ADP-核糖基化可逆修饰在DNA损伤应答及癌症治疗中的研究进展

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收稿日期: 2021-05-20; 接受日期: 2021-06-15; 网络版发表日期: 2021-09-13

国家自然科学基金(批准号: 32071277, 31670812)和河北省教育厅重点项目(批准号: ZD2020183)资助

摘要 细胞基因组DNA遭受到各种内外源因素的攻击可以诱发多种类型的DNA损伤。DNA损伤应答系统(DNA damage response, DDR)能及时识别、修复受损的DNA, 维持基因组稳定性, 避免肿瘤等多种疾病发生。DDR受到多种蛋白质翻译后修饰的严格调控, ADP-核糖基化(ADP-ribosylation)是其中最为重要的修饰类型之一。ADP-核糖基化是一种动态可逆的翻译后修饰, ADP-核糖基化与去核糖基化之间保持动态平衡, 精密调控DNA损伤应答过程。鉴于ADP-核糖基化在DNA损伤修复中的独特功能, 靶向这一可逆过程的抑制剂已被开发或有望作为一类用于癌症治疗的靶向药物。本文就ADP-核糖基化可逆修饰在DNA损伤修复及癌症治疗中的研究进展进行综述。

关键词 ADP-核糖基化, 去ADP-核糖基化, DNA损伤应答, 癌症治疗

细胞受到诸如氧化应激、辐射等各种内外源危害时可以引起包括DNA双链断裂(DNA double-strand break, DSB)在内的多种DNA损伤^[1]。DNA损伤积累将引起基因组不稳定, 最终导致肿瘤等多种疾病发生^[2]。DDR能够及时修复DNA损伤, 维持基因组稳定性。DNA损伤应答过程受到多种蛋白质翻译后修饰的严格调控, 包括泛素化、磷酸化、糖基化及ADP-核糖基化修饰等^[3-6]。在诸多修饰类型中, ADP-核糖基化由于涉及众多生理和病理过程, 如信号转导、蛋白运输、转录、DNA损伤修复、细胞周期调控、凋亡及坏死等, 受到越来越多的关注。ADP-核糖基化是烟酰胺腺

嘌呤二核苷酸(NAD⁺)中的ADP-核糖基(ADP-ribose, ADPR)以单个(mono-ADP-ribose, MAR)或多个(poly-ADP-ribose, PAR)形式与底物蛋白质的特定氨基酸残基发生共价连接反应, 可分为单ADP-核糖基化(mono-ADP-ribosylation, MARylation, MAR修饰)和多聚ADP-核糖基化(Poly-ADP-ribosylation, PARylation, PAR修饰)^[7,8]。在哺乳动物中, ADP-核糖基化修饰由ADP-核糖转移酶(ADP-ribosyltransferase, ART)超家族负责催化, 包括PARPs(poly ADP-ribose polymerases, PARPs)和ARTCs(clostridial-toxin-like ARTs, ARTCs)。ADP-核糖基化作为一种快速可逆翻译后修饰, 涉及一

引用格式: 闫珍珍, 杨肖云, 王亚光, 等. ADP-核糖基化可逆修饰在DNA损伤应答及癌症治疗中的研究进展. 中国科学: 生命科学, 2021, 51: 1218-1228
Yan Z Z, Yang X Y, Wang Y G, et al. Progress in reversible ADP- ribosylation modification in DNA damage repair and cancer treatment (in Chinese).
Sci Sin Vitae, 2021, 51: 1218-1228, doi: 10.1360/SSV-2021-0211

系列Writers, Readers, Erasers等酶和蛋白的调控(图1, 表1)^[9-13]. Writers即催化形成ADP-核糖基化修饰的酶 PARPs和ARTCs. Erasers负责移除MAR或PAR修饰, 主要包括PARG, ARH1, ARH3, TARG和MacroD1/2. 一些含有Macro, WWE, PBZ^[14], BRCT^[15,16], FHA^[15], OB折叠^[17], PIN^[18], RRM及GAR结构域的蛋白能够识别修饰蛋白上的ADPR基团, 被称作Readers.

