·综述·

多聚ADP核糖聚合酶1在口腔鳞状细胞癌精准诊疗中的作用机制及转化价值

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【摘要】 缺少有效分子靶点是阻碍口腔鳞状细胞癌(OSCC)精准诊疗进步的关键因素。多聚ADP核糖聚合酶1(PARP1)具有执行DNA损伤反应、处理氧化应激压力、抑制细胞程序性死亡等功能,是癌细胞应对生存压力的重要工具,也是适用于多种癌症治疗的分子靶点。研究显示,PARP1在OSCC诊疗中具有强大的潜力:一方面PARP1分子显像技术可用于OSCC的在体诊断,另一方面PARP抑制剂与放化疗联合应用在OSCC临床前测试中取得了良好的疗效。本文总结了PARP1在癌症治疗中的作用机制,重点阐述了PARP1应用于OSCC精准诊疗的研究进展,以促进PARP1靶点在OSCC中的临床应用转化。

【关键词】 口腔肿瘤; 多聚ADP核糖聚合酶1; 多(ADP核糖)聚合酶抑制剂; 精准医学; 分子显像

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The importance of poly (ADP-ribose) polymerase 1 in precision medicine of oral squamous cell carcinoma

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【Abstract】 The lack of effective molecular targets is a critical problem hindering the advance of precision medicine in oral squamous cell carcinoma (OSCC). Poly (ADP-ribose) polymerase 1 (PARP1) is a pleiotropic gene involved in several cellular functions, e.g., executing DNA damage response, processing oxidative stress, and inhibiting programmed cell death, making it an important tool for cancer cells to cope with survival pressures and a molecular target suitable for the treatment of various cancers. Recent research progress has shown that PARP1 has great potential in the diagnosis and treatment of OSCC. On one hand, molecular imaging techniques can be used for the *in vivo* diagnosis of PARP1 expression and distribution. On the other hand, the combined application of PARP inhibitors with radiochemotherapy has achieved great therapeutic effects in preclinical tests. This article summarized the mechanisms of PARP1 in cancer treatment, with a focus on elucidating the research progress in the precision medicine of OSCC using PARP1 as a molecular target, to promote the clinical application of PARP1 targeting in the treatment of OSCC.

【Key words】 Mouth neoplasms; Poly (ADP-ribose) polymerase 1; Poly (ADP-ribose) polymerase inhibitors; Precision medicine; Molecular imaging

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21世纪以来生命科学发展迅速,基因组学等生物技术的广泛应用大大加深了研究者对疾病分子机理的理解,新的分子靶点促进了靶向药物研发,癌症精准医疗水平得到大幅度提升。相应地,我国多种癌症类型的患者预后得到明显改善[1]。例如,国家癌症中心数据显示,2016年中国乳腺癌患者的5年生存率超过82%,显著好于20年前的状况[2]。相较之下,口腔鳞状细胞癌(oral squamous cell carcinoma,OSCC)的治疗方式和预后并未取得较大进步。经过20余年的发展,晚期(Ⅲ和Ⅳ期)OSCC的5年生存率依然停滞在50%~60%[3-6]。作为头颈部鳞状细胞癌的一种主要亚型,OSCC的临床治疗同样以外科手术和局部放疗为主,必要时辅助系统性化疗。相较于乳腺癌,目前临床上少有分子靶向疗法用于

