase IV (Ligase IV) complex to complete the end joining. SFPQ activates RAD51, PARP1 recruits FUS, and the paraspeckles recruit RPLP0, localizing at the DNA damage site.

图2　核旁斑在DDR通路中的作用图(由Figdraw绘制)

Fig.2　The role of paraspeckles in the DDR pathway diagram (by Figdraw)

表1 核旁斑蛋白的分类及其在DDR中的功能(根据参考文献[36]修改)

Table 1 Classification of paraspeckle proteins and their function in the DDR (modified from the reference [36])

核旁斑蛋白 Paraspeckle proteins	别称 Another name	分类 Classification	分子功能 Molecular function	DDR中的功能 Function in the DDR	参考文献 References
NONO	p4nrb	Ia	RBP	HR/NHEJ	[47-49,53-54,57]
SFPQ	PSF	Ia	RBP	HR/NHEJ	[48,53-54]
RBM14	CoAA	Ia	RBP	NHEJ	[58-60]
FUS	TLS	Ib	RBP	HR/NHEJ/BER	[55-56]
BRG1	SMARCA4	/	ATPase	HR	[61-64]
DAZAP1	/	Ib	RBP	HR*	[65-67]
PSPC1	PSP1	IIIb	RBP	NHEJ*	[50-51]

RBP: RNA结合蛋白; HR: 同源重组; NHEJ: 非同源末端连接; BER: 碱基切除修复; (*): 文献数据提示可能的DDR调控途径。/: 无意义。

RBP: RNA binding protein; HR: homologous recombination; NHEJ: non-homologous end joining; BER: base excision repair; (*): possible DDR regulated pathway as suggested by literature data. /: meaningless.

PSPC1可能可以取代NONO与SFPQ合作, 从而参与NHEJ, 即通过调节G_1/S周期检验点影响DDR过程。在细胞DNA损伤时, PSPCI蛋白水平增加从而导致细胞阻滞在S期, 利于DNA修复的进行; 而当敲低PSPC1时, 细胞逃逸G_1/S期检查点而更多的进入G_2/M期[52], DNA无法被修复而导致损伤程度增加, 最终导致更多的细胞死亡。

3.3 核旁斑激活DNA损伤修复通路修复DNA损伤

HR是应对复制应激的关键机制, 作为DSB修复的一种重要方式, 其可能受到*NEAT1*信号转导的影响。*NEAT1*沉默可以抑制血管平滑肌细胞中核旁斑结构的形成以及细胞增殖和迁移, 也会下调DDR相关蛋白的表达, 包括CHK1、CHK2、RPA32(replication protein A 32 kDa subunit)、BRCA1(breast cancer susceptibility gene 1)和RAD51(DNA repair protein RAD51 homolog 1), 并导致细胞中DNA损伤的积累。同样有研究发现在间充质干细胞中, *NEAT1*敲低会导致γ-H2AX表达水平升高和BRCA1和RPA32表达水平降低[36]。这些报道表明, *NEAT1*介导的核旁斑形成可能通过影响BRCA1/RPA32表达及其相关HR通路来调节DDR过程。

KUHNERT等[53]证实了NONO参与HR途径, 证明它与SFPQ一起直接与TopBP1(DNA topoisomerase II binding protein 1)相互作用, 并共定位于激光诱导的DNA损伤位点。TopBP1能够在体内与一种DNA损伤修复因子NBS1(nijmegen breakage syndrome protein 1)结合, 从而调节其向DNA损伤位点的募集; TopBP1沉默也会导致HR修复频率降低。

NONO和SFPQ同时也是NHEJ的两个重要因子, NONO/SFPQ可产生一种异二聚体, 该异二聚体可以与Ku70/Ku80相互作用, 促进DNA底物的结合, Ku-DNA复合物招募DNA-PK激酶蛋白亚基激活其激酶活性, 将自身磷酸化启动NHEJ通路, 然后召集XRCC4/Ligase IV完成连接[49,54]。据报道, SFPQ通过促进同源配对重组过程中D环的形成, 对HR通路激活至关重要。此外, SFPQ可作为RAD51的激活剂和抑制剂, 对HR通路进行严格调节。FUS在DSB和SSB修复中都起着重要作用, 它可以被PARP1募集以促进BER蛋白在DNA损伤部位的募集; FUS耗竭导致DDR减弱, 损害HR和NHEJ活性[55-56]。