迄今, ADP-核糖基化修饰已被发现50多年, 是DNA损伤应答过程中的一种重要翻译后修饰. 它可将DNA损伤修复相关蛋白募集至DNA损伤部位进行DNA修复, 从而有助于维持基因组稳定性^[19-21]. 近年来, 许多研究显示, ADP-核糖基化与炎症、神经退行性疾病和癌症等疾病密切相关^[22-25]. 本文总结了ADP-核糖基化可逆修饰在DNA损伤应答中的功能及在癌症治疗中的潜在应用价值.

1 DNA损伤修复中的PAR修饰和MAR修饰

ADP-核糖基化修饰在DNA损伤应答、细胞应激、转录、免疫反应、衰老和细胞死亡等多种生物学过程中调节受体蛋白的结构和功能^[19,24,26]. 两种不同类型的ADP-核糖基化即MAR与PAR修饰存在功能上的区别. MAR修饰仅将单个ADPR加到靶蛋白特定氨基酸位点上, 而PAR修饰能将多达200个ADPR的聚合物加到靶蛋白特定修饰位点, 产生线性和分支PAR链^[27]. 尽管这两种修饰都能调控靶蛋白的功能, 但PAR修饰能通过PAR结合基序等结构域募集PAR结合蛋白(Readers), 从而使得PAR可作为一种高密度蛋白结合骨架, 有利于高度复杂的蛋白复合体集结.

1.1 催化PAR修饰的酶在DDR中的作用

PAR修饰在DNA损伤应答中的功能已经被阐明.

图 1 ADP-核糖基化可逆修饰系统. 多种因子参与细胞内可逆ADP核糖基化修饰. PARPs和ARTCs作为“写手”的角色, 将单个或多个ADP-核糖基团添加到靶蛋白特定的氨基酸位点上. 靶蛋白上的ADP-核糖可以被含有Macro, WWE, PAR结合锌指, BRCT, FHA, OB折叠, PIN, RRM或GAR结构域的“读者”识别. “擦除器”包括PAR糖水解酶、ADP-核糖水解酶1/3、TARG1和MacroD1/2, 负责去除ADP-核糖

Figure 1 Reversible ADP-ribosylation modification system. Various effectors participate in intracellular ADP-ribosylation dynamics. PARPs and ARTCs act as “writers” that add mono or poly ADP-ribose units to specific sites of target proteins. The ADP-ribose moieties on target proteins can be recognized by “readers” containing Macro, WWE, PAR-binding zinc finger (PBZ), BRCT, FHA, OB folding, PIN, RRM, or GAR domains. The removal of ADP-ribose chains is catalyzed by “erasers”, which include PAR glycohydrolase (PARG), ADP-ribosyl hydrolase 1/3 (ARH1/3), TARG1, and MacroD1/2

该修饰由PARPs酶家族中的PARP1, PARP2, PARP5A和PARP5B四个成员完成催化. 在PAR修饰反应过程中, PARPs以NAD⁺为底物, 将多个ADPR基团通过

表 1 ADP-核糖基化修饰系统

Table 1 ADP-ribosylation modification system

ADP-核糖基化修饰(Writers)	修饰类型	氨基酸残基	ADP-核糖基化水解酶(Erasers)
PARP1/2/5A/5B	PAR	Asp/Glu/Ser	PARG/ARH3/TARG1/MacroD
PARP3/4/6/7-12/14-16	MAR	Asp/Glu	TARG1/MacroD
ARTC1/5	MAR	Arg	ARH1

O-糖苷键聚合成长的线性或分支形式的PAR链共价连接至靶蛋白的谷氨酸、天冬氨酸、丝氨酸等氨基酸上,并生成副产物烟酰胺^[27]。PARP1和PARP2是细胞中占主导地位的PARP酶家族成员,是DNA损伤的主要感受器(sensor)^[19,28]。PARP1在细胞中含量最丰富(100万~200万分子/细胞),负责约90%的PAR修饰。而PARP2负责剩余10%的PAR修饰^[7,29,30]。PARP1可识别DNA单链断裂(single-strand break, SSB)和DSB位点,并催化自身进行PARylation修饰^[29]。而一旦PARP1被损伤激活,PARP2便能识别依赖于PARP1的PAR修饰,并在DNA损伤位点催化PAR修饰^[31,32]。PARP1除了修饰自身的PAR外,还能对很多核糖体蛋白进行修饰,进而影响蛋白翻译。由此反映出ADP-核糖基化修饰与核糖体生物合成之间的潜在关联,提示该修饰广泛影响细胞核内的生物学过程,从而调控细胞DNA损伤修复^[33]。PARP5A/5B介导的PAR修饰主要涉及Wnt信号通路激活、端粒长度及囊泡运输等^[34,35]。

