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·述 评·

基于合成致死的抗肿瘤药物研发进展

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【摘要】合成致死是指在两个非致死基因中任何一个基因发生突变均不影响细胞存活，但当两个基因同时发生突变时，能够特异性导致细胞死亡。恶性肿瘤由于DNA复制和修复的错误积累了大量的基因突变，因此可抑制与这些基因具有合成致死关系的另一个基因，从而选择性地杀死肿瘤细胞，而不影响正常细胞。近年来，合成致死原理已经成功应用于肿瘤的靶向治疗。本文综述了合成致死的基本原理、合成致死相互作用的筛选方法、合成致死在DNA损伤修复领域的研究现状、合成致死在抗肿瘤药物研发中的挑战及展望。

【关键词】合成致死；DNA损伤修复；PARP抑制剂；抗肿瘤药物

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Research progress for the development of anti-tumor drugs based on synthetic lethality

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【**Abstract**】Synthetic lethality describes a phenomenon where mutation of any one of two non-lethal genes does not affect cell survival, whereas mutation of both genes significantly compromise cell viability. Malignant tumors accumulate a large number of genetic mutations due to errors in DNA replication and repair. Inhibiting another gene that has a synthetic lethal relationship with one of these genes may selectively kill tumor cells without affecting normal cells. In recent years, the principle of synthetic lethality has been successfully applied to the targeted therapy of tumors. This article reviews the basic principles of synthetic lethality, the screening methods for synthetic lethal interactions, the research status of synthetic lethality in the field of DNA damage repair, and the challenges and prospects of synthetic lethality in the development of antitumor drugs.

【**Keywords**】Synthetic lethality; DNA damage repair; PARP inhibitor; Anti-tumor drug

“合成致死”现象的发现已有近100年的历史，但一直没有得到重视。直到2014年，全球第一个按照“合成致死”原理设计的抗癌药物PARP抑制剂奥拉帕尼被批准用于治疗卵巢癌，此后，制药界掀起了利用“合成致死”原理研发创新药物的热潮。“合成致死”为靶向肿瘤抑制基因以及那些含有“不可成药”（Undruggable）蛋白突变和/或具有常规靶向疗法耐药突变的癌症治疗提供了新思路，成

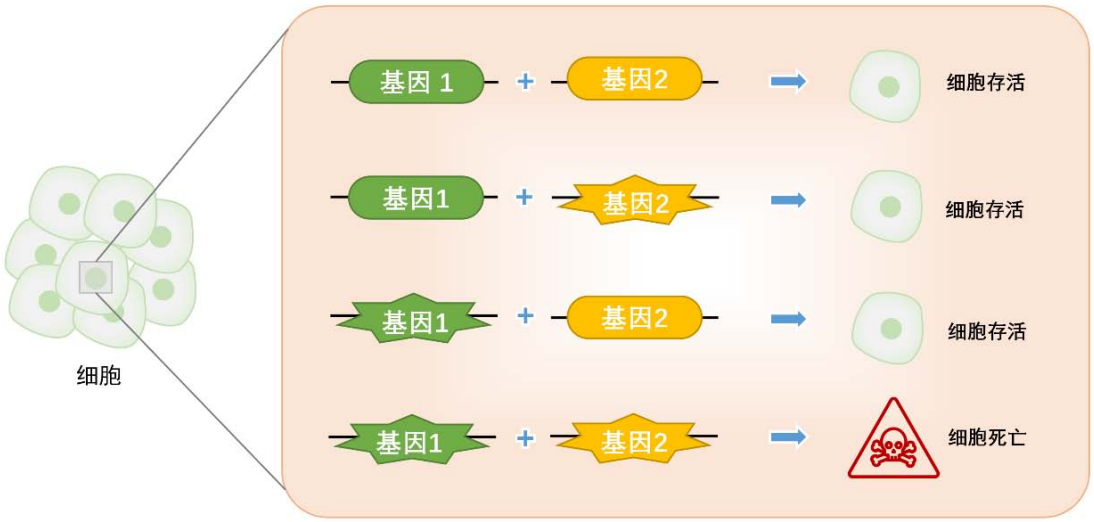
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为肿瘤治疗的未来方向之一。本文将系统介绍合成致死的基本原理、合成致死相互作用的筛选方法、合成致死在DNA损伤修复领域的研究现状以及合成致死在抗肿瘤药物研发中的挑战与展望。

