合成致死在精准肿瘤学中的应用

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2018-02-07 收稿, 2018-03-19 修回, 2018-03-21 接受, 2018-04-08 网络版发表

国家重点研发计划(2016YFC1302100)、国家自然科学基金(81472827 和 81773023)、中国科学院“百人计划”和中国科学院前沿科学重点研究项目(QYZDB-SSW-SMC038)资助

摘要 合成致死是指两个非致死性基因同时失活从而导致细胞死亡的现象。近来, 合成致死原理已经成功用于癌症精准治疗。癌症在其发生、发展和恶化过程中, 积累了大量不能靶向的驱动突变, 我们可以用药物精准抑制这些突变的合成致死搭档, 从而特异性杀死癌细胞, 不危害健康细胞。本文详细介绍了癌症的驱动突变, 探讨了合成致死原理及其在癌症精准治疗中的应用; 进一步探讨了基于DNA修复机制的*BRCA1/2*缺陷, 激活*RAS*突变, *MYC*突变, 肿瘤抑制基因*TP53*以及功能性缺失*PTEN*的合成致死性研究进展; 最后展望了这种策略在无法靶向的驱动突变应用前景, 为实现更有效、毒性更低的精准治疗提供方向, 是抗癌药物研究的新热点。

关键词 合成/复合致死, 肿瘤, 驱动突变, 精准肿瘤学

肿瘤是复杂的多基因突变疾病。肿瘤的发生是体细胞基因信息在结构或功能上变异累积的结果, 是一个多步骤多基因突变发生过程。癌基因的激活和抑癌基因的失活, 使得细胞逐步演化获得了一些共同特性, 如自给自足的生长信号、抗生长信号不敏感、抵抗细胞死亡能力、无限增殖能力、持续的血管生成、细胞能量异常、组织浸润和转移、基因组不稳定和突变及促进癌症的炎症能力, 甚至是逃避机体免疫能力等^[1,2]。癌症是一大类恶性肿瘤的统称, 严重威胁到人类健康和生命。随着发病率持续上升, 癌症成为人们关注的社会问题^[3]。

1 驱动突变

肿瘤发生、发展和恶化的分子基础逐渐被阐释。尤其是随着二代测序技术的发展, 美国政府2015年发起癌症基因组计划(The Cancer Genome Atlas,

TCGA), 使用创新基因组分析技术全面阐释癌症的分子基础, 旨在找到有关致癌和抑癌基因, 了解癌细胞发生和发展的机制, 从而帮助产生新的癌症疗法和预防策略^[4]。研究发现癌细胞在基因水平上存在成千上万的分子突变。但实际上只有少数突变(理论上不超过10个)可能是肿瘤形成所必需的^[5], 我们把这些突变称为驱动突变(driver mutation), 而其他突变则称为过客突变(passenger mutation)。驱动突变可以定义为增加肿瘤细胞的适应性(增殖潜能), 是导致癌症发生发展的关键突变。常见的驱动突变形式包括点突变、短片段插入或缺失突变, 基因重排、扩增或缺失^[6]。驱动突变也可以根据基因突变在编码蛋白质的功能性作用进行分类。产生功能获得性突变的“致癌基因”(oncogene)和产生功能缺失的“抑癌基因”(tumor suppressor gene)突变^[7]。这两种类型的突变共同驱动癌症的发生和发展。靶向驱动突变已成功应

引用格式: 乔红霞, 黄国翔, 黄映辉, 等. 合成致死在精准肿瘤学中的应用. 科学通报, 2018, 63: 1123–1129

Qiao H X, Huang G X, Huang Y H, et al. Application of synthetic lethality in the precise oncology (in Chinese). Chin Sci Bull, 2018, 63: 1123–1129, doi: 10.1360/N972018-00152

用于治疗人类的各种癌症^[8,9].

靶向治疗起源于20世纪90年代,癌症生物学开始广泛被人类所了解,靶向治疗进而得以发展.早期成功的靶向治疗范例包括Imatinib治疗慢性髓细胞白血病,和Gefitinib和Erlotinib治疗表皮生长因子受体(epidermal growth factor receptor, EGFR)敏感突变阳性的非小细胞肺癌(non-small cell lung cancer, NSCLC).

