·综　述·

组蛋白修饰调控53BP1与染色质结合功能的研究进展

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[摘　要]　p53结合蛋白1(p53-binding protein 1,53BP1)在协调DNA双链断裂(DNA double strand break,DSB)修复途径选择中起关键作用。关于53BP1募集到受损染色质中的基本分子机制,以及组蛋白修饰在53BP1募集中的作用,已有大量文献报道了全新的见解。H4K20me2和H2AK15ub是决定53BP1能否结合到受损染色质中的关键因素。最新证据表明,H3K18、H3K56乙酰化及H4K16乙酰化/甲基化对53BP1募集均有一定程度的影响。文章对53BP1的结构、53BP1募集的分子机制和组蛋白修饰在调节53BP1募集中的作用进行了综述,并为癌症治疗提供新的思路。

[关键词]　p53结合蛋白1;组蛋白修饰;DNA双链断裂

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Research progress of histone modification regulating the binding function of 53BP1 to chromatin

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[**Abstract**]　p53 binding protein 1(53BP1) plays a crucial role in coordinating the selection of DNA double-strand break(DSB) repair pathway. Underlying molecular mechanisms of 53BP1 recruitment to damaged chromatin and the function of histone modifications in that process have been reported in extensive literature. H4K20me2 and H2AK15ub are the key factors that determine whether 53BP1 can bind to damaged chromatin. Recent evidence suggests that the acetylation of H3K18 and H3K56, as well as the acetylation/methylation of H4K16, have a certain effect on 53BP1 recruitment. This article reviews the structure of 53BP1, the molecular mechanism of 53BP1 recruitment, and the role of histone modifications in regulating 53BP1 recruitment, and provides new ideas for cancer therapy.

[**Key words**]　53BP1;histone modification;DNA double-strand break

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DNA是细胞生命周期中最重要的生物大分子。在真核细胞中,DNA浓缩成染色质[1]。染色质的核心单位是核小体,它由146 bp的DNA缠绕组蛋白八聚体1.75圈而形成[2]。组蛋白八聚体由组蛋白H2A、H2B、H3和H4各2个分子构成,它是真核细胞染色体中核小体的核心颗粒[3]。DNA在代谢的过程中,会受到外源性损伤因子和内源性DNA损伤的影响,如电离辐射、紫外线辐射、化学试剂、DNA去嘌呤化等。一旦DNA发生损伤而不能被及时修复时,细胞将发生衰老、自噬和凋亡[4]。

DSB是引发基因组不稳定的最主要因素,而DSB修复途径对基因组完整性的维持至关重要[5]。

真核生物修复DSB主要有两种途径：同源重组（homologous recombination，HR）修复和非同源末端连接（non-homologous end-joining，NHEJ）修复。NHEJ修复在G1期占主导地位，而HR修复在S、G2期更具优势[6]。在细胞周期的不同时期，DNA损伤信号引起的组蛋白修饰不同。而不同的组蛋白修饰将决定p53结合蛋白1（p53-binding protein 1，53BP1）或乳腺癌1易感蛋白（breast cancer type 1 susceptibility protein，BRCA1）是否结合到受损的染色质中。在G1期，53BP1结合到DNA末端，保护DNA末端免受核酸酶切割处理，这有利于NHEJ修复途径的顺利进行。而在S、G2期，BRCA1结合到DSB位点并启动末端切除，从而推动HR修复的进行[7]。确定组蛋白修饰如何调节这两个过程，对于理解DSB修复过程和寻找新的癌症治疗方法至关重要。

53BP1在DSB位点的募集主要受几种修复调节因子的影响，如共济失调毛细血管扩张突变（ataxia-telangiectasia mutated，ATM）和RAP1相互作用因子1（RAP1-interacting factor 1，RIF1）[8]。53BP1与染色质的结合被认为主要受几个组蛋白修饰的调节。例如，53BP1的Tudor结构域识别H4K20me2过程，是53BP1结合染色质最关键的步骤[8]。H2AK15ub增强了53BP1与受损染色质的结合，其泛素化过程是由E3连接酶RNF8和RNF168催化的[9]。然而，参与53BP1与染色质结合的组蛋白修饰远不止这两种。通过单独或者联合抑制组蛋白的修饰，人们发现H3K18、H3K56、H4K16乙酰化以及H4K16甲基化也参与调节53BP1与染色质的结合[8,10-11]。因此，本文将重点阐述53BP1募集分子机制和组蛋白修饰对53BP1结合染色质的影响。