PAR修饰对于DNA损伤发生后的染色质解压缩,DNA损伤修复因子的招募至关重要。一个ADPR含有两个带负电荷的磷酸基团,因此,PAR链给DNA损伤部位带来大量负电荷^[36]。DNA本身也带负电荷,由于电荷排斥作用,PAR化修饰将影响染色质的高级结构,从而有助于DNA修复。PAR修饰的蛋白包括组蛋白^[37,38]、DNA蛋白激酶^[39,40]、p53^[41]、Ku复合物^[19,42]、DNA糖基化酶8-氧鸟嘌呤糖基化酶1(8-oxo-guanine-DNA glycosylase 1, OGG1)^[43]、PCNA^[44]及RUNX^[45]等。此外,含有PAR结合基序或结构域的蛋白可被PAR信号招募至DNA损伤位点,如XRCC1^[46]、DNA连接酶III^[47]和CHFR^[14]等,促进DNA损伤修复。因此,DNA损伤引起的PAR修饰作为一种对接信号和大量DDR相关蛋白组装的支架,有利于高效启动DNA损伤应答^[19,20]。

1.2 催化MAR修饰的酶在DDR中的作用

PARPs家族成员中的PARP3, 4, 6, 7~12, 14~16缺失负责聚合物延伸的保守催化氨基酸——谷氨酸,因此只能催化底物进行MAR修饰^[48]。许多证据表明,与PAR修饰类似,MAR修饰在DNA损伤应答中也发挥重要作用。例如,在DT40细胞中,PARP3能够被SSB激活,发生自身MAR修饰,同时催化组蛋白H2B发生MAR修饰,进而可能改变核小体的结构,促进DNA损伤应答

因子参与损伤反应^[49]。在DSB修复过程中,PARP3能够与DNA修复因子APLF结合,促进APLF在DSB位点处的积累,进而募集更多的损伤修复因子参与DSB修复^[50]。PARP10作为单ADP-核糖转移酶,在DNA损伤修复中也具有重要调控功能。PARP10的酶活突变体失去对跨损伤修复的促进作用,但PARP10参与跨损伤修复的调控底物还需进一步探索。此外,PARP10与PCNA的相互作用能够促进PARP10的单ADP-核糖转移酶活性,而PARP10可以通过促进PCNA的泛素化,来加强对跨损伤合成聚合酶的招募和提高跨损伤修复效率^[51]。而其他参与MAR修饰的PARPs家族成员在DNA损伤应答中的作用有待深入研究。

此外,人类ARTCs酶家族中的ARTC1, 5具有精氨酸特异性MAR修饰活性^[52],而ARTC3, 4由于缺失了关键的R-S-EXE催化基序而不具有催化活性。ARTCs酶家族蛋白表达于细胞表面、内质网或分泌到胞外,但这些蛋白在DNA损伤应答中的作用还是未知的。今后对这些单ADP-核糖基转移酶的研究可能揭示单ADP-核糖基化修饰在DNA损伤应答中的功能多样性。

2 DNA损伤修复中的去ADP-核糖基化修饰

与其他翻译后修饰一样,PAR和MAR修饰同样受到精密调控。值得注意的是,PAR是一种多聚合物,DNA损伤修复因子被募集后仅能到DNA损伤位点附近,PAR必须被迅速降解以便将DNA损伤修复因子直接加载到损伤位点进行修复。若不能及时去除PAR聚合物很可能会将损伤修复因子滞留在DNA损伤位点附近,导致细胞对DNA损伤高度敏感^[53,54]。因此,负责去ADP-核糖基化修饰的水解酶在DNA损伤应答中也发挥重要作用。去PAR修饰能促进释放DNA损伤修复相关蛋白到达DNA损伤位点从而完成修复。

2.1 多聚(ADP-核糖)水解酶(PARG)对ADP-核糖基化的调控及其在DDR中的作用

PAR修饰在DNA损伤后几秒钟内发生,而去PAR修饰在随后的几分钟后开始^[19,55]。不同的ADP-核糖基水解酶可以水解不同形式的ADP-核糖基化(图1)。PARG主要负责去PAR修饰,参与DNA损伤修复过程中约90%的去PAR修饰反应^[56]。PARG蛋白由976个氨