然而,在许多驱动突变中,有些突变不能直接由小分子或抗体靶向^[10,11].例如,基因突变或缺失引起肿瘤抑制基因的功能缺失无法通过小分子抑制剂及RNA恢复基因原有功能^[12].从药物发现的角度来看,功能缺失突变是很难解决的,如与张力蛋白同源在10号染色体有缺失的磷酸酶基因(phosphatase and tensin homolog deleted on chromosome ten, *PTEN*).有些癌基因同样难以靶向^[13],如*MYC*, *TP53*及*RAS*等.因此,对不能靶向的驱动突变,采用合成致死原理是一个理想的癌症治疗策略.

2 合成致死

合成致死(synthetic lethality, SL)的概念是从模式生物的遗传研究中发现和提出的,例如果蝇^[14,15]和酵母^[11].20世纪初期美国遗传学家Bridges^[16]首次描述合成致死,他描述杂交黑腹果蝇中一些非等位基因中的基因组合同时突变是致命的.

Synthetic在古希腊语中意思是两个实体形式组合成一个新的东西^[17],因此合成致死可以定义为当A基因和B基因当中任何一个基因发生突变还有生存能力,但是当两个基因同时发生突变就会引起死亡(图1).合成致死也被定义为一类两个遗传事件共同发生,导致有机体或者细胞死亡的遗传作用.尽管在功能性缺失突变体最为人们熟知,其他类型的组合也可以导致合成致死,包括基因的高表达,化合物作用或环境改变等^[17-21].合成致死这一概念可以延伸到合成致病(synthetic sickness, SS)及合成剂量致死(synthetic dosage lethality, SDL).SS是指基因A和基因B同时突变对细胞存活有一定影响^[17];SDL是指基因B过度表达或过度激活导致细胞对基因A的依赖性,即尽管正常细胞可以耐受基因A的低表达,但在过度表达基因B的肿瘤细胞中,基因A的低表达是致命的^[22].

如何为不能靶向的驱动突变寻找合适的合成致死靶点,一种就是从以前模式生物研究发现的合成致死关系中选择合适靶点.但一般过往研究的靶点

图1 (网络版彩色)合成致死概念图示.野生型A基因和B基因合成致死相互作用,白色框代表突变体.只有在AB突变组合中观察到的致死表型

Figure 1 (Color online) Schematic representation of synthetic lethality. Two genes (A and B) are referred to be “synthetic lethal” if mutation of either gene alone is compatible with viability but simultaneous mutation of both genes causes death. A white frame denotes a mutation

数会偏少和效率较低,还有就是利用高通量RNA干扰(RNA interference, RNAi)技术来为不能靶向的驱动突变寻找合适的合成致死靶点^[23].RNAi是双链RNA分子诱发的基因沉默过程,可体现在转录或转录后水平.RNAi技术与合成致死原理结合进一步加快了合成致死的研究.

近几年,合成致死原理引起肿瘤生物学家的注意,是由于他们发现基因间的功能性关系信息并且在遗传筛选中较易获得^[24].合成致死被用于确定基因间功能相互作用的遗传研究已达数十年,最近用于开发新的基因型选择抗癌剂,为肿瘤治疗识别新的治疗靶点和治疗反馈相关的基因表征,提供了间接治疗尚无药物可及的靶点的可能性^[20,25].表1列举FDA批准的PARP抑制剂及其功能.

3 合成致死原理在肿瘤精准治疗中的应用

3.1 BRCA和PARP抑制剂

乳腺癌易感基因(breast cancer susceptibility gene,

表1 FDA批准的PARP抑制剂

Table 1 PARP inhibitors approved by FDA

药物	靶向目标	功能	参考文献
Rucaparib	PARP	阻断碱基切除修复	[26]
Niraparib	PARP	抑制细胞对DNA损伤修复	[27]
Olaparib	PARP	阻断碱基切除修复	[28]
Veliparib	PARP	抑制肿瘤生长	[29,30]

BRCA)主要有两种类型, *BRCA1*和*BRCA2*基因. *BRCA1*、*BRCA2*基因具有肿瘤抑制和DNA修复功能^[31-35]. *BRCA1*、*BRCA2*突变可导致乳腺癌和卵巢癌^[36]. 聚腺苷二磷酸核糖聚合酶(poly(ADP-ribose)polymerase, PARP)对于细胞的稳定和存活非常重要, PARP失去酶活力会加速细胞的不稳定. PARP剪切被认为是细胞凋亡的一个重要指标^[37]. 基于合成致死原理治疗肿瘤方面的研究, 具有里程碑意义的是*BRCA*与*PARP*基因.