1 53BP1的结构

53BP1由1 972个氨基酸组成，其N端富含丝/苏氨酸-谷氨酰胺，具有ATM、RIF1、Pax反活化域相互作用蛋白（pax transactivation-domain interacting protein，PTIP）以及细胞周期依赖性激酶（cyclin-dependent kinases，CDK）等重要激酶的磷酸化调控位点[12]。foci形成区（foci-forming region，FFR）是53BP1募集的重要结构域。FFR包括寡聚域（oligomerization domain，OD）、串联的Tudor结构域以及泛素化依赖的基序（ubiquitination dependent recruitment，UDR）[13-15]。C端由两个串联的BRCA1羧基末端（BRCA1 carboxyl-terminal，BRCT）结构域组成，是53BP1和其他蛋白质相互作用的区域[16]。

2 53BP1募集的分子机制

2.1 53BP1乙酰化和磷酸化

53BP1的翻译后修饰可决定其能否募集到DSB位点，而乙酰化则是最常见的修饰之一。经过质谱分析，CREB结合蛋白（CREB binding protein，CBP）可以促使53BP1的重要结构域Tudor和UDR的赖氨酸1626/1628残基发生乙酰化。53BP1赖氨酸1626/1628残基乙酰化后，53BP1与核小体之间的相互作用被阻碍。当发生DSB时，53BP1的乙酰化过程受到调控。组蛋白去乙酰化酶2（histone deacetylase，HDAC2）是使53BP1去乙酰化的关键因子[15]。在HDAC2的作用下，53BP1才被允许募集到受损的染色质中。

53BP1在不同细胞周期进程中发生不同的修饰。在有丝分裂过程中，53BP1的UDR基序磷酸化后，可避免53BP1过早地募集到染色质中。在有丝分裂早期和中期，53BP1的UDR基序的苏氨酸1609和丝氨酸1618残基处于磷酸化状态[17]。已有相关文献表明，UDR基序磷酸化是由CDK1和polo样激酶1（polo like kinase 1，PLK1）联合介导的[18-19]。在有丝分裂后期和末期，蛋白磷酸酶4的催化亚基（protein phosphatase 4 catalytic subunit，PP4C）发生磷酸化。随后，PP4C使UDR基序丝氨酸1618残基去磷酸化[17,20]。当细胞进入G1期，53BP1去磷酸化彻底完成，并恢复其在DNA损伤反应（DNA damage response，DDR）中的功能。

2.2 53BP1募集过程

在DNA发生损伤前，53BP1的Tudor结构域被Tudor相互作用修复调节因子（Tudor-interacting repair regulator，TIRR）掩盖[21]。TIRR是53BP1募集的抑制剂，它调控53BP1在DNA损伤前后的募集[21-22]。由于Tudor结构域与TIRR相结合，这阻碍了53BP1与H4K20me2的结合[23-27]。此外，组蛋白H3K18、H3K56和H4K16均处于乙酰化状态，共同阻止53BP1与染色质的结合[8,10,28]。组蛋白H4K20me2与53BP1的结合位点被甲基赖氨酸结合蛋白1（methyl-Lysine binding protein 1，L3MBTL1）和赖氨酸去甲基酶4A（lysine demethylase 4a，KDM4A）掩盖[29-30]。当DNA发生损伤时，由减数分裂重组蛋白11（meiotic recombination 11，MRE11）、DNA损伤修复蛋白50（DNA repair protein 50，RAD50）、尼梅亨断裂综合征基因1（Nijmegen breakage syndrome 1，NBS1）组成的MRN复合体和DNA依赖性蛋白激酶（DNA-dependent protein kinase，DNA-PK）共同识别