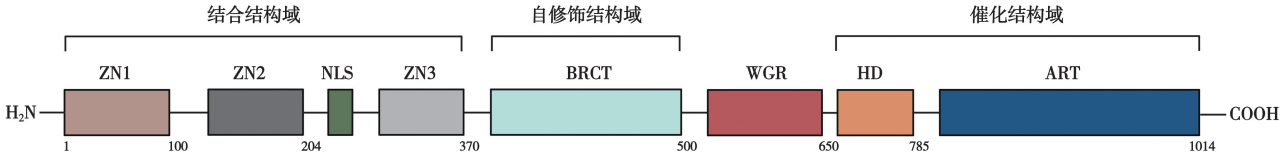

图1 多聚ADP核糖聚合酶1(PARP1)蛋白结构域图解 ZN1、ZN2、ZN3:锌指结构域1、锌指结构域2、锌指结构域3;NLS:核定位信号区;BRCT:乳腺癌易感蛋白-羧基末端修饰域;WGR:富含色氨酸-甘氨酸-精氨酸域;HD:螺旋结构域;ART:ADP核糖转移酶域;ZN1、ZN3和WGR结构域协同结合DNA损伤位点,WGR结构域与ZN1、ZN3、HD、ART和DNA相互作用,是复合物的核心组分。

OSCC患者。因此,缺少精准、高效的分子靶点及相应的靶向药物是OSCC精准医疗进步缓慢的重要因素。

OSCC致病因素复杂,除烟酒外,人乳头瘤病毒(human papilloma virus, HPV)感染和范可尼贫血(fanconi anemia, *FA*)基因突变均是常见的致癌因素[7]。不仅如此,OSCC基因突变类型复杂多变,其中蕴藏着多种潜在的分子靶点[8]。多聚ADP核糖聚合酶1[poly(ADP-ribose) polymerase 1, PARP1]是一个备受关注的癌症治疗分子靶点[9]。

*PARP1*是一个功能多向性的基因,在DNA损伤修复、代谢稳态调控、活性氧化物抑制、基因转录表达和信号通路转导等方面扮演着重要角色[10-14]。PARP1属于多聚二磷酸腺苷酸核糖聚合酶(PARP)家族的一员,其功能主要通过多聚ADP核糖基化修饰靶标蛋白实现的[15]。人体细胞拥有17种PARP酶,通过1个共同的催化结构域(图1)结合底物β-烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+),将NAD^+的ADP核糖单元转移到靶标蛋白的受体亲核氨基酸残基上,同时释放烟酰胺(nicotinamide, NAM)作为副产物[15]。PARP家族中PARP1、PARP2和PARP3蛋白主要定位在细胞核,其中PARP1在DNA损伤响应时承担超过90%的ADP核糖基化酶活性[16]。OSCC通常高表达PARP1,意味着OSCC对PARP1功能具有依赖性[17-22]。

一、多聚ADP核糖聚合酶1是参与DNA损伤响应与修复的关键基因

细胞在日常新陈代谢或放化疗时不断暴露在各种基因毒性环境中,导致DNA损伤。细胞需要及时修复DNA损伤,以保持基因组完整性,因此拥有一系列分子生物学机制来检测和修复受损的DNA[23-27]。*PARP1*是DNA损伤应答与修复的重要基因,在早期阶段即感知并结合到DNA损伤部位,将一个带负电荷的聚合物,即多聚ADP核糖,修饰到自身和许多靶标蛋白上[10,15],进而激活PARP1并发挥靶标蛋白功能,以应对细胞生存压力(图2)。

ARP1蛋白常用来处理DNA损伤,参与的通路包括碱基切除修复(base excision repair, BER)、核苷酸切除修复(nucleotide excision repair, NER)、DNA单链断裂修复(single strand break repair, SSBR)和DNA双链断裂修复(double strand break repair, DSBR)。

1. 碱基切除修复:BER多用于修复内源性碱基损伤,包括氧化碱基损伤、烷基化损伤和无碱基位点等类型[28]。BER通过DNA糖基化酶识别受损的DNA碱基,剪切并生成1个无嘌呤/无嘧啶的位点,产生的无碱基位点由AP核酸内切酶