1 合成致死的概念

合成致死最初由遗传学家Calvin Bridges在研究黑腹果蝇杂交时首次发现[1]，由Theodore Dobzhansky在1946年正式命名[2]。“合成致死”的概念虽源于对果蝇的遗传研究，但可延伸到其它生物体。本质上，“合成致死”定义的是两个基因之间的相互关系，当其中任意一个基因发生突变或功能失活时并不会对细胞或生物体的存活造成影响，但两个基因同时突变或失活将会导致细胞或生物体的死亡[3]（见图1）。利用合成致死原理进行肿瘤治疗被认为是很有前景的一种肿瘤精准治疗策略，但是如何高效准确地发现具有合成致死关系的基因对是当前面临的主要挑战。



注：星型框代表基因突变或功能失活

图1 合成致死作用原理示意图

2 合成致死基因对筛选方法

目前，合成致死相互作用基因对的筛选方法主要包括酵母筛选、药物筛选、RNA干扰筛选、CRISPR筛选和生物信息学筛选等。

酵母筛选是最早被用于鉴定合成致死相互作用基因的方法。1997年Hartwell首次提出酵母筛选方法[4]，经过25年的发展，酵母筛选在识别合成致死基因对领域已取得了长足进步，特别是通过高通量杂交策略极大促进了遗传相互作用的量化和双突变体的大规模发现[5, 6]。目前，利用酵母筛选已经成功鉴定了人类细胞中存在的多个合成致死相互作用，比如CKS1B–PLK1[7]、RAD54B–FEN[8]等。药物筛选是利用针对特定靶标的药物分子发现合成致死相互作用的一种策略。主要基于细胞系突变数据和高通量药物筛选数据，识别可能构成合成致死相互作用的敏感突变。高通量药物筛选方法已被应用于CDK1/2、PLK1和WEE1等基因突变的癌症中合成致死相互作用基因对的筛选，并取得了良好的进展[9]。RNA干扰筛选是通过促进特定的mRNA降解来筛选转录后基因，可分为短发夹RNA（short hairpin RNA，shRNA）筛选和小干扰RNA（small interfering RNA，siRNA）筛选[10]。RNA干扰技术的出现使合成致死概念更广泛地应用于人类细胞系统，并允许鉴定新基因和涉及多种生物过程的遗传网络[11]。自2008年首次使用siRNA来识别肿瘤抑制基因VHL的合成致死基因以来[12]，随着RNA干扰技术的不断进步和高通量筛选的应用，已发现了更多新的合成致死基因对，例如SMARCA2–SMARCA4、ARID1A–ARID1B[13]等。CRISPR是一种特异性、高效和可扩展的基因组编辑技术，可实现靶向基因的完全敲除[14]。与RNA干扰基因敲除不同，CRISPR文库可以靶向蛋白质编码序列和调控元件，包括启动子、增强子、转录microRNA和长非编码RNA等。随着CRISPR技术的进步，现在已可以系统地绘制人类癌细胞中的遗传相互作用网络图谱。因

此，这种强大的遗传工具无疑将加速合成致死基因对的发现[15, 16]。与全基因组siRNA或基于CRISPR的人类细胞系筛选方法相比，生物信息学筛选可以快速预测具有潜在合成致死关系的基因对，是一种很有吸引力的合成致死基因对发现方法[17]。这种方法通过使用表达谱数据、shRNA筛选结果和拷贝数数据对基因对相互作用进行评分从而预测合成致死相互作用[18]。目前已使用生物信息学筛选方法发现了多个合成致死基因对，例如IDH1-ACACA[19]、ALDH2-BRIP1[20]等。