Farmer等人^[38]及Bryant等人^[39]分别在体外研究中证实了存在*BRCA1*或者*BRCA2*基因突变的癌细胞对PARP抑制剂的作用敏感性非常高, 甚至在某些细胞中, *BRCA2*突变细胞株的敏感性是*BRCA1*和*BRCA2*基因野生型细胞株的1000多倍^[38]. 他们将这一存在于PARP和*BRCA1/2*之间的相互作用关系归入合成致死现象^[40].

基于实验室观察, 许多PARP抑制剂获得FDA批准用于临床, 包括2014年的Olaparib^[41], 2016年的Veliparib, Rucaparib和2017年的Neratinib. 实际上PARP抑制剂是第一种成功利用合成致死概念获得批准在临床上使用的抗癌药物^[38,39].

3.2 RAS

*RAS*基因家族与人类肿瘤相关的基因有3种, 分别是*HRAS*, *NRAS*和*KRAS*. *RAS*蛋白作为大多数生长因子, 细胞因子和激素重要的中间体, 调控细胞的生长、增殖、分化和死亡. 四分之一的癌症中具有*RAS*突变, 其中一些特定癌症如结直肠癌, 具有功能获得性*RAS*突变^[31]. 由于*RAS*蛋白结构的复杂性, 导致无法直接靶向*RAS*.

Luo等人^[42]进行全基因组RNAi筛选与*KRAS*具有合成致死作用的基因, 研究发现在结肠癌中, Polo样激酶1(polo-like Kinase 1, PLK1)被抑制后导致存在*RAS*突变的细胞死亡. Puyol等人^[43]在小鼠肿瘤模型中发现*KRAS*和细胞周期蛋白依赖性激酶4(cyclin-dependent kinase4, CDK4)存在合成致死作用, 对存在*KRAS*致癌基因的NSCLC患者治疗有益. Unni等人^[44]研究发现在肺腺癌中, *KRAS*和*EGFR*存在合成致死关系. Wang等人^[45]研究发现, 通过使用全基因组基于CRISPR筛选14个人类急性髓系白血病细胞系必需的基因, 出现最多的是与突变型*RAS*存在合成致死作用的基因.

3.3 TP53

p53在细胞中起到应对各种压力的信号激活和调节的作用, 如细胞凋亡、细胞周期阻滞、DNA修复及代谢^[46,47]. *TP53*基因是迄今发现与人类肿瘤相关性最高的基因. 由于p53蛋白结构的复杂性, 临床上无法直接靶向.

Zhang等人^[48]研究筛选对*TP53*突变肿瘤细胞有较好杀伤作用的多个化合物, 发现在前列腺癌中, 紫杉醇处理*TP53*突变肿瘤细胞后影响了微管相关蛋白4(microtubule-associated protein 4, MAP-4)表达导致细胞死亡. Sur等人^[49]研究发现, 在结肠癌中, *TP53*缺失的癌细胞对PLK1抑制剂非常敏感. Morandell等人^[50]研究发现, 在肺癌中, 阻断MAPK活化激酶2(MAPK-activated kinase, MK2)可使*TP53*突变的肿瘤细胞对化疗更加敏感. Pan等人^[51]研究发现B淋巴瘤-2基因(B-cell lymphoma-2, *Bcl-2*)和p53存在合成致死作用, 并且延长了耐受性急性骨髓性白血病小鼠模型的生存期. Palanichamy等人^[52]研究证明, 在胶质母细胞瘤细胞中, 磷脂酰肌醇醚脂类似物(phosphatidylinositol ether lipid analogue, PIA)和*TP53*存在合成致死作用.

3.4 MYC

*MYC*是人类癌症中最常见, 表达异常的癌基因之一^[53]. *MYC*作为骨髓细胞瘤病毒致癌基因的同源物, 是一种转录因子. *MYC*基因家族包括*C-MYC*, *N-MYC*和*L-MYC*, 经常发生扩增易位, 并且在许多类型肿瘤中过表达, *MYC*在大多数人类恶性肿瘤的增殖, 生长和代谢中起关键作用^[13,54,55]. 因蛋白结构性原因, 目前无法找到直接靶向c-Myc的小分子.