DSB末端，并激活ATM[31]。ATM介导53BP1的磷酸化，并与RIF1共同促进53BP1-TIRR复合体的解离[22-23]。同时，ATM迅速磷酸化组蛋白H2A的丝氨酸139残基，使之转变为γH2AX。γH2AX持续放大损伤信号，并通过蛋白质相互作用网络招募DNA损伤检查点蛋白调节子1(mediator of DNA damage checkpoint protein 1，MDC1)[32]。此外，ATM还激活了检查点激酶1(checkpoint kinase 1，CHK1)。CHK1使抗沉默因子1A(anti-silencing function 1a，ASF1A)发生磷酸化[33]。磷酸化的ASF1A与MDC1的相互作用增强了MDC1与ATM的相互作用，继而使MDC1-RNF8-RNF168-组蛋白泛素化-53BP1轴的信号级联反应激活[34](图1)。MDC1促使泛素连接酶RNF8和RNF168募集到受损染色质[35]。SIRT3以RNF8依赖的方式被募集到染色质中[10]。SIRT7以聚(ADP-核糖)聚合酶1[poly(ADP-ribose) polymerase 1，PARP1]依赖的方式被募集到受损染色质中[36]。SIRT3和SIRT7分别介导H3K56和H3K18去乙酰化。HDAC介导H4K16ac去乙酰化。随后，GLP以ATM依赖的方式募集到受损染色质中，介导H4K16甲基化[37]。H4K16me1提高了53BP1的Tudor结构域对H4K20me2的亲和力[8]。同时，H4K20me2以依赖RNF8的方式与L3MBTL1和KDM4A解离，并暴露其识别53BP1的结合位点[38-39]。RNF8和RNF168共同促使H2AK15泛素化为H2AK15ub[40]。53BP1通过其UDR基序和Tudor结构域分别与H2AK15ub和H4K20me2结合[41-42](图2)。53BP1从核质转移到受损染色质中，并与下游因子相互作用。RIF1被募集到DSB位点，与53BP1的N端相互作用[43]。REV7(DNA聚合酶ζ的小亚基，又称为MAD2L2)则以53BP1、RIF1和ATM依赖的方式募集到染色质中[44]。53BP1-RIF1-REV7共同保护DSB末端免受羧基末端结合蛋白相互作用蛋白(CtBP interacting protein，CtIP)的切割处理[45]。