基酸组成, 作为一种单基因蛋白, 通过可变剪切方式产生5个不同PARG剪接体, 它们主要分布在细胞核、细胞质和线粒体中^[57,58]. PARG的催化结构域位于其C端macro结构域, 具有糖苷内切及外切酶活性. 它识别DNA损伤处的PAR修饰, 水解PAR链中两个ADP-核糖基之间的糖苷键^[56,59,60], 但它不能切除第一个ADPR和氨基酸受体之间的酯键, 从而保留底物上最末端的ADP-核糖^[61]. 因此, PARG将PAR修饰变成MAR修饰. PARG对于细胞功能至关重要, PARG缺失将导致小鼠胚胎死亡^[62]. 最近的研究也证实, PARG在DNA损伤修复中发挥重要作用. PARG敲除引起DNA单链和双链断裂修复缺陷^[53].

2.2 其他ADP-核糖水解酶对ADP-核糖基化的调控及其在DDR中的作用

除PARG外, 其他几种ADP-核糖基水解酶, 如TARG1, MacroD1/D2, ARH1/3和NUDT16/5也在MAR或PAR水解过程中发挥重要作用. 其中TARG1, MacroD1/D2也具有macro结构域^[11,63,64]. TARG1分子量为18.7 kD, 主要去除天冬氨酸和谷氨酸上的ADP-核糖基化修饰. 由于PARG并不能去除第一个ADPR和氨基酸受体之间的酯键, 所以TARG在这一过程中发挥重要作用. TARG1被PAR信号募集至损伤位点后, 在PARG介导的去PAR修饰之后从天冬氨酸或谷氨酸侧链上切除最后一个ADPR^[11,65]. 此外, TARG1也可以直接从天冬氨酸和谷氨酸中去除整个PAR链, 具有较弱的去PAR修饰功能^[11]. MacroD1/D2具有与PARG和TARG1中类似的macro结构域. MacroD1/D2与TARG1类似, 需要从受体蛋白天冬氨酸和谷氨酸残基上去除近端的ADPR, 发挥MAR水解酶的作用^[12,66]. ARH1和ARH3(ADP-核糖水解酶1和3)分子量均为39 kD, 氨基酸序列相似度约为16%. ARH1主要水解受体蛋白精氨酸上的单ADPR^[67]. ARH3不仅水解PAR, 还负责丝氨酸和ADPR之间酯键的水解^[68]. 最近的研究表明, 由PARP1, PARP2和HPF1协同催化的丝氨酸-ADP-核糖基化是在DNA损伤应答中最主要的ADP-核糖基化形式^[69,70]. 因此, ARH3作为DNA损伤应答过程中唯一能特异性水解丝氨酸ADP-核糖基的酶, 其在DNA损伤修复中的作用尤为重要. 最近本课题组和英国AheI课题组研究发现, ARH3在DNA损伤修复中发挥重要作用, 有可能作为潜在的肿瘤治疗靶点^[71,72]. NUDT16为Nu-

dix超家族水解酶成员, 广泛存在于包括古生物、细菌和真核生物在内的所有生物体中. PAR链和MAR均可以作为NUDT16的底物^[73]. 然而, 由于NUDT16具有磷酸酶特性, 催化水解后核糖-5'-磷酸被保留在受体蛋白上, 而磷酸核糖-AMP被释放. Nudix家族另一个成员NUDT5消化产物与NUDT16类似, 除了消化PAR后降解游离的ADPR外, 还能与PAR和PARG相互作用. 最新研究表明, NUDT5产生的AMP和ATP能被用于染色质重塑^[74]. ENPP是一种最近鉴定的PAR/MAR磷酸二酯酶, 与NUDT16类似, ENPP催化后也在受体蛋白上的PAR/MAR结合位点保留一个核糖-5'-磷酸^[75].