不同核旁斑蛋白在DDR中的功能总结如表1所示[47-51,52-67]。

4 核旁斑介导DNA损伤应答在癌症发生发展中的作用

癌症作为世界第二大死因, 对人类健康构成严重威胁, 放化疗是目前临床治疗癌症最有效的手段之一[68]。有研究证明核旁斑是响应致癌应激而组装的, 并且缺乏*NEAT1*会使癌前细胞的活力下降[8]。核旁斑在致癌作用中的影响正在逐渐显现。在不同类型癌症中的实验数据表明, 核旁斑参与了DDR。

4.1 癌细胞中核旁斑的异常表达影响DNA损伤应答过程

在多发性骨髓瘤(multiple myeloma, MM)患者中*NEAT1*失调。实验表明, *NEAT1*沉默对MM细胞的增殖和活力产生负面影响, 这表明其可能在DDR中发挥作用。实验发现*NEAT1*至少通过两种不同的机制参与几乎所有DDR过程。一方面, *NEAT1*正向调

节必需核旁斑蛋白的翻译后稳定，这些蛋白几乎参与所有DDR系统，从而提高它们在细胞内的可用性。另一方面，*NEAT1*作为分子轴的主要调节因子起着至关重要的作用，该分子轴包括ATM和DNA-PK激酶蛋白的催化亚基，以及它们的直接靶标pRPA32和pCHK2[69]。*NEAT1*以及核旁斑蛋白可能代表着MM治疗的潜在治疗靶点。

4.2 核旁斑介导DNA损伤应答调控癌症化疗耐药性

未能正确修复DNA是基因突变和癌基因激活的主要原因。化疗药物通常通过诱导癌细胞中的DNA损伤起作用，癌细胞可以通过促进DDR来降低化疗的效果[70]。

*NEAT1*主要通过增强癌细胞的同源重组能力来增强癌症的化疗耐药性。在MM细胞中，*NEAT1*通过上调HR通路中的关键分子RPA32的表达来促进DDR过程，从而增强细胞对硼替佐米和卡非佐米的耐药性。然而，沉默*NEAT1*可以降低RPA32的表达水平，诱导大量的DNA损伤，并增强MM细胞对硼替佐米和卡非佐米的敏感性[71]。最近的研究表明，*NEAT1*与卵巢癌中的HR相关蛋白RAD51和FOXM1(forkhead box protein M1)呈正相关，并且敲除*NEAT1*可通过抑制HR使癌细胞对铂类化疗药物敏感[72]。此外，*NEAT1*还可以通过促进HRR相关蛋白ATR的表达来减少DNA损伤的数量，从而增强骨肉瘤细胞对博来霉素的耐药性[73]。

*NEAT1*还可以通过促进癌细胞的细胞周期进展来诱导化疗耐药性。细胞周期的G_0/G_1期是细胞体积生长以及DNA复制和合成准备的重要时期。*NEAT1*可以通过调节细胞周期的G_0/G_1期来影响癌细胞的化疗耐药性。源自乳腺癌紫杉醇耐药SKBR-3/PR细胞外泌体的*NEAT1*可通过调节细胞周期的G_0/G_1期来诱导紫杉醇耐药。CXCL12在促进癌症化疗耐药性方面起着重要的调节作用。在乳腺癌紫杉醇耐药SKBR-3/PR细胞中，敲低*NEAT1*可以上调miR-133b的表达，下调下游CXCL12蛋白的表达，从而促进G_0/G_1期细胞周期停滞，增强SKBR-3/PR细胞对紫杉醇的敏感性[74]。