3 DNA损伤修复途径相关的合成致死靶点

随着筛选技术的发展，越来越多的合成致死基因对被发现，然而在众多的合成致死基因对研究中，DNA损伤修复（DNA Damage Repair，DDR）相关的合成致死基因对研究最为深入[1, 21-23]。众所周知，每个细胞的基因组都不断受到内源性和外源性DNA损伤因素攻击，为了确保基因组的稳定性以及遗传物质的准确复制和传递，细胞和生物体进化出各种DNA修复途径以保证存活。这种由DNA损伤传感器、介质和效应蛋白组成的复杂网络即DDR，需要严格的时空控制，以确保修复酶能对特异的DNA损伤方式进行精准调控[24]。对于不同原因造成的不同类型的DNA损伤，其修复机制各不相同，图2简要概括了DDR的不同交互模式，其中，PARP、ATM、ATR、CHK1、DNA-PK和WEE1等基因在DDR通路中具有重要作用，因此成为合成致死研究的主要靶标。

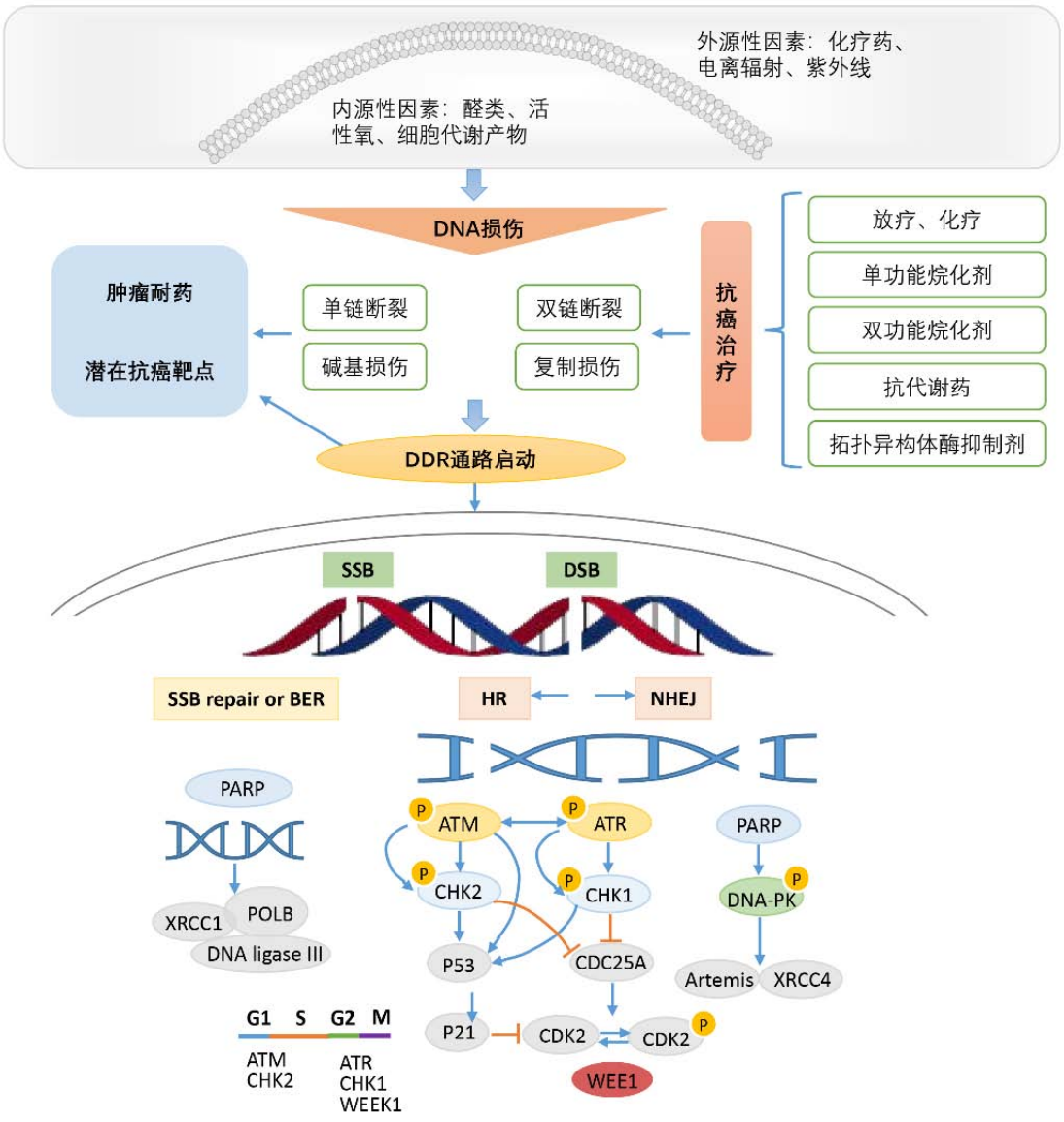


图2 DDR的不同交互模式

3.1 PARP

PARP是一类DNA修复酶，对DNA损伤的修复、染色体及基因组稳定性的维持至关重要。目前已发现17个PARP家族成员，其中PARP1和PARP2在DNA修复中发挥重要作用[25, 26]。PARP1通过修复DNA单链断裂（Single Strand Break，SSB）和双链断裂（Double Strand Break，DSB）调节细胞增殖和分化[27]。PARP1抑制与BRCA1/2之间的合成致死性已被临床证实。临床前研究和临床试验数据均显示PARP1抑制剂对BRCA1/2缺陷型肿瘤具有显著抗肿瘤作用，是合成致死性癌症治疗方法的成功例子[28-30]。除BRCA1/2外，还有一些基因也报道与PARP1具有合成致死相互作用，比如PTEN[31]、IDH[32]、ARID1A和PBRM1[33]等。

3.2 ATM、ATR和DNA-PK