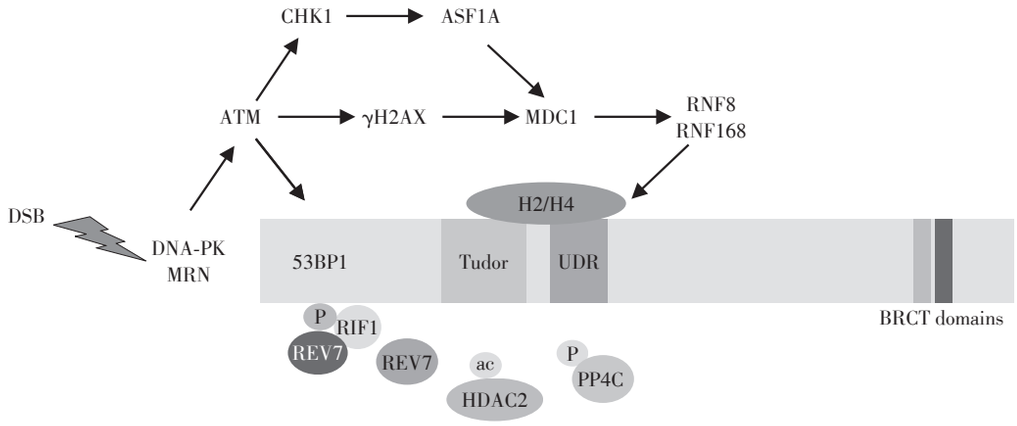

图1　53BP1募集的基本分子机制

Figure 1　The basic molecular mechanism of 53BP1 recruitment

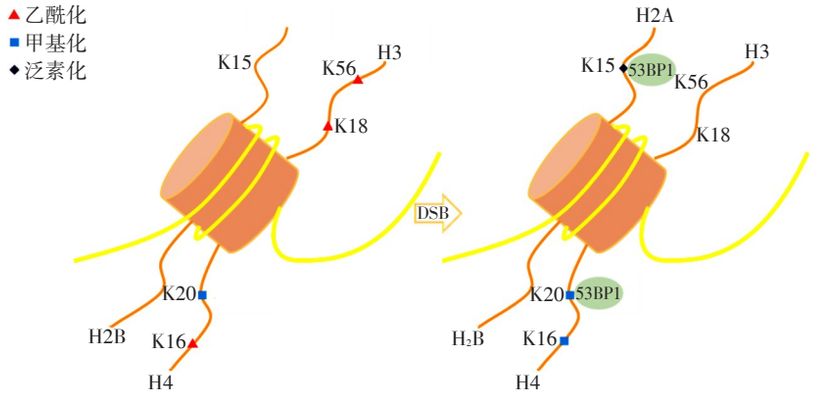

图2　组蛋白在DSB前后的修饰

Figure 2　Modification of histone before and after DSB

3 参与53BP1募集的组蛋白及其作用机制

3.1 H2AK15

组蛋白H2AK15ub是由53BP1选择性识别的[46]。H2AK15泛素化是决定53BP1的UDR基序能否识别H2AK15ub最重要的步骤。当53BP1结合H2AK15ub后，53BP1才能及时有效地募集到DSB位点[47]。H2AK15的泛素化依赖于泛素连接酶RNF8和RNF168[40]。然而，最新研究表明，H2AK15ub不完全在53BP1募集中发挥作用。在发生DSB时，细胞中发生一系列蛋白质磷酸化事件，其中包括部分泛素的苏氨酸12残基磷酸化（pUbT12）事件。泛素苏氨酸12残基发生磷酸化在H2AK15泛素化和DDR调节中有着意想不到的作用。在RNF168的催化下，磷酸化的泛素苏氨酸12残基促使H2AK15发生泛素化产生H2AKpubT12。而苏氨酸12残基位于53BP1和H2AK15ub复合体相互识别的界面，苏氨酸12磷酸化极大地破坏了53BP1和H2AK15ub相互作用的稳定性[41]。H2AKpubT12对53BP1的最直接影响是53BP1不能识别含有H2AKpubT12的染色质区域，取而代之的是该染色质区域被RNF169、DNA损伤修复蛋白51（DNA repair protein 51，RAD51）以及BRCA1识别。过多的泛素苏氨酸12残基发生磷酸化还可能不受控制地刺激RNF169的激活[41]。RNF169是RNF168的同源物[48]，RNF169通过对泛素结构的竞争来限制RNF168介导的信号转导，最终也会抑制53BP1募集到DSB中[40]。由此可见，H2AK15ub可能通过泛素苏氨酸12残基的磷酸化和去磷酸化来调节53BP1募集。

3.2 H4K20

作为在53BP1募集中最关键的组蛋白之一，H4K20是否甲基化可以决定G1、G2和S期修复途径的选择[49]。H4K20me2确保53BP1-RIF1-REV7复合物被募集到染色质中[50]。另外，组蛋白H4K20在未甲基化时促进53BP1移除和BRCA1募集[51]。在G1期，H4K20me2在53BP1结合位点处于饱和水平，这促使53BP1-RIF1-REV7复合物募集到DSB，并促使BRCA1从DSB移除。在S、G2期，H4K20me2的浓度下降使得53BP1-RIF1-REV7复合物移除。随后，未甲基化状态的组蛋白H4K20浓度相对增加，并促使BRCA1募集到DSB[52]。组蛋白H4K20代表修复途径的开关，它确保NHEJ修复在G1期占主导地位，而HR修复在S、G2期更具优势[6]。总而言之，H4K20me2对于53BP1在染色质的募集是非常重要的[47]。