与PARG类似, 这些ADPR水解酶在DNA损伤修复中均发挥重要作用. 研究显示, TARG1对于DNA单链断裂修复是必需的^[20,64]. MacroD1/D2能够被募集至DNA损伤位点参与修复^[76,77]. 当DNA损伤发生时, PARP在DNA损伤位点产生PAR化修饰, 随后PARG和ARH3被招募到DNA损伤处进行去修饰, ARH3可彻底去除DNA损伤诱导的丝氨酸-ADP-核糖基化修饰, 但PARG作用后在DNA损伤处留下MAR修饰. 因此, TARG1, MacroD1和MacroD2可能在PARG下游发挥作用, 去除DNA损伤部位残留的MAR^[22,78]. 总之, 在DNA损伤修复过程中, 不同ADP-核糖基水解酶有不同的底物及亚细胞定位, 共同协调完成去ADP-核糖基化修饰.

除蛋白质外, DNA和RNA也可以发生ADP-核糖化反应. 有研究表明, RNA可以被单ADP-核糖基化修饰, 人源PARP10, PARP11, PARP15以及PARP同源物TRPT1作为Writer参与RNA磷酸化末端的ADP-核糖基化, 细胞ADP-核糖基水解酶(PARG, TARG1, Macro1, MacroD2和ARH3)等可以作为Eraser, 去除RNA的ADP-核糖基化^[79].

3 PARP抑制剂在癌症治疗中的应用

PAR修饰在DNA损伤修复过程中扮演重要角色^[28,80]. 许多DNA损伤修复因子可以识别PAR修饰信号, 并介导这些因子在DNA损伤位点早期的快速募集, 从而实现DNA损伤的高效修复^[19,80]. 缺失PAR修饰可抑制SSB和DSB修复^[16,81,82]. 由于PAR修饰在DNA损伤修复中的独特功能, PARP抑制剂(PARP inhibitor, PARPi)已被开发为一类利用合成致死策略用于癌症治

疗的靶向药物^[83,84]。目前已经有4种小分子PARPi成为美国食品药品监督管理局(Food and Drug Administration, FDA)批准的抗癌药物,包括olaparib, rucaparib, niraparib和talazoparib^[85]。这些抑制剂是PARP1/2竞争性抑制剂,与细胞内的NAD⁺竞争性结合PARP1/2^[86]。它们既抑制PARP1/2的催化活性,阻断PAR链形成,抑制蛋白PAR修饰的发生,阻断DNA损伤修复信号。同时,这些抑制剂又能将PARP1/2滞留在DNA损伤处形成PARP-DNA复合物,阻断受损DNA中PARP1/2的释放,造成复制叉停滞,最终导致癌细胞死亡^[54]。

Olaparib是第一个获得FDA批准用于治疗BRCA突变的晚期卵巢癌的PARPi。在随后的几年里,olaparib不断被FDA批准扩大适应症,用于包括三阴性乳腺癌和带有BRCA突变的胰腺癌等癌症的治疗^[87]。2020年5月,美国FDA正式批准olaparib用于同源重组修复(homologous recombination repair, HR)基因突变的前列腺癌治疗,这成为该药获批的第四个癌种适应症^[88]。此外,PARPi也在对DNA修复缺陷和低存活率的其他类型癌症,如前列腺癌的III期临床肺癌取得阳性结果,针对胃癌、小细胞肺癌和非小细胞肺癌的研究已进入III期临床^[89-92]。食管癌、子宫内膜癌、宫颈癌、黑色素瘤、膀胱癌和白血病等癌症也在进行临床前试验^[93-96]。PARPi有望成为极具潜力的广谱抗肿瘤药。

虽然PARPi在治疗多种癌症显示出广阔前景,然而,长期使用PARPi可以诱发化学耐药性^[97,98],主要原因之一是PARPi诱导细胞过表达PARP^[99]。同时,一些携带BRCA突变或DNA损伤修复缺陷的肿瘤细胞对PARPi并不敏感^[97,100]。目前,PARPi仅能抑制PARP1和PARP2的催化活性^[54,56]。除PARP1与PARP2外,其他PARPs家族成员(如PARP3和PARP10)也通过催化ADP-核糖基化修饰参与DNA损伤修复^[50,51,101,102],提示这些PARPs仍在DNA损伤修复中发挥一定作用。因此,亟需开发一种新型的癌症化学疗法,以克服对PARPi不敏感的DNA修复缺陷肿瘤治疗的挑战。