ATM是一种350 kDa的丝氨酸/苏氨酸激酶，属于磷脂酰肌醇-3-激酶相关蛋白激酶PIKK家族[34]。ATM存在于所有组织中，并在DDR中发挥关键作用。该激酶由DSB募集和激活，从而启动DNA检查点反应并通过非同源末端连接（Non-Homologous End Joining，NHEJ）或同源重组（Homologous Recombination，HR）促进断裂染色体的修复[35]。ATR是PIKK家族的另一个成员，也是参与DDR的关键激酶之一[36]。与ATM不同，ATR是细胞存活所必需的酶，其突变或失活会导致小鼠胚胎致死和人类细胞死亡，该激酶可被持续的SSB信号激活[37]。研究显示，ATR通过在复制叉处磷酸化DNA合成相关酶，进而调节核苷酸水平、复制叉进程、细胞周期和DNA修复等[38]。同属PIKK家族成员的DNA-PK，由Ku蛋白的异二聚体（Ku70/Ku80）和催化亚基DNA-PKcs组成，在NHEJ修复中起关键作用[39]。当DSB发生时，DNA-PKcs被Ku蛋白的异二聚体招募，识别并结合断裂的DNA末端，从而形成活性异二聚体DNA-PK并启动DNA修复，然后通过催化磷酸化NHEJ核心成分以紧密对齐和连接两端，促进DNA修复完成[40]。最近的研究表明，靶向DNA-PK可增加细胞放射疗法和DNA损伤剂的敏感性[41]。

大量研究表明，ATM、ATR和DNA-PK参与调控DDR中多个相互关联的信号通路，因此，这些激酶与DDR通路中众多基因存在合成致死相互作用。已有报道显示DNA-PKcs- MSH3[42]、ATM- MEK1/2[43]基因对之间具有合成致死作用。而在BRCA1突变的细胞中，ATM和DNA-PKcs也具有合成致死作用[44]。相较于ATM和DNA-PKcs，ATR与DNA损伤剂具有更强的合成致死性[45]。ATR也被证明与ATM/CHK1/2/p53以及其他一些DSB修复因子具有合成致死性，而Ku70、Ku80、BRCA2、XRCC3和XRCC1的缺陷增加了ATR和CHK1合成致死的敏感性[46-51]。由于ATM也参与DSB修复和细胞周期检查点激活，所以在涉及ATM、ATR及DNA-PK相关的合成致死关系中，ATM-ATR之间的合成致死作用最为显著，因此也备受关注，并被业界认为是继PARP-BRCA1/2之后的最有希望的合成致死基因对之一。