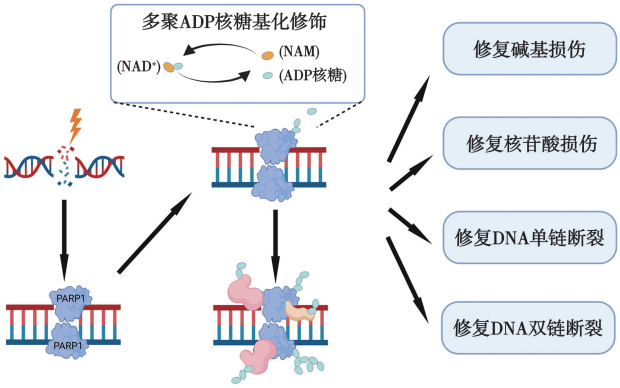

图2 多聚ADP核糖聚合酶1(PARP1)蛋白参与DNA损伤响应与修复 当DNA发生损伤,PARP1蛋白识别DNA损伤并结合于损伤位点,以β-烟酰胺腺嘌呤二核苷酸(NAD^+)和ATP为底物,生成烟酰胺(NAM)和ADP核糖,ADP核糖与PARP1或其他DNA修复蛋白结合,进行多聚ADP-核糖基化修饰,参与修复碱基损伤、核苷酸损伤、DNA单链断裂和双链断裂。

进一步处理而产生DNA单链断裂(single-strand break, SSB),进而被PARP1介导的SSBR通路修复[24,29]。PARP1在BER中的直接作用尚不清楚,但现有证据表明BER并不依赖PARP1完成修复[10]。

2. 核苷酸切除修复:NER能够去除多种类型的DNA损伤,例如紫外线(UV)辐射引起的环丁烷-嘧啶二聚体(cyclobutane pyrimidine dimer, CPD)、化疗药物顺铂引起的链内交联损伤、活性氧(reactive oxygen species, ROS)造成的环嘌呤等[30]。Pines等[31]发现,PARP1通过聚ADP核糖修饰作用增加了损伤特异性DNA结合蛋白2(damage specific DNA binding protein 2, DDB2)基因的稳定性和染色质滞留时间,并且招募染色质重塑酶(chromodomain helicase DNA binding protein 1 like, CHD1L),进而促进NER。

3. 单链断裂修复:PARP1在SSB的检测和修复中起关键作用[10,32]。PARP1能够快速地检测并结合到SSB上去,接着通过多聚ADP核糖修饰激活PARP1,激活后的PARP1将进一步修饰多种靶标蛋白,如XRCC1,召集它们到SSB处参与修复[33]。人类和小鼠细胞*XRCC1*突变导致SSBR缺陷,未及时修复而累积的SSB广泛激活PARP1,引起细胞内库存的NAD^+耗竭,从而导致细胞死亡[34]。

4. 双链断裂修复:相较于SSB等损伤类型,DNA双链断裂(double-strand break, DSB)危害更大,如果不能及时修复会导致细胞基因组改变或死[35]。放化疗一般通过制造DSB

消灭癌细胞。*PARP1*是识别DSB的重要基因,通过召集多个基因促进DSB修复[16]。例如,关键DNA损伤响应基因编码的共济失调-毛细血管扩张突变(ataxia-telangiectasia mutated,ATM)激酶就具有聚ADP核糖修饰位点,其功能受到PARP1酶活性的影响[36]。相应地,PARP抑制剂能够增加多种癌症的放化疗敏感性[13,37]。

二、多聚ADP核糖聚合酶1抑制剂与合成致死

癌细胞生存增殖过程中遭受较多的DNA损伤,因此更加依赖PARP1的功能。然而不同个体肿瘤之间对PARP抑制剂的敏感性差异很大。研究发现,部分癌症如乳腺癌易感基因(breast cancer susceptibility gene,*BRCA*)发生基因突变而对PARP抑制剂异常敏感,进而揭示了合成致死(synthetic lethality)效应[38]。这是因为在使用PARP抑制剂处理癌细胞时,DNA单链断裂未能及时修复,导致DNA复制期间DSB的累积,需要*BRCA*基因介导的同源重组(homologous recombination,HR)机制进行修复(图3)。因此,HR缺陷的肿瘤因合成致死对PARP抑制剂极其敏感。临床上已经利用*BRCA*突变作为HR缺陷的生物标志物,指导PARP抑制剂的应用[39]。值得注意的是,一些未发现*BRCA*突变的肿瘤对PARP抑制剂也很敏感,意味着存在多种机制造成HR缺陷,这些肿瘤也可以通过PARP抑制剂制造“合成致死”进行治疗[11]。