4.3 核旁斑介导DNA损伤应答调控癌症放疗抗性

临床数据显示，放疗抵抗患者的肿瘤组织中*NEAT1*表达水平显著升高，提示核旁斑可能通过提升HR/NHEJ效率降低辐射敏感性[58]。

研究表明，在胃癌放射治疗后*NEAT1*水平升高，*NEAT1*敲低可通过靶向miR-27b-3p促进细胞凋亡来增强胃癌的放射敏感性[75]。在MDA-MB-231三阴性乳腺癌细胞中NQO1[NAD(P)H:quinone oxidoreductase 1]的表达水平决定了其放射敏感性，而*NEAT1*可正向调控NQO1的表达，敲低*NEAT1*后癌细胞对辐射的敏感性增加[76]。同时，*NEAT1*还可通过诱导肝细胞癌中的细胞自噬来抑制放射抗性[77]或通过抑制鼻咽癌的细胞凋亡来增强放射抗性[78]。

NONO作为核旁斑的重要组分，也被发现通过促进辐射诱导的DSB的修复来增强癌症放疗耐药性。RPLP0是一种以核糖体非依赖性方式发挥作用的核糖体蛋白，被辐射诱导的核旁斑募集，其核定位通过NONO依赖的相分离实现，其功能独立于核糖体组装；并且核旁斑能通过NONO-RPLP0相互作用促进DNA-PK和NHEJ依赖性DNA修复的激活[58]，从而增强修复效率。

5 小结与展望

核旁斑与不同因子作用能缓解DNA损伤，但DDR与核旁斑数量和形态是否有关还不得而知。在癌症中，核旁斑介导DDR可以影响癌细胞的增殖，又与化疗耐药性及放疗抗性密切相关，作为RNA-蛋白质动态组装体，其突破了DDR由蛋白质中心调控的传统范式，未来可能成为癌症的潜在治疗靶点。

尽管已有研究取得重要进展，核旁斑在DDR中的分子机制仍存在诸多争议：如*NEAT1*异构体(*NEAT1-1*与*NEAT1-2*)是否在损伤类型特异性响应中发挥差异功能尚不明确，其在不同肿瘤微环境或衰老组织中的功能异质性尚未被系统阐明，需结合单细胞测序进一步解析。目前的研究多数都集中在探讨*NEAT1*或核旁斑蛋白单独的作用，很少将核旁斑作为一个整体去研究，尽管这些都是核旁斑必不可少的组成成分，但其整体功能可能要比单独*NEAT1*或核旁蛋白复杂得多，这些都有待进一步研究。

目前DDR抑制剂与化疗和放疗的联合应用在各种癌症中的作用正在积极探索，但主要是靶向参与DDR机制的关键蛋白[79]。而核旁斑又与DDR密切相关，可能具备早期诊断、靶向治疗和预测预后的临床应用价值，未来也可整合单细胞多组学和超分辨成像技术，解析其互作网络，靶向*NEAT1*或结合

蛋白, 开发小分子抑制剂破坏*NEAT1*相分离(如靶向*NEAT1*的G-四链体结构), 或联合PARP抑制剂增强放疗敏感性, 为开发新型肿瘤靶向治疗策略提供潜在分子靶点。

参考文献(References)

[1] FOX A H, LAMOND A I. Paraspeckles [J]. Cold Spring Harb Perspect Biol, 2010, 2(7): a000687.

[2] ANDERSEN J S, LYON C E, FOX A H, et al. Directed proteomic analysis of the human nucleolus [J]. Curr Biol, 2002, 12(1): 1-11.

[3] HIROSE T, VIRNICCHI G, TANIGAWA A, et al. NEAT1 long noncoding RNA regulates transcription via protein sequestration within subnuclear bodies [J]. Mol Biol Cell, 2014, 25(1): 169-83.

[4] ZHANG Z, CARMICHAEL G G. The fate of dsRNA in the nucleus: a p54(NRB)-containing complex mediates the nuclear retention of promiscuously A-to-I edited RNAs [J]. Cell, 2001, 106(4): 465-75.

[5] PRASANTH K V, PRASANTH S G, XUAN Z, et al. Regulating gene expression through RNA nuclear retention [J]. Cell, 2005, 123(2): 249-63.

[6] HAKEM R. DNA-damage repair; the good, the bad, and the ugly [J]. EMBO J, 2008, 27(4): 589-605.