3.3 CHK1

CHK1是DNA损伤反应通路中的细胞周期检查点激酶，该激酶由ATR磷酸化并激活[52]。当发生DNA损伤并启动修复时，CHK1可促进细胞S和G2/M期周期阻滞，并在多个位点磷酸化和降解CDC25A、CDC25B和CDC25C磷酸化酶，从而增加CDK磷酸化[53]。研究发现，DNA聚合酶家族B亚基（POLE、POL2和POLA）的沉默导致肿瘤细胞对CHK1抑制剂的敏感性增加[54]。DNA多聚酶家族B的缺失与CHK1抑制剂结合导致癌细胞DNA损伤、复制应激和凋亡的增加。此外，CHK1还能激活WEE1激酶，抑制CDK1[55]。由于在DDR中的重要作用，CHK1已被认为是重要的肿瘤治疗靶标。

3.4 WEE1

WEE1是细胞周期检查点的关键控制器，特别是在细胞周期G2阶段，因此，WEE1可以看作是G2阻滞的看门人，并作为细胞有丝分裂抑制剂[56]。研究显示，当被DNA损伤激活时，它会通过CDK1和CDK2的磷酸化调节G2/M和S检查点来防止细胞进入有丝分裂，从而保证细胞有额外时间进行修复[57]。目前已发现与WEE1具有合成致死的靶基因包括ATR、TP53和CHK1等[58-60]。由于WEE1在G2细胞周期检查点的重要作用，它的抑制对那些具有TP53信号传导缺陷的细胞特别有效。因此，与TP53具有合成致死相互作用使WEE1逐渐成为肿瘤治疗中的一个重要靶点，有望成为合成致死的明日之星。

3.5 CDK12

CDK12是在研究细胞周期调节因子CDC2时被首次发现[61]。虽然它与在细胞周期调节中发挥作用的CDK亚家族的其他成员具有结构相似性，但CDK12是一种转录激酶，参与DNA修复的基因转录[62]，调节响应压力和热休克的特定基因以及DNA

损伤[63]。由于卵巢癌、HER-2阳性乳腺癌和肺腺癌[64]等多种肿瘤中常常发现CDK12的基因突变或功能丧失，因此，探索与CDK12有合成致死作用的基因成为近年来的一个研究热点，目前已发现PARP[65]、MYC[66]和EWS/FLI[67]等多个基因与CDK12具有合成致死作用。

3.6 DNA损伤修复通路中其它的合成致死靶点

随着高通量测序技术和CRISPR基因编辑技术的发展，目前已经发现在DNA损伤修复中更多新的合成致死靶点，他们在临床前研究中显示出良好的肿瘤治疗效果，具有较好的开发潜力。表1总结了DNA损伤修复中其它的合成致死靶点。

表1 DNA损伤修复通路中其它的合成致死靶点汇总

靶标	作用机制	适应症
ARID1A[68]	靶向SWI/SNF复合物，调节染色质重塑	肺癌
CDC6[69]	作用于DNA复制起始蛋白，调节细胞周期	肺癌
CDK1[70]	调节细胞周期G1/S和G2/M的转变	无
CDK2[71]	调节细胞周期G1/S的过渡	无
CDK17[72]	调节细胞周期G2/M的过渡	乳腺癌
RAD50[73]	组成MRN复合物，在ATM介导的检查点中，通过非同源端连接和同源重组激活修复DNA双链断裂	转移性小细胞癌
RAD51[74]	通过同源重组修复DNA双链断裂	无
RAD52[75]	通过同源重组修复DNA双链断裂	白血病
CHEK1[76]	丝氨酸苏氨酸蛋白激酶，触发细胞周期阻滞以应对DNA损伤，响应ATR和ATM信号，磷酸化CDC25A以延迟DNA双链断裂后的细胞周期进程	卵巢癌
CHEK2[77]	丝氨酸苏氨酸蛋白激酶，触发细胞周期阻滞以应对DNA损伤，响应ATR和ATM信号，磷酸化CDC25A以延迟DNA双链断裂后的细胞周期进程	头颈部癌
GATA2[78]	锌指转录因子，调节基因转录	肺癌
KRAS[79]	调节内皮细胞内皮素-1基因表达的转录激活因子	肺癌
MRE11[80]	组成MRN复合物，在ATM介导的检查点中，通过非同源端连接和同源重组激活修复DNA双链断裂	无
MYC[81]	调节细胞周期进程，转录和凋亡	成神经细胞瘤
NBN[82]	组成MRN复合物，在ATM介导的检查点中，通过非源端连接和同源重组激活修复DNA双链断裂。	急性白血病
PAK3[83]	丝氨酸苏氨酸蛋白激酶，调节细胞周期、细胞迁移和细胞凋亡	宫颈癌
PLK1[84]	丝氨酸苏氨酸蛋白激酶，调节细胞增殖和凋亡，触发G2/M转换	肺癌
TP53[85]	肿瘤抑制，调节细胞周期、衰老和凋亡	前列腺癌
53BP1[86]	促进非同源端连接途径修复DNA双链断裂，限制同源重组	淋巴瘤