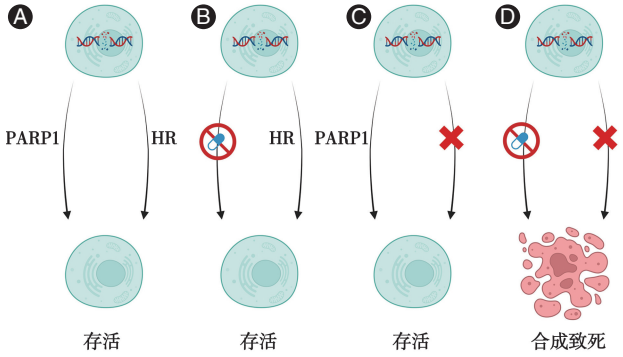

图3 阻断多聚ADP核糖聚合酶1(PARP1)与同源重组(HR)修复途径诱导细胞合成致死效应图解 A:正常细胞出现DNA损伤时可通过2种主要DNA损伤修复途径PARP1和HR来修复DNA损伤,细胞得以存活;B:正常细胞的PARP1修复途径被药物阻断,HR修复途径发挥主要DNA损伤修复功能,细胞存活;C:正常细胞HR修复途径受损,PARP1修复途径发挥主要DNA损伤修复功能,细胞存活;D:当细胞的2条主要DNA损伤修复通路同时受损,DNA损伤无法及时被修复,细胞最终死亡。

HR缺陷在以OSCC为主的头颈部癌症中也较为常见[40]。有研究发现,头颈鳞状细胞癌中约6%的*BRCA1*、7%的*BRCA2*、1%~16%的*ATM*、4%~10%的*ATR*基因突变会导致HR缺陷[41-42]。此外,约35%~52%头颈部鳞状细胞癌患者至少丢失了一份抑癌基因*SMAD4*拷贝,*SMAD4*基因拷贝丢失与*FANC/BRCA*基因表达下调相关,也会引起HR功能损失[43-44]。需要指出的是,正常细胞一般具有完整的HR机制,不会因PARP抑制而产生“合成致死”效应,因此PARP抑制剂对正常组织细胞基本无毒副作用。OSCC缺少疗效显著的靶向药物[45],临床及科研人员都有较高的积极性进一步开发PARP抑制剂用于OSCC治疗。

三、开发多聚ADP核糖聚合酶1用于口腔鳞状细胞癌分子诊断

由于PARP抑制剂临床应用的成功,PARP1也成为癌症分子诊断的热门靶点。肿瘤组织较正常组织显著高表达PARP1[22]。基于此,针对PARP1表达水平和分布的分子显像技术正在成为指导癌症治疗的新兴途径[46]。

现有临床前和临床研究结果显示,PARP1在OSCC精准诊疗中具有巨大潜力[18,47-48]。基于光学原理和核素示踪剂研发的PARP1分子显像技术在癌症诊断测试中表现优异[17-18,20,46,49-50]。研究人员经化学修饰PARP抑制剂olaparib研发了荧光探针,通过活体小鼠影像实验和OSCC组织样本检测PARP1的表达和分布,发现该探针局部用药时能够鉴别口腔中的肿瘤组织,可用于OSCC诊断并辅助指导手术;对比新鲜活检标本检测结果,该荧光探针的肿瘤组织特异性和灵敏度均>95%[17,20]。正电子发射断层扫描技术(positron emission tomography,PET)是活体诊断PARP1的重要医学影像工具。PARP1的PET探针多以正电子核素氟-18作为示踪剂标记PARP抑制剂,进而通过体内体外实验测试探针的分子靶向性和成像效果。有研究显示,以olaparib为母核的PARP1探针在OSCC小鼠模型PET成像试验中表现优异,可区分健康舌体和舌肿瘤[51-52]。Schöder等[21]进一步开展了一期临床试验,招募了11位口腔/口咽鳞状细胞癌患者,测试了^{18}F-olaparib对比临床标准^{18}F-FDG探针的PET/CT成像效果,初步确定了^{18}F-olaparib的成像对比度更高,可用于OSCC诊断。