[7] TAIANA E, FAVASULI V, RONCHETTI D, et al. Long noncoding RNA NEAT1 targeting impairs the DNA repair machinery and triggers anti-tumor activity in multiple myeloma [J]. Leukemia, 2020, 34(1): 234-44.

[8] ADRIAENS C, STANDAERT L, BARRA J, et al. p53 induces formation of NEAT1 lncRNA-containing paraspeckles that modulate replication stress response and chemosensitivity [J]. Nat Med, 2016, 22(8): 861-8.

[9] BOND C S, FOX A H. Paraspeckles: nuclear bodies built on long noncoding RNA [J]. J Cell Biol, 2009, 186(5): 637-44.

[10] CLEMSON C M, HUTCHINSON J N, SARA S A, et al. An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckle [J]. Mol Cell, 2009, 33(6): 717-26.

[11] ZHAO M, LIU S, WANG Y, et al. The mitochondria-paraspeckle axis regulates the survival of transplanted stem cells under oxidative stress conditions [J]. Theranostics, 2024, 14(4): 1517-33.

[12] NAGANUMA T, HIROSE T. Paraspeckle formation during the biogenesis of long non-coding RNAs [J]. RNA Biol, 2013, 10(3): 456-61.

[13] YAMAZAKI T, SOUQUERE S, CHUJO T, et al. Functional domains of NEAT1 architectural lncRNA induce paraspeckle assembly through phase separation [J]. Mol Cell, 2018, 70(6): 1038-53,e7.

[14] SOUQUERE S, BEAUCLAIR G, HARPER F, et al. Highly ordered spatial organization of the structural long noncoding NEAT1 RNAs within paraspeckle nuclear bodies [J]. Mol Biol Cell, 2010, 21(22): 4020-7.

[15] WANG Y, HU S B, WANG M R, et al. Genome-wide screening of NEAT1 regulators reveals cross-regulation between paraspeckles and mitochondria [J]. Nat Cell Biol, 2018, 20(10): 1145-58.

[16] NAGANUMA T, NAKAGAWA S, TANIGAWA A, et al. Alternative 3′-end processing of long noncoding RNA initiates construction of nuclear paraspeckles [J]. EMBO J, 2012, 31(20): 4020-34.

[17] SCHELL B, LEGRAND P, FRIBOURG S. Crystal structure of SFPQ-NONO heterodimer [J]. Biochimie, 2022, 198: 1-7.

[18] TAKEIWA T, IKEDA K, HORIE K, et al. Role of RNA binding proteins of the *Drosophila* behavior and human splicing (DBHS) family in health and cancer[J]. RNA Biol, 2024, 21(1): 1-17.

[19] KNOTT G J, BOND C S, FOX A H. The DBHS proteins SFPQ, NONO and PSPC1: a multipurpose molecular scaffold [J]. Nucleic Acids Res, 2016, 44(9): 3989-4004.

[20] COUVÉ S, ISHCHENKO A A, FEDOROVA O S, et al. Direct DNA lesion reversal and excision repair in *Escherichia coli* [J]. EcoSal Plus, 2013, 5(2): 101128.

[21] CARUSILLO A, MUSSOLINO C. DNA damage: from threat to treatment [J]. Cells, 2020, 9(7): 1665.

[22] CADET J, WAGNER J R. DNA base damage by reactive oxygen species, oxidizing agents, and UV radiation[J]. Cold Spring Harb Perspect Biol, 2013, 5(2): a012559.

[23] MAVRAGANI I V, LASKARATOU D A, FREY B, et al. Key mechanisms involved in ionizing radiation-induced systemic effects. A current review[J]. Toxicol Res, 2015, 5(1): 12-33.

[24] WARDMAN P. The importance of radiation chemistry to radiation and free radical biology (The 2008 Silvanus Thompson Memorial Lecture) [J]. Br J Radiol, 2009, 82(974): 89-104.

[25] MORGIL G K, ÇOK İ. Evaluation and comparison of DNA alkylation and oxidative damage in e-cigarette and heated tobacco users [J]. Toxicol Mech Methods, 2025, 35(2): 125-35.