Wang等人^[56]研究发现, 在结肠癌中, 由肿瘤坏死因子相关凋亡诱导配体(tumor necrosis factor-related apoptosis-inducing ligand, TRAIL)和死亡受体5(death receptor 5, DR5)激动剂诱导的c-Myc介导合成致死(*MYC-SL*). 使用不同的TRAIL死亡受体的拮抗性单克隆抗体, DR5的激活导致*MYC*过表达肿瘤细胞选择性死亡. Pourdehnad等人^[53]研究发现血癌细胞中, *MYC*表达量增加的同时也选择性增加了翻译起始因子4E结合蛋白1(eukaryotic translation initiation factor 4E-binding protein 1, 4EBP1)的表达, c-Myc和4EBP1之间存在合成致死关系. Romero等人^[57]研究发现在小细胞肺癌细胞中, 染色质重构因

子(brahma-related gene 1, BRG1)和c-Myc相关因子MAX存在合成致死作用.

3.5 PTEN

PTEN与蛋白质合成、细胞周期、迁移、生长的失调相关. *PTEN*是迄今为止发现的第一个具有磷酸酶活性的抑癌基因,是在人类肿瘤中最常见的突变基因之一. 由于PTEN蛋白结构的复杂性,无法直接靶向.

Mendes-Pereira等人^[58]研究发现, *PTEN*缺失导致肿瘤细胞的同源重组(homologous recombination, HR)缺陷,由*PTEN*缺失引起的HR缺陷使肿瘤细胞对PARP抑制剂敏感. 结果表明,PARP抑制剂的临床评估延伸到*PTEN*突变的肿瘤患者. Mereniuk等人^[59]研究发现, DNA修复蛋白多核苷酸激酶3磷酸酶(poly-nucleotide kinase 3'-phosphatase, PNKP)和*PTEN*在多种不同肿瘤细胞系中存在合成致死关系. 在*PTEN*敲除后PNKP的抑制增强了细胞对放射的敏感性. Ren等人^[60]研究发现,在前列腺癌细胞中同时抑制PI3K/Akt和死亡负调节因子BCL-XL与*PTEN*的合成致死相互作用. Zhao等人^[61]研究发现,在前列腺癌中,染色质解旋酶DNA结合蛋白(chromodomain-helicase-DNA-binding protein, CHD1)是*PTEN*缺失型癌症中必须合成的基因.

随着对合成致死的研究的深入,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^[62],如Adriaens等人^[63]研究发现, lncRNA NEAT1在前列腺癌细胞中显著过表达,参与p53负反馈回路,靶向人类癌细胞系NEAT1,诱导PARP抑制剂和p53化学治疗剂与NEAT1的合成致死作用. miRNA-206在结肠癌起到肿瘤抑制作用, Han等人^[64]研究发现, miRNA-206与过表达MYC人癌细胞有合成致死作用.

目前,合成致死原理应用于各种癌症中,为癌症治疗提供了新的方向. 表2列举部分利用合成致死原理潜在靶向治疗癌症的例子.

4 前景与展望

合成致死相互作用代表了选择性杀死肿瘤细胞

表2 合成致死在各类癌症诊疗中的应用

Table 2 Synthetic lethality in application of diagnosis and treatment in various cancer

癌症类型	基因	参考文献
乳腺癌	PARP-BRCA	[36]
卵巢癌	PARP-BRCA, miRNA-206-MYC	[36,64]
肺癌	CDK4-RAS, EGFR-KRAS, MK2-TP53, BRG1-MYC	[43,44,50,57]
白血病	Bcl-2-TP53	[51]
结肠癌	PLK1-RAS, DR5-MYC, LncNEAT1-TP53, PLK1-TP53	[42,49,56,63]
前列腺癌	MAP4-TP53, BCL-XL-PTEN, CHD1-PTEN	[48,60,61]
脑癌	PIA-TP53	[52]
血癌	4EBP1-MYC	[53]

的非常有前景的治疗手段. 近年来,关于合成致死的抗癌疗法受到了越来越多的关注.