4 PARG抑制剂在肿瘤治疗中的应用

越来越多的证据表明,PARG也在DNA损伤修复中发挥重要作用。在DNA损伤诱导PAR修饰发生后,PARG的macro结构域与PAR相互作用从而将PARG募

集至DNA损伤位点^[103]。缺乏PARG的细胞存在严重的DSB和SSB修复缺陷^[104,105]。由于PAR修饰在DNA损伤应答中是瞬时可逆的调控过程,PARP和PARG催化活性之间的平衡对于高效DNA损伤应答必不可少^[106]。因此,抑制PARG酶活性也会损害DNA损伤修复。基于PARG在DNA损伤修复中的重要功能,靶向PARG可以选择性杀死具有DNA损伤修复缺陷的肿瘤细胞,有望成为癌症化疗的一种新型合成致死策略。与PARPs包含多个成员不同,PARG家族成员单一,这就赋予了靶向PARG治疗癌症的专一性,并且避免了肿瘤细胞对PARPi耐药性的问题。此外,PARP1在细胞中含量非常丰富,每个细胞估计有10⁶个分子^[107,108]。相反,每个细胞约有2000个PARG分子^[109],这表明PARG可能是DNA损伤修复途径中更可行的药物靶点,抑制PARG应该具有更高的效力和特异性^[19]。

4.1 PARG抑制剂PDD00017273在肿瘤治疗中的应用

近日,研究人员开发了一种细胞渗透性抑制PARG的药物:喹啉二酮类抑制剂PDD00017273。PDD00017273对PARG的抑制呈剂量依赖性,低浓度(0.3 μmol/L)对PARG有明显的抑制作用。当PDD00017273处理乳腺癌MCF7细胞时,细胞出现DNA损伤增加、存活率降低等现象。在检测的几种乳腺癌细胞系中,大多数对PDD00017273不敏感,包括具有BRCA突变的癌细胞,而BRCA无突变的细胞系对PDD00017273特别敏感^[110]。这提示PARG可能与PARPi的作用机制不同,PARG抑制剂(PARG inhibitor, PARGi)敏感性的作用机制及意义仍有待阐明。

此外,英国科学家Taylor团队^[111]报道:长期的PDD00017273处理可以诱导细胞产生复制叉停滞,甚至垮塌,进而导致DNA损伤的累积和复制突变,造成细胞克隆潜能的降低。此研究表明,由于DNA复制缺陷导致复制叉停滞和持续的复制压力导致卵巢癌细胞系和源自患者活体组织的体外模型对PDD00017273敏感。PDD00017273通过抑制DNA复制因子导致细胞合成致死。同时,抑制PARG使细胞对靶向CHK1激酶的药物更加敏感。由于PARGi和PARPi的敏感性无交叉现象,PARGi具有作为补充策略用于治疗卵巢癌的潜力。同时,PDD00017273也作为单一疗法和联合疗法在体外成功地应用于胰腺导管腺癌(pancreatic ductal

adenocarcinoma, PDAC)的治疗^[112]。然而, 由于代谢活性较差, 这种PARGi尚不能用于体内癌症治疗。

4.2 PARG抑制剂Gallotannin在肿瘤治疗中的应用

Gallotannin也是一种被广泛使用的PARG抑制剂, 主要通过抑制PARG的ADP-核糖基化水解酶活性发挥作用。Gallotannin在氧化应激刺激的细胞死亡中具有保护作用^[113,114]。当氧化应激药物刺激小鼠的神经元细胞或星形胶质细胞后, 会导致大量细胞死亡。Gallotannin能够阻止细胞中NAD⁺的耗损, 促使PAR的积累, 进而抑制PARP1的过度激活来保护神经细胞的死亡^[113]。在没有外源DNA损伤诱导剂作用下, Gallotannin处理正常细胞, 会促使PAR链在细胞中的累积, 导致细胞复制叉崩溃, 并诱导细胞发生HR修复反应。而在HR修复缺陷的肿瘤细胞中, Gallotannin会导致细胞发生合成致死^[115]。Al-Halabi等人^[116]证明, Gallotannin可以抑制NF- κ B来减缓人类结肠癌异种移植的生长。基质金属蛋白酶在有转移的腺癌和晚期肿瘤中表达上调, Gallotannin可以使基质金属蛋白酶明显减少^[117]。由此可见, Gallotannin抑制剂的深入研究为未来临床癌症的治疗提供了很大的理论应用前景。