4 临床研究的合成致死靶点小分子抑制剂

4.1 PARP抑制剂

到目前为止，PARP抑制剂仍然是“合成致死”领域唯一成功上市的小分子靶向药物。目前已有五种PARP抑制剂被美国食品和药物管理局（Food and Drug Administration，FDA）和欧洲药品管理局（European Medicines Agency，EMA）批准上市（见图3），包括奥拉帕尼（Olaparib）、卢卡帕尼（Rucaparib）、尼拉帕尼（Niraparib）、他拉唑帕尼（Talazoparib）和维利帕尼（Veliparib）[87-91]。但是，目前报道的大多数PARP抑制剂都包含芳酰胺结构，该结构与关键辅酶NAD^+烟酰胺结构具有相似性[92]，因此可能会脱靶而引起细胞毒性。另外，大多数的抑制剂缺乏PARP1和PARP2选择性[93]，以及现有PARP抑制剂耐药性的出现也是当前面临的挑战[94]。研发高选择性、安全性、并可克服耐药的新型PARP抑制剂仍然具有重要意义。

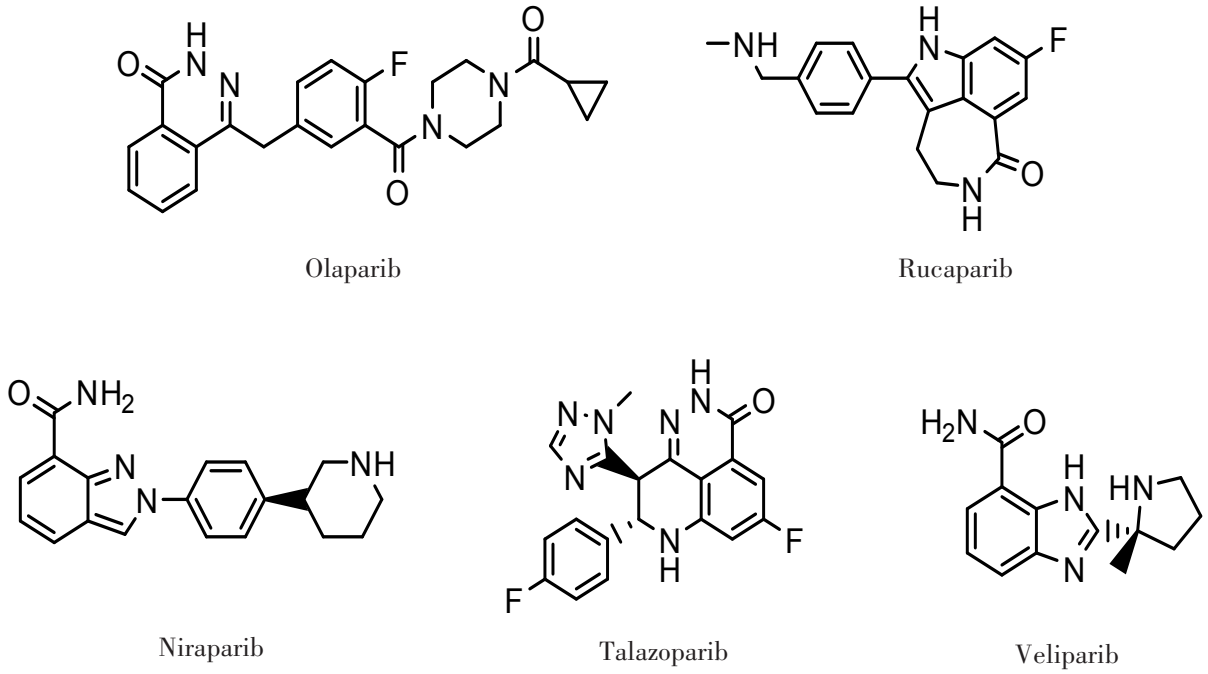


图3 已被批准上市的PARP抑制剂

4.2 非PARP DNA损伤修复抑制剂

除了PARP抑制剂外，其他DDR抑制剂的研发近年来也获得了迅速发展，目前已有多个高活性、选择性的小分子抑制剂报道，包括ATM、ATR、CHK1、WEE1和CDK12抑制剂。图4列出了近年来研发的典型DDR抑制剂，其中包括两种ATM抑制剂：AZD1390和AZD156，AZD1390和AZD156正在进行临床试验，用于治疗各类晚期实体瘤和卵巢癌等[95,96]；四种DNA-PK抑制剂：CC-115、AZD7648、M9831和M3814，这些抑制剂在多种晚期实体瘤及肝胆癌的临床试验中都显示出良好的疗效[97]；四种ATR抑制剂：Berzosertib、AZD6738、BAY1895344和M4344，它们在临床实验中作为单药或与放化疗等药物联合治疗各类晚期实体瘤[98,99]；三种CHK1抑制剂：Prexasertib、GDC-0575和SRA737，这些化合物正在进行临床试验，用于治疗乳腺癌、卵巢癌和肺癌等[100-102]；一种WEE1抑制剂：AZD1775，AZD1775与吉西他滨、顺铂或卡铂联合治疗乳腺癌和胶质母细胞瘤等的临床试验正在开展[103]；一种CDK12抑制剂：Dinaciclib，其与PARP抑制剂Veliparib正在进行联用治疗晚期实体瘤的临床试验[104]。

5 挑战与展望

基于合成致死原理的肿瘤治疗策略具有特异性强、毒副作用低等优点，已成为肿瘤药物研发的趋势。随着合成致死相关研究的深入，其概念由基因间的相互关系已延伸至基因与药物、药物与药物间的相互关系。根据细胞遗传背景的不同，筛选策略