不同的肿瘤类型可能具有不同的DNA修复途径,这是转化的缺陷,每种肿瘤类型都需要在分子水平上进行定义. 这将更好地界定使用合成致死方法在各种肿瘤类型中靶向哪些途径,扩大了该方法在药物开发中的适用性. 以类似的方式,一旦为所有肿瘤类型定义了这样的途径,它们可以用作对这些试剂的预测反应的生物标志物. 因此,合成致死可以比原来想象的形成更广泛的应用.

目前,只有一种基于合成致死原理的药物批准在临床上使用,即PARP抑制剂治疗BRCA突变的肿瘤细胞^[11]. 还有很多合成致死药物处于试验阶段,这些试验大多数基于药物和药物之间的合成致死关系. 肿瘤的发生可能存在多个基因发生突变,其他信号通路的激活可能导致肿瘤对靶向治疗药物的耐药性,当合成致死药物和其他已知的化疗药物联合使用,可以提高抗癌药物的功效,可能会从根本上改变癌症的治疗方式. 合成致死这一概念可能代表了现代肿瘤治疗中最重要的进展之一. 综上所述,合成致死的概念在抗癌药物发现中具有巨大潜力,其最重要的特点在于可以选择性杀死肿瘤细胞并实现个性化的抗癌疗法. 虽然“合成致死”一词已经普遍使用,但是Synthetic lethality指的是两种基因变化所产生的复合效果,或许可以理解成“复合致死”,我们也希望更多学者在将来研究中使用“复合致死”来描述这一现象.