[26] PANDIR D. DNA damage in human germ cell exposed to the some food additives *in vitro* [J]. Cytotechnology, 2016, 68(4): 725-33.

[27] CADET J, DOUKI T, RAVANAT J L. Oxidatively generated base damage to cellular DNA [J]. Free Radic Biol Med, 2010, 49(1): 9-21.

[28] CADET J, DOUKI T, RAVANAT J L. Measurement of oxidatively generated base damage in cellular DNA [J]. Mutat Res, 2011, 711(1/2): 3-12.

[29] SANCAR A, LINDSEY-BOLTZ L A, UNSAL-KAÇMAZ K, et al. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints[J]. Annu Rev Biochem, 2004, 73: 39-85.

[30] LIANG Y, YUAN Q, ZHENG Q, et al. DNA damage atlas: an atlas of DNA damage and repair [J]. Nucleic Acids Res, 2024, 52(D1): D1218-D26.

[31] DIANOV G L, PARSONS J L. Co-ordination of DNA single strand break repair [J]. DNA Repair, 2007, 6(4): 454-460.

[32] HALIM C E, DENG S, CRASTA K C, et al. Interplay between the cytoskeleton and dna damage response in cancer progression [J]. Cancers, 2025, 17(8): 1378.

[33] SCULLY R, PANDAY A, ELANGO R, et al. DNA double-strand break repair-pathway choice in somatic mammalian cells [J]. Nat Rev Mol Cell Biol, 2019, 20(11): 698-714.

[34] ARNOULT N, CORREIA A, MA J, et al. Regulation of DNA repair pathway choice in S and G_2 phases by the NHEJ inhibitor CYREN [J]. Nature, 2017, 549(7673): 548-52.

[35] CHATTERJEE N, WALKER G C. Mechanisms of DNA damage, repair, and mutagenesis [J]. Environ Mol Mutagen, 2017, 58(5):