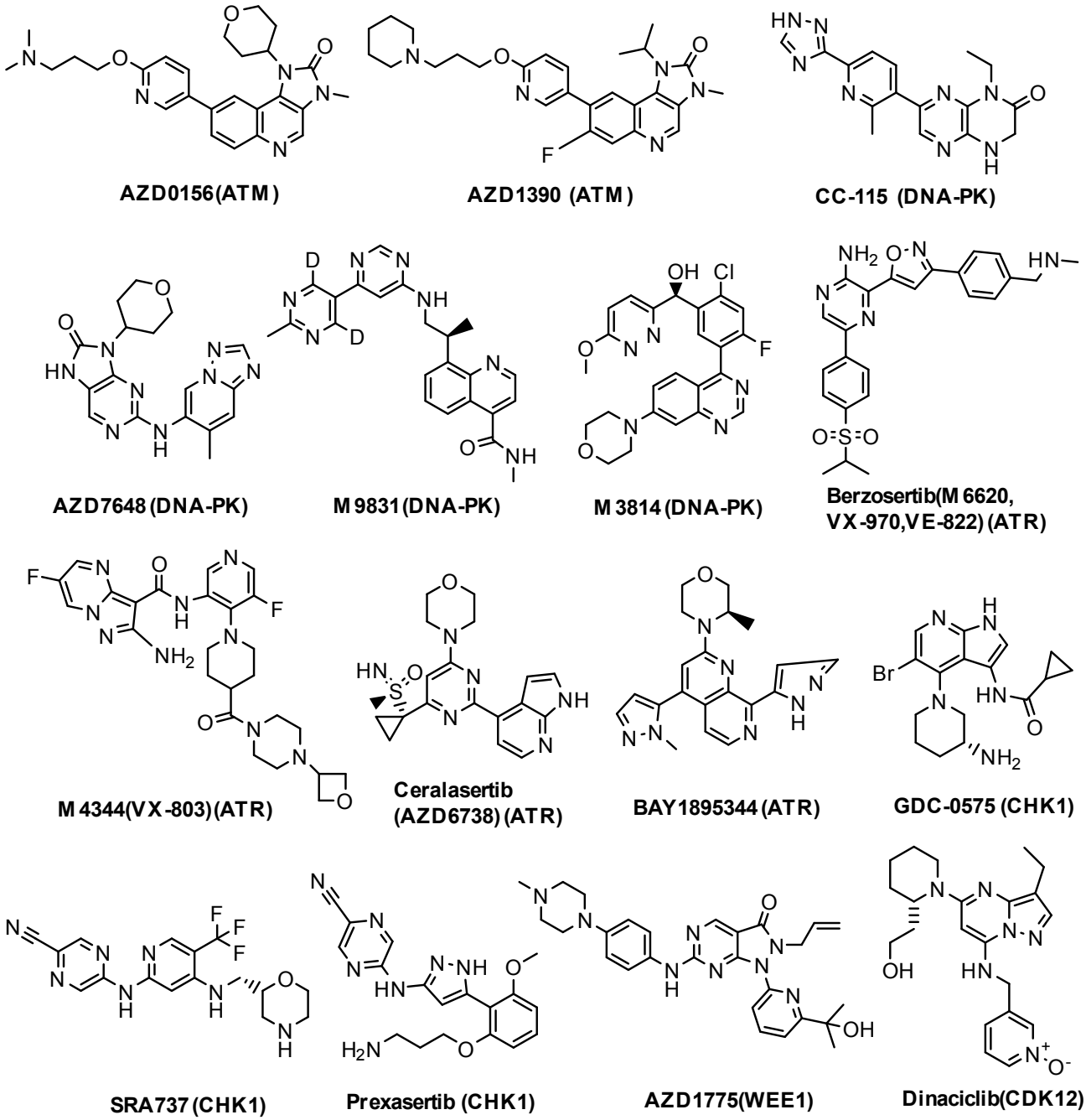


图4　进入临床试验的ATM、ATR、CHK1、WEE1和CDK12抑制剂

上也呈现出多样性[105]。既有筛选癌基因的合成致死基因，比如RAS-CDK4/6[106]、EGFR-KRAS [107]、MYC-BRG1[108]，也有筛选抑癌基因的合成致死基因，例如p53-WEE1[109]、PTEN-PNKP[110]等，以及筛选已有药物的增敏基因，如紫杉醇[111]和顺铂[112]的增敏基因ATR等。然而，在众多的合成致死基因对的研究中，针对DDR通路的合成致死基因对的筛选与研究仍然是最为广泛，并且DDR通路上重要靶点的小分子抑制剂进入临床试验也是最多，包括5个被FDA和EMA批准上市的PAPP抑制剂。虽然合成致死疗法已经取得了长足进步，但是其在肿瘤治疗中仍然存在许多亟待解决的问题，例如，在不同遗传背景下如何准确识别和验证潜在的合成致死伴侣基因仍然是一个挑战，DNA损伤信号通路存在相互交叉和负反馈调节等现象，如何最大限度地发挥相关抑制剂的治疗潜力是需要面对的难题。另外，合成致死抑制剂与其他抗癌药物联合使用可能带来未知的治疗效果或毒副反应，这些都需要开展深入的临床研究。

随着对合成致死研究的逐渐深入，其应用范围

也进一步拓展，比如与表观遗传相关的合成致死基因，例如ARID1A-EZH2、PRMT5-MTAP、SETD2-WEE1、KMT2C-PARP[113]等。另外，人们认识到合成致死不只发生在编码基因之间，长链非编码RNA（Long non-coding RNA，lncRNA）与微小RNA（MicroRNA，miRNA）也可以和蛋白发生合成致死相互作用，例如，lncRNA与TP53[114]、miRNA-206与MYC [115]等。总之，“合成致死”因为其更侧重于对患者正常细胞的保护，选择性地破坏癌细胞而备受关注，目前已成为一种很有前途的肿瘤靶向治疗方法。随着新的实验和筛选方法的发展，应用合成致死概念，针对患者的遗传背景来选择药物靶点，必将成为一种有效的治疗选择，并为肿瘤患者的靶向治疗带来深刻的变革。

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