参考文献

- 1 Hanahan D, Weinberg R A. The hallmarks of cancer. *Cell*, 2000, 100: 57–70
- 2 Hahn W C, Weinberg R A. Rules for making human tumor cells. *N Engl J Med*, 2002, 347: 1593–1603
- 3 Han Q D. Reflections on the guidance of early detection, early diagnosis and early treatment of cancer (in Chinese). *Med Philos*, 2017, 38: 2–6 [韩启德. 对癌症早发现、早诊断、早治疗方针的考量. *医学与哲学*, 2017, 38: 2–6]
- 4 Chin L, Andersen J N, Futreal P A. Cancer genomics: From discovery science to personalized medicine. *Nat Med*, 2011, 17: 297–303
- 5 Ashworth A, Lord C J, Reis-Filho J S. Genetic interactions in cancer progression and treatment. *Cell*, 2011, 145: 30–38
- 6 Stratton M R, Campbell P J, Futreal P A. The cancer genome. *Nature*, 2009, 458: 719–724
- 7 Santarosa M, Ashworth A. Haploinsufficiency for tumour suppressor genes: When you don't need to go all the way. *Biochim Biophys Acta*, 2004, 1654: 105–122
- 8 Vogelstein B, Papadopoulos N, Velculescu V E, et al. Cancer genome landscapes. *Science*, 2013, 339: 1546–1558
- 9 Patel M N, Halling-Brown M D, Tym J E, et al. Objective assessment of cancer genes for drug discovery. *Nat Rev Drug Discov*, 2013, 12: 35–50
- 10 Pagliarini R, Shao W, Sellers W R. Oncogene addiction: Pathways of therapeutic response, resistance, and road maps toward a cure. *EMBO Rep*, 2015, 16: 280–296
- 11 O'neil N J, Bailey M L, Hieter P. Synthetic lethality and cancer. *Nat Rev Genet*, 2017, 18: 613–623
- 12 Hartwell L H, Szankasi P, Roberts C J, et al. Integrating genetic approaches into the discovery of anticancer drugs. *Science*, 1997, 278: 1064–1068
- 13 Beijersbergen R L, Wessels L F A, Bernards R. Synthetic lethality in cancer therapeutics. *Annu Rev Cancer Biol*, 2017, 1: 141–161
- 14 Dobzhansky T. Genetics of natural populations; Recombination and variability in populations of *Drosophila pseudoobscura*. *Genetics*, 1946, 31: 269–290
- 15 Lucchesi J C. Synthetic lethality and semi-lethality among functionally related mutants of *Drosophila melanogaster*. *Genetics*, 1968, 59: 37–44
- 16 Bridges C B. The origin of variations in sexual and sex-limited characters. *Am Nat*, 1922, 56: 51–63
- 17 Nijman S M. Synthetic lethality: General principles, utility and detection using genetic screens in human cells. *FEBS Lett*, 2011, 585: 1–6
- 18 Kaelin W G Jr. The concept of synthetic lethality in the context of anticancer therapy. *Nat Rev Cancer*, 2005, 5: 689–698
- 19 Lehar J, Stockwell B R, Giaever G, et al. Combination chemical genetics. *Nat Chem Biol*, 2008, 4: 674–681
- 20 Luo J, Solimini N L, Elledge S J. Principles of cancer therapy: Oncogene and non-oncogene addiction. *Cell*, 2009, 136: 823–837
- 21 Hillenmeyer M E, Fung E, Wildenhain J, et al. The chemical genomic portrait of yeast: Uncovering a phenotype for all genes. *Science*, 2008, 320: 362–365
- 22 Measday V, Hieter P. Synthetic dosage lethality. *Methods Enzymol*, 2002, 350: 316–326
- 23 Gao S, Yang C, Jiang S, et al. Applications of RNA interference high-throughput screening technology in cancer biology and virology. *Protein Cell*, 2014, 5: 805–815
- 24 Dixon S J, Costanzo M, Baryshnikova A, et al. Systematic mapping of genetic interaction networks. *Annu Rev Genet*, 2009, 43: 601–625
- 25 Kaelin W G Jr. Synthetic lethality: A framework for the development of wiser cancer therapeutics. *Genome Med*, 2009, 1: 99
- 26 Ihnen M, Zu Eulenburg C, Kolarova T, et al. Therapeutic potential of the poly(ADP-ribose) polymerase inhibitor rucaparib for the treatment of sporadic human ovarian cancer. *Mol Cancer Ther*, 2013, 12: 1002–1015
- 27 Jones P, Altamura S, Boueres J, et al. Discovery of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (MK-4827): A novel oral poly(ADP-ribose)polymerase (PARP) inhibitor efficacious in *BRCA-1* and -2 mutant tumors. *J Med Chem*, 2009, 52: 7170–7185
- 28 Evers B, Drost R, Schut E, et al. Selective inhibition of *BRCA2*-deficient mammary tumor cell growth by AZD2281 and cisplatin. *Clin Cancer Res*, 2008, 14: 3916–3925
- 29 Donawho C K, Luo Y, Luo Y, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. *Clin Cancer Res*, 2007, 13: 2728–2737
- 30 Penning T D, Zhu G D, Gandhi V B, et al. Discovery of the poly(ADP-ribose) polymerase (PARP) inhibitor 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (ABT-888) for the treatment of cancer. *J Med Chem*, 2009, 52: 514–523
- 31 Chan D A, Giaccia A J. Harnessing synthetic lethal interactions in anticancer drug discovery. *Nat Rev Drug Discov*, 2011, 10: 351–364
- 32 Loh V M Jr, Cockcroft X L, Dillon K J, et al. Phthalazinones. Part 1: The design and synthesis of a novel series of potent inhibitors of poly(ADP-ribose)polymerase. *Bioorg Med Chem Lett*, 2005, 15: 2235–2238
- 33 Pivazyan A D, Birks E M, Wood T G, et al. Inhibition of poly(ADP-ribose)polymerase activity by nucleoside analogs of thymidine. *Biochem Pharmacol*, 1992, 44: 947–953
- 34 Skaltitzky D J, Marakovits J T, Maegley K A, et al. Tricyclic benzimidazoles as potent poly(ADP-ribose) polymerase-1 inhibitors. *J Med Chem*, 2003, 46: 210–213