235-63.
[36] TAIANA E, RONCHETTI D, TODOERTI K, et al. LncRNA NEAT1 in paraspeckles: a structural scaffold for cellular DNA damage response systems [J]? Noncoding RNA, 2020, 6(3): 26.
[37] OLIVIER M, HOLLSTEIN M, HAINAUT P. TP53 mutations in human cancers: origins, consequences, and clinical use [J]. Cold Spring Harb Perspect Biol, 2010, 2(1): a001008.
[38] ZHAO S, WEN H, WANG B, et al. p53: a player in the tumor microenvironment [J]. Oncol Res, 2025, 33(4): 795-810.
[39] WILLIAMS A B, SCHUMACHER B. p53 in the DNA-damage-repair process [J]. Cold Spring Harb Perspect Med, 2016, 6(5): a026070.
[40] SENGUPTA S, HARRIS C C. p53: traffic cop at the crossroads of DNA repair and recombination [J]. Nat Rev Mol Cell Biol, 2005, 6(1): 44-55.
[41] ADRIAENS C, MARINE J C. NEAT1-containing paraspeckles: central hubs in stress response and tumor formation [J]. Cell Cycle, 2017, 16(2): 137-8.
[42] MELLO S S, SINOW C, RAJ N, et al. Neat1 is a p53-inducible lincRNA essential for transformation suppression [J]. Genes Dev, 2017, 31(11): 1095-108.
[43] BLUME C J, HOTZ-WAGENBLATT A, HÜLLEIN J, et al. p53-dependent non-coding RNA networks in chronic lymphocytic leukemia [J]. Leukemia, 2015, 29(10): 2015-23.
[44] ZHANG S, KIM E J, HUANG J, et al. NEAT1 repression by MED12 creates chemosensitivity in p53 wild-type breast cancer cells [J]. FEBS J, 2024, 291(9): 1909-24.
[45] LI X, WANG X, SONG W, et al. Oncogenic properties of NEAT1 in prostate cancer cells depend on the CDC5L-AGRN transcriptional regulation circuit [J]. Cancer Res, 2018, 78(15): 4138-49.
[46] LIU K, LEI S, KUANG Y, et al. A novel mechanism of the c-Myc/NEAT1 axis mediating colorectal cancer cell response to photodynamic therapy treatment [J]. Front Oncol, 2021, 11: 652831.
[47] SU T T. Cellular responses to DNA damage: one signal, multiple choices [J]. Annu Rev Genet, 2006, 40: 187-208.
[48] ROBERTS E C, HAMMOND K, TRAISH A M, et al. Identification of G2/M targets for the MAP kinase pathway by functional proteomics [J]. Proteomics, 2006, 6(16): 4541-53.
[49] BLADEN C L, UDAYAKUMAR D, TAKEDA Y, et al. Identification of the polypyrimidine tract binding protein-associated splicing factor. P54(Nrb) complex as a candidate DNA double-strand break rejoining factor [J]. J Biol Chem, 2005, 280(7): 5205-10.
[50] ALFANO L, COSTA C, CAPORASO A, et al. NONO regulates the intra-S-phase checkpoint in response to UV radiation[J]. Oncogene, 2016, 35(5): 567-76.
[51] LI S, LI Z, SHU F J, et al. Double-strand break repair deficiency in NONO knockout murine embryonic fibroblasts and compensation by spontaneous upregulation of the PSPC1 paralog [J]. Nucleic Acids Res, 2014, 42(15): 9771-80.
[52] GAO X, KONG L, LU X, et al. Paraspeckle protein 1 (PSPC1) is involved in the cisplatin induced DNA damage response: role in G1/S checkpoint [J]. PLoS One, 2014, 9(5): e97174.
[53] KUHNERT A, SCHMIDT U, MONAJEMBASHI S, et al. Proteomic identification of PSF and p54(NRB) as TopBP1-interacting proteins [J]. J Cell Biochem, 2012, 113(5): 1744-53.
[54] KRIETSCH J, CARON M C, GAGNÉ J P, et al. PARP activation regulates the rna-binding protein NONO in the DNA damage response to DNA double-strand breaks [J]. Nucleic Acids Res, 2012, 40(20): 10287-301.
[55] WANG H, GUO W, MITRA J, et al. Mutant FUS causes DNA ligation defects to inhibit oxidative damage repair in amyotrophic lateral sclerosis [J]. Nat. Commun, 2018, 9(1): 3683.
[56] WANG W Y, PAN L, SU S C, et al. Interaction of FUS and HDAC1 regulates DNA damage response and repair in neurons [J]. Nat Neurosci, 2013, 16(10): 1383-91.
[57] WANG Y L, ZHAO W W, BAI S M, et al. DNA damage-induced paraspeckle formation enhances DNA repair and tumor radioresistance by recruiting ribosomal protein P0 [J]. Cell Death Dis, 2022, 13(8): 709.
[58] IWASAKI T, CHIN W W, KO L. Identification and characterization of RRM-containing coactivator activator (CoAA) as TRBP-interacting protein, and its splice variant as a coactivator modulator (CoAM) [J]. J Biol Chem, 2001, 276(36): 33375-83.
[59] YUAN M, EBERHART C G, KAI M. RNA binding protein RBM14 promotes radio-resistance in glioblastoma by regulating DNA repair and cell differentiation [J]. Oncotarget, 2014, 5(9): 2820-6.
[60] SIMON NE, YUAN M, KAI M. RNA-binding protein RBM14 regulates dissociation and association of non-homologous end joining proteins [J]. Cell Cycle, 2017, 16(12): 1175-80.
[61] BOCHAR D A, WANG L, BENIYA H, et al. BRCA1 is associated with a human SWI/SNF-related complex: linking chromatin remodeling to breast cancer [J]. Cell, 2000, 102(2): 257-65.
[62] DE CASTRO R O, PREVIATO L, GOITEA V, et al. The chromatin-remodeling subunit Baf200 promotes homology-directed DNA repair and regulates distinct chromatin-remodeling complexes [J]. J Biol Chem, 2017, 292(20): 8459-8471.
[63] HILL D A, DE LASERNA I L, VEAL T M, et al. BRCA1 interacts with dominant negative SWI/SNF enzymes without affecting homologous recombination or radiation-induced gene activation of p21 or Mdm2 [J]. J Cell Biochem, 2004, 91(5): 987-98.
[64] KAKAROUGKAS A, ISMAIL A, CHAMBERS A L, et al. Requirement for PBAF in transcriptional repression and repair at DNA breaks in actively transcribed regions of chromatin [J]. Mol Cell, 2014, 55(5): 723-32.
[65] GOINA E, SKOKO N, PAGANI F. Binding of DAZAP1 and hnRNPA1/A2 to an exonic splicing silencer in a natural BRCA1 exon 18 mutant [J]. Mol Cell Biol, 2008, 28(11): 3850-60.
[66] CLOUTIER A, SHKRETA L, TOUTANT J, er al. hnRNP A1/A2 and Sam68 collaborate with SRSF10 to control the alternative splicing response to oxaliplatin-mediated DNA damage [J]. Sci Rep, 2018, 8(1): 2206.
[67] HALEY B, PAUNESKU T, PROTIĆ M, et al. Response of heterogeneous ribonuclear proteins (hnRNP) to ionising radiation and their involvement in DNA damage repair [J]. Int J Radiat Biol, 2009, 85(8): 643-55.
[68] KAUR R, BHARDWAJ A, GUPTA S. Cancer treatment therapies: traditional to modern approaches to combat cancan [J]. Mol Biol Rep, 2023, 50(11): 9663-76.
[69] TAIANA E, BANDINI C, FAVASULI V K, et al. Activation of long non-coding RNA NEAT1 leads to survival advantage of multiple myeloma cells by supporting a positive regulatory loop