四、多聚ADP核糖聚合酶1抑制剂用于口腔鳞状细胞癌治疗的研究进展

放化疗主要通过诱导DNA损伤来产生细胞毒性,意味着DNA损伤修复效率是决定OSCC治疗效果的核心因素,而PARP1有望成为其中关键的治疗靶点[53]。近年来,若干研究的实验结果支持特定场景下PARP抑制剂治疗OSCC的良好疗效。一项Ⅱ期随机临床试验结果显示,45%的OSCC患者对基于olaparib的治疗方案有反应(Ki67降低至少25%),79%的样本观察到肿瘤细胞增殖降低[54]。由于PARP1在处理DNA损伤方面具有重要功能,PARP抑制剂与放化疗联用治疗OSCC时普遍表现优异,这在临床前[55-61]及临床研究[53,62-65]中均有体现。此外,通过联合应用其他靶向药物,PARP抑制剂也能产生更好的疗效。Yin等[66]报道,PARP抑制剂促进硫氧还蛋白还原酶1(thioredoxin reductase 1,TrxR1)的失活,致使OSCC细胞毒性ROS累积和DNA损伤,当与凋亡诱导药物APR-246联合应用时产生协同作用。

PARP抑制剂的敏感性还取决于PARP1的表达水平[67-68]。尽管OSCC中PARP1表达水平普遍高于正常组织,但同时需要注意肿瘤之间PARP1表达水平有着显著的个体化差异,而该差异与PARP抑制剂敏感性有着密切的联系。Wang等[47]

报道,因为顺铂和5-氟尿嘧啶治疗增强了PARP1表达,导致复发性OSCC细胞中PARP1表达显著上调、化疗药物耐受性增加,而PARP抑制剂部分逆转了复发性癌细胞的耐药性。

HPV阳性OSCC具有独特的生物学特征,其放化疗预后远远好于HPV阴性的患者:HPV/p16阳性患者5年生存率62%,显著高于阴性患者的26%[35,69-71]。HPV影响多条DNA损伤反应机制,如FA通路[37,72]、转化生长因子β(transforming growth factor-β,TGF-β)信号通路[48,73]和*ATM*等基因功能[74-75]。因此,HPV阳性OSCC更加依赖PARP1进行DNA损伤修复,导致其对PARP抑制剂敏感性升高且适合与放化疗联合应用[48,76-77]。例如,Zuo等[37]揭示了HPV造成*FA*基因*XPF*功能抑制,导致HPV阳性OSCC对顺铂更敏感,而olaparib的联合应用进一步提升顺铂治疗效果。这也与Lombardi等[78]的发现一致,即*FA*基因变异的OSCC依赖PARP1修复顺铂等药物造成的链间交联损伤。Güster等[79]测试了olaparib与放疗联合应用的效果,发现HPV阳性OSCC细胞产生了显著的放射增敏效果。这些研究同时对比了HPV阴性的OSCC细胞系,发现同样的处理方式在HPV阴性癌细胞上取得的治疗效果较差。

五、总结与展望

综上所述,PARP1有望成为诊断和治疗OSCC的重要分子靶点。PARP1蛋白在修复DNA损伤方面有着重要功能,因此抑制PARP会增加放化疗的效果。不仅如此,PARP抑制剂也适合与免疫疗法联合应用。鉴于已经有综述重点分析了PARP抑制剂调控OSCC免疫的研究进展[53],不再赘述。PARP抑制剂的治疗潜力毋庸置疑,向临床转化的关键在于:如何筛选合适的OSCC患者进行治疗?本研究认为,通过分子显像技术检测PARP1的表达和分布是指导PARP抑制剂精准应用的必由之路。

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