- 35 Rouleau M, Patel A, Hendzel M J, et al. PARP inhibition: *PARP1* and beyond. *Nat Rev Cancer*, 2010, 10: 293–301
- 36 Shaheen M, Allen C, Nickoloff J A, et al. Synthetic lethality: Exploiting the addiction of cancer to DNA repair. *Blood*, 2011, 117: 6074–6082
- 37 Oliver F J, De La Rubia G, Rolli V, et al. Importance of poly(ADP-ribose) polymerase and its cleavage in apoptosis. Lesson from an un-cleavable mutant. *J Biol Chem*, 1998, 273: 33533–33539
- 38 Farmer H, McCabe N, Lord C J, et al. Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy. *Nature*, 2005, 434: 917–921
- 39 Bryant H E, Schultz N, Thomas H D, et al. Specific killing of *BRCA2*-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*, 2005, 434: 913–917
- 40 Iglehart J D, Silver D P. Synthetic lethality—A new direction in cancer-drug development. *N Engl J Med*, 2009, 361: 189–191
- 41 Fong P C, Boss D S, Yap T A, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*, 2009, 361: 123–134
- 42 Luo J, Emanuele M J, Li D, et al. A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the *RAS* oncogene. *Cell*, 2009, 137: 835–848
- 43 Puyol M, Martin A, Dubus P, et al. A synthetic lethal interaction between *K-RAS* oncogenes and *cdk4* unveils a therapeutic strategy for non-small cell lung carcinoma. *Cancer Cell*, 2010, 18: 63–73
- 44 Unni A M, Lockwood W W, Zejnullahu K, et al. Evidence that synthetic lethality underlies the mutual exclusivity of oncogenic *KRAS* and *EGFR* mutations in lung adenocarcinoma. *Elife*, 2015, 4: e06907
- 45 Wang T, Yu H, Hughes N W, et al. Gene essentiality profiling reveals gene networks and synthetic lethal interactions with oncogenic *RAS*. *Cell*, 2017, 168: 890–903.e815
- 46 Vousden K H, Lu X. Live or let die: The cell's response to p53. *Nat Rev Cancer*, 2002, 2: 594–604
- 47 Reinhardt H C, Schumacher B. The p53 network: Cellular and systemic DNA damage responses in aging and cancer. *Trends Genet*, 2012, 28: 128–136
- 48 Zhang C C, Yang J M, Bash-Babula J, et al. DNA damage increases sensitivity to vinca alkaloids and decreases sensitivity to taxanes through p53-dependent repression of microtubule-associated protein 4. *Cancer Res*, 1999, 59: 3663–3670
- 49 Sur S, Pagliarini R, Bunz F, et al. A panel of isogenic human cancer cells suggests a therapeutic approach for cancers with inactivated p53. *Proc Natl Acad Sci USA*, 2009, 106: 3964–3969
- 50 Morandell S, Reinhardt H C, Cannell I G, et al. A reversible gene-targeting strategy identifies synthetic lethal interactions between *MK2* and p53 in the DNA damage response *in vivo*. *Cell Rep*, 2013, 5: 868–877
- 51 Pan R, Ruvolo V, Mu H, et al. Synthetic lethality of combined bcl-2 inhibition and p53 activation in AML: Mechanisms and superior anti-leukemic efficacy. *Cancer Cell*, 2017, 32: 748–760.e746
- 52 Palanichamy K, Patel D, Jacob J R, et al. Lack of constitutively active DNA repair sensitizes glioblastomas to Akt inhibition and induces synthetic lethality with radiation treatment in a p53-dependent manner. *Mol Cancer Ther*, 2018, 17: 336–346
- 53 Pourdehnad M, Truitt M L, Siddiqi I N, et al. MYC and mTOR converge on a common node in protein synthesis control that confers synthetic lethality in MYC-driven cancers. *Proc Natl Acad Sci USA*, 2013, 110: 11988–11993
- 54 Shachaf C M, Kopelman A M, Arvanitis C, et al. MYC inactivation uncovers pluripotent differentiation and tumour dormancy in hepatocellular cancer. *Nature*, 2004, 431: 1112–1117
- 55 Soucek L, Whitfield J, Martins C P, et al. Modelling MYC inhibition as a cancer therapy. *Nature*, 2008, 455: 679–683
- 56 Wang Y, Engels I H, Knee D A, et al. Synthetic lethal targeting of MYC by activation of the DR5 death receptor pathway. *Cancer Cell*, 2004, 5: 501–512
- 57 Romero O A, Torres-Diz M, Pros E, et al. MAX inactivation in small cell lung cancer disrupts MYC-SWI/SNF programs and is synthetic lethal with *BRG1*. *Cancer Discov*, 2014, 4: 292–303
- 58 Mendes-Pereira A M, Martin S A, Brough R, et al. Synthetic lethal targeting of *PTEN* mutant cells with PARP inhibitors. *EMBO Mol Med*, 2009, 1: 315–322
- 59 Mereniuk T R, El Gendy M A, Mendes-Pereira A M, et al. Synthetic lethal targeting of *PTEN*-deficient cancer cells using selective disruption of polynucleotide kinase/phosphatase. *Mol Cancer Ther*, 2013, 12: 2135–2144
- 60 Ren W, Joshi R, Mathew P. Synthetic lethality in *PTEN*-mutant prostate cancer is induced by combinatorial PI3K/Akt and BCL-XL inhibition. *Mol Cancer Res*, 2016, 14: 1176–1181
- 61 Zhao D, Lu X, Wang G, et al. Synthetic essentiality of chromatin remodelling factor CHD1 in *PTEN*-deficient cancer. *Nature*, 2017, 542: 484–488
- 62 Zhang C, Wang X W, Wang L, et al. The mystery of “junk” DNA (in Chinese). *Chin Sci Bull*, 61: 3079–3084 [张常, 王新文, 王亮, 等. “垃圾”DNA 的奥秘. 科学通报, 2016, 61: 3079–3084]
- 63 Adriaens C, Standaert L, Barra J, et al. P53 induces formation of NEAT1 lncRNA-containing paraspeckles that modulate replication stress response and chemosensitivity. *Nat Med*, 2016, 22: 861–868
- 64 Han H, Chen Y, Cheng L, et al. MicroRNA-206 impairs c-MYC-driven cancer in a synthetic lethal manner by directly inhibiting MAP3K13. *Oncotarget*, 2016, 7: 16409–16419