4.3 PARG抑制剂COH34在肿瘤治疗中的应用

最近报道了一种具有高效、细胞通透性和肿瘤细胞杀伤力的新PARGi COH34^[53]。COH34在纳摩尔浓度下抑制PARG活性, 并在体内外诱导肿瘤细胞死亡。COH34具有较强的药效, IC₅₀值为0.37 nmol/L, 高特异性抑制PARG, 与其他水解酶, 如TARG1和ARH3没有交叉抑制。抑制去PAR修饰后, DDR蛋白(如XRCC1, APLF和CHFR)被滞留在DNA的受损部位, 从而阻断正常DNA损伤应答。COH34对BRCA1/BRCA2缺陷的细胞, 甚至是对Olaparib耐药的细胞均具有合成致死效应。研究显示, COH34是一种非常具有前景的先导化合物, 可用于开发癌症治疗的去PAR修饰类抑制剂。因此, 与PARPi类似, PARGi也有可能

未来用于个体化的癌症治疗。

5 总结

ADP-核糖基化修饰是一种动态调节的可逆翻译后修饰, 在早期DNA损伤应答中起着重要作用。它通过将大量的损伤应答因子募集至DNA损伤位点附近, 产生快速DNA损伤应答。PAR修饰直接通过每个ADPR单元中的负电荷影响染色质重塑。ADP-核糖基化修饰还可以通过cross-talk作用调节DNA损伤修复蛋白其他类型的翻译后修饰, 例如磷酸化和泛素化等^[118]。关于PAR的合成、识别和降解, 仍然存在许多有趣的问题, 解决这些问题才能充分理解PAR修饰在DNA损伤应答中的功能。随着蛋白质组学的发展, 可以研究并发现更多位点特异性的PAR修饰蛋白, 从而阐明它们在DNA损伤应答中的潜在作用。不同的去PAR修饰酶可以直接去除不同氨基酸位点上的PAR修饰。除了DDR, PAR修饰还参与许多生物学过程。对其他依赖PAR修饰的生物学功能的机制研究也能为理解DNA损伤应答提供新线索。

靶向PAR和去PAR修饰是肿瘤化疗的理想靶点。在FDA成功批准和临床广泛应用PARP抑制剂的鼓舞下, 针对DNA损伤应答通路的药物靶点开发已成为研究热点。其中一些靶点, 如ATR, ATM, CHK1/2, WEE1已经在具有DNA损伤修复缺陷的肿瘤或与化学靶向药物联合使用进入临床研发阶段。同时, 对PARPi的耐药性问题也需要寻找一些新型替代性治疗策略。PAR-Gi可能作为一类可替代PARPi的新型抑制剂, 克服PARPi的化疗耐药性。本课题组^[71]最近发现了ARH3的首个小分子抑制剂AI26, AI26在细胞水平有效抑制ARH3的酶活性, 明显削弱DNA损伤修复。同时, 携带DNA损伤修复基因缺陷和对PARPi不敏感的肿瘤细胞对AI26高度敏感。然而, 还需要更多的研究来证明这些抑制剂的治疗潜力。综上所述, 靶向ADP-核糖基化可逆修饰抑制剂的进一步研究可能会对临床癌症治疗产生巨大影响。

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Progress in reversible ADP- ribosylation modification in DNA damage repair and cancer treatment

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Cellular genomic DNA is attacked by various internal and external stimuli, inducing multiple types of DNA damage. DNA damage response (DDR) can hastily repair DNA damage, maintain genome stability, and avoid tumors and other diseases. DDR is regulated by diverse protein posttranslational modifications. ADP-ribosylation is one of the most important modifications in DDR. ADP-ribosylation is a dynamic and reversible posttranslational modification. The dynamic balance between ADP-ribosylation and de-ADP-ribosylation precisely regulates DDR. Given the unique function of ADP-ribosylation in DNA damage repair, inhibitors targeting this reversible process have been developed and are expected to be a new class of chemotherapeutics for cancer treatment. This review introduces the research progress of reversible ADP-ribosylation modification in DNA damage repair and cancer treatment.

ADP-ribosylation, de-ADP-ribosylation, DNA damage response, cancer therapy

doi: [10.1360/SSV-2021-0211](https://doi.org/10.1360/SSV-2021-0211)