正常情况下，即使H4K20me2的浓度处于饱和状态也无法识别53BP1，其原因可从H4K20me2和53BP1这两个角度进行阐释。首先，53BP1无法识别H4K20me2是因为正常状态下，H4K20me2被埋藏于染色质中。H4K20me2是由赖氨酸甲基转移酶5A（lysine methyltransferase 5A，KMT5A）和组蛋白甲基转移酶（suppressor of variegation 4-20 homolog，Suv4-20H）协同作用而产生。由KMT5A催化的第一次甲基化产生的H4K20me1促进了Suv4-20H募集，而Suv4-20H的募集又催化H4K20me1发生第二次甲基化[53]。经过两次甲基化的组蛋白H4K20将一直埋藏于染色质中，直到发生DSB时才暴露出来[54]。H4K20me2一直埋藏在染色质中无法被53BP1识别，是因为其结合位点被各种结合蛋白覆盖，其中最关键的结合蛋白是L3MBTL1[29]和KDM4A[30]，KDM4A、L3MBTL1共同竞争53BP1和H4K20me2的结合位点，阻碍了53BP1识别H4K20me2。其次，53BP1无法识别H4K20me2的另一个原因是53BP1被TIRR掩盖。TIRR抑制53BP1与H4K20me2之间的相互作用，它掩盖了53BP1的Tudor结构域[24]。总而言之，L3MBTL1和TIRR通过阻止H4K20me2与53BP1的Tudor结构域之间的相互作用来抑制53BP1对DSB的募集。在发生DSB时，ATM促进53BP1-TIRR复合物解离，使得53BP1能够识别H4K20me2[23,27]。ATM与MDC1的结合使MDC1-RNF8-RNF168-组蛋白泛素化-53BP1轴的信号级联反应激活。含缬氨酸蛋白（valosin-containing protein，VCP）以RNF8和泛素依赖的方式募集到DSB中，并介导L3MBTL1与H4K20me2分离[38]。同时，KDM4A被蛋白酶体以RNF8依赖的方式降解，这些都是53BP1与H4K20me2结合的前提[39]。这些研究共同证明了H4K20me2如何以RNF8/RNF168依赖的方式与53BP1结合。

组蛋白H2AK15的泛素化和H4K20的甲基化过程在DDR中联系紧密。相关文献表明，RNF8和RNF168介导的H2AK15泛素化和KMT5A的募集存在一定关联。KMT5A在DDR中的活性是H4K20甲基化所必需的[38]。因此，RNF8、RNF168和KMT5A在53BP1募集中的作用可以从两个方面解释。首先，作为组蛋白甲基转移酶，在特定的DSB位点KMT5A可以诱导H4K20发生甲基化；其次，KMT5A还是一种泛素化调节因子，可以增强RNF168介导的H2AK15泛素化[39]。

3.3 H3K18

组蛋白H3K18以SIRT7介导的H3K18ac去乙酰化方式来调控53BP1募集[28]。SIRT7属于sirtuin家族成员，这个家族的一个关键功能是调节和维持基因组的稳定性[55]。SIRT7以PARP1依赖的方式被招募到DSB位点，并作用于组蛋白[28]。SIRT7可使组蛋白的启动子区域脱乙酰化，并选择性地去乙酰化H3K18ac的启动子区域[56]。SIRT7在表观遗传学上控制与线粒体生物发生、核糖体生物合成和DNA损伤反应相关基因的转录[57]。SIRT7可以被DNA[58]和RNA[59]激活，以水解组蛋白H3K18赖氨酸残基的乙酰基[60]。SIRT7缺失使细胞对多种遗传毒物敏感[61-63]。SIRT7缺失还导致早衰以及胚胎存活率降低，这与基因修复缺陷有关[11]。在色氨酸2，3-双加氧酶(tryptophan 2，3-dioxygenase，TDO)活性被抑制的情况下，使用双氯乙基亚硝脲(bis-chloroethyl-nitrosourea，BCNU)诱导胶质母细胞瘤细胞发生DSB后，细胞表现出γH2AX信号增强和53BP1向染色质募集缺陷。TDO抑制减少了SIRT7脱乙酰酶在染色质中的募集，从而增加了组蛋白H3K18乙酰化——这是阻止53BP1募集到DSB位点的关键标志[64]。但是这个新的调节途径还没确定53BP1是如何与H3K18相互作用的。目前，已有研究表明，H3K18ac并没有通过影响H4K20me2、H2AK15ub与53BP1的结合来阻碍53BP1募集[28]。