Summary for “合成致死在精准肿瘤学中的应用”

Application of synthetic lethality in the precise oncology

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Cancer is a leading cause of death in both developed and developing countries. Most cancers occur as a result of somatically acquired alternations in the genomes of normal cells. The somatic alterations presented in a cancer genome can reach about ten thousands. However, a few such alterations that are able to drive initiation and progression of cancer are defined as “driver” mutations, while all other mutations are assumed to be randomly acquired and termed as “passenger” mutations. Driver mutations confer growth advantage on the cells carrying them and have been positively selected during the evolution of the cancer. Accumulating driver mutations in a cell genome likely result in multi-step mutations of encoded proteins or non-coding transcripts, which change their biological functions of the proteins and transcripts. Driver mutations potentially have been classified into two categories: “oncogenes” that are likely resulted from gain-of-function mutations and “tumor suppressor genes” that may be due to loss-of-function mutations. Together these two types of mutations drive cancer initiation and development. Targeting driver gene mutations have been successfully applied to the treatment of various cancers in humans. In this review, we introduce the concept of driver and passenger mutations, and theory of synthetic lethality (SL). Furthermore, we address the application of SL by targeting synthetic lethal partner of these “driver” genes and the clinical trial that can be designed based on the theory of SL. Synthetic lethal interactions arise when the perturbation of more than one genes simultaneously results in the loss of viability, whereas a deficiency in only one of these genes does not. SL might be extended to synthetic sickness, which is referred to the sickness but not lethality in cells resulting from mutations of those genes, and synthetic dosage lethality by targeting its partner to kill cells with overexpression of one gene. This theory has been applied to genetic studies to determine functional interactions among different genes for decades and has been exploited for the development of new genotype-selective anticancer agents in engineered human tumor cells. In precision oncology, the theory of SL provides greater promise in specifically targeting cancer cells with genetic mutations but not in normal cells. For example, targeting both of the breast-cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2*) deficiencies dramatically sensitized cells to poly(ADP-ribose) polymerase (PARP) inhibitors due to associated defective homologous recombination, which leads to dysfunction of DNA repair in cancer cells. Moreover, oncogenic drivers such as RAS, P53 are not “druggable”, but recently these oncogenic drivers have been studied in successfully screening for their synthetic lethal partners or agents. If a synthetic lethal agent can be combined with conventionally chemotherapy, this will probably benefit cancer patients. Therefore, the application of the SL in cancer researches and clinical trials might represent one of the most important technological breakthrough in the treatment of cancer in the era of precision oncology.

synthetic lethality, tumor, driver mutation, precision oncology

doi: 10.1360/N972018-00152