with DNA repair proteins [J]. Haematologica, 2023, 108(1): 219-33.

[70] ALHMOUD J F, WOOLLEY J F, AL MOUSTAFA A E, et al. DNA damage/repair management in cancers [J]. Cancers, 2020, 12(4): 1050.

[71] LONG F, LI X, PAN J, et al. The role of lncRNA NEAT1 in human cancer chemoresistance [J]. Cancer Cell Int, 2024, 24(1): 236.

[72] LIU Y, LIU G. Targeting NEAT1 affects the sensitivity to PARPi in serous ovarian cancer by regulating the homologous recombination repair pathway [J]. J Cancer, 2024, 15(5): 1397-413.

[73] HU Y, YANG Q, WANG L, et al. Knockdown of the oncogene lncRNA NEAT1 restores the availability of miR-34c and improves the sensitivity to cisplatin in osteosarcoma [J]. Biosci Rep, 2018, 38(3): BSR20180375.

[74] WEI X, TAO S, MAO H, et al. Exosomal lncRNA NEAT1 induces paclitaxel resistance in breast cancer cells and promotes cell migration by targeting miR-133b [J]. Gene, 2023, 860: 147230.

[75] JIANG Y, JIN S, TAN S, et al. Long noncoding RNA NEAT1 regulates radio-sensitivity via microRNA-27b-3p in gastric cancer [J]. Cancer Cell Int, 2020, 20(1): 581.

[76] LIN L C, LEE H T, CHIEN P J, et al. NAD(P)H: quinone oxidoreductase 1 determines radiosensitivity of triple negative breast cancer cells and is controlled by long non-coding RNA NEAT1 [J]. Int J Med Sci, 2020, 17(14): 2214-24.

[77] SAKAGUCHI H, TSUCHIYA H, KITAGAWA Y, et al. NEAT1 confers radioresistance to hepatocellular carcinoma cells by inducing autophagy through GABARAP [J]. Int J Mol Sci, 2022, 23(2): 711.

[78] LU Y, LI T, WEI G, et al. The long non-coding RNA NEAT1 regulates epithelial to mesenchymal transition and radioresistance in through miR-204/ZEB1 axis in nasopharyngeal carcinoma [J]. Tumour Biol, 2016, 37(9): 11733-41.

[79] 郑雪怡, 谢丹, 蔡木炎. DNA损伤反应及其抑制剂的现状与未来[J].中国细胞生物学学报(ZHENG X Y, XIE D, CAI M Y. Current status and future prospects of DNA damage response and its inhibitors [J]. Chinese Journal of Cell Biology), 2025, 47(3): 542-59.