3.4 H3K56

组蛋白H3K56位于核小体的DNA进出位点，其乙酰化与DNA损伤后的转录和细胞存活等重要细胞功能相关[65-66]。在发生DSB时，RNF8介导SIRT3定位于受损染色质中，并与53BP1共同定位[10]。随后，SIRT3介导H3K56ac去乙酰化，并促使53BP1募集到受损染色质中[10]。由于SIRT3和组蛋白H3K56在53BP1募集中的稳定作用，细胞在遗传毒性应激下依然能够稳定地存活[67-68]。目前，尚未阐明53BP1是否通过特定的结构域特异性识别H3K56。

3.5 H4K16

H4K16ac是由Tat相互作用蛋白60(Tat interactive protein 60，Tip60)乙酰基转移酶复合物催化产生的[69-70]，它通过破坏H4K16和Tudor结构域之间的盐桥来减弱53BP1与H4K20me2的结合[54,71]。相反，H4K16ac去乙酰化则增强53BP1与H4K20me2结合以及53BP1 foci形成[54]。相关文献解释了Tip60如何调节组蛋白的修饰和53BP1募集。在S、G2期中，HR修复途径的激活依赖于BRCA1、53BP1与关键相互作用伙伴的结合[72]。在G1期，H4K16的乙酰化水平随DNA损伤程度变化。当发生DSB时，HDAC催化H4K16ac加速去乙酰化[71]。在S、G2期，Tip60促使H4K16发生乙酰化，使得53BP1在DSB中的积累减少[73]。另外，Tip60在调节53BP1募集中除了调节H4K16乙酰化，还能通过乙酰化H2AK15来阻止H2AK15泛素化[74]。相反，由RNF168介导的H2AK15泛素化过程则抑制Tip60对H4K16乙酰化作用[74]。总之，H2AK15的泛素化或乙酰化以及Tip60介导的组蛋白H4K16乙酰化过程相互影响，共同确保53BP1在正确的时期募集到染色质中。

最近一项研究表明组蛋白H4K16me1也参与53BP1的募集。H4K16甲基化主要受GLP调控。抑制GLP可阻止DNA修复进程，这可能是由于GLP可以抑制相关修复因子的募集。例如，通过抑制GLP可减弱BRCA1募集从而抑制HR修复[75-76]。然而，也有人报道，抑制GLP使NHEJ修复效率降低，而并不影响HR修复[77]。这是因为GLP被抑制后，53BP1募集也受影响[8]。GLP调控的53BP1募集可能主要来自于H4K16me1和53BP1之间的相互作用。在DDR中，H4K16me1水平与H4K16ac水平表现出相反的变化[8]。H4K16的赖氨酸残基甲基化与乙酰化相互竞争，H4K16甲基化水平增加可以抑制H4K16乙酰化，从而确保53BP1募集。GLP除了可以调节H4K16的甲基化，还可以通过介导MDC1甲基化来促进53BP1募集[37,78]。MDC1是53BP1在DSB位点积累所必需的。当发生DSB时，GLP以ATM依赖的方式被招募到受损染色质中[78]。随后，GLP介导的MDC1甲基化可增强ATM的活性，从而扩大受损染色质周围的损伤信号。

在发生DSB时，相对于H4K16me1水平的大幅增加，H4K20me2水平的增加却相当有限[8]。这或许是因为H4K20me2在DSB发生前就已经大量积累在染色质中[54]，所以H4K20me2在DNA发生损伤时不会增加太明显[8,79]。目前，已有相关研究介绍了H4K16me1和H4K20me2的抑制对53BP1 foci形成的影响。共同抑制H4K16me1[80]和H4K20me2[81]比单独抑制能更有效地抑制53BP1募集[8]。究其原因是H4K16me1提高了53BP1的Tudor结构域对H4K20me2的亲和力。因此，H4K16me1与H4K20me2可能联合调控53BP1募集[8]。

4 总结与展望

在DSB修复相关研究领域中，53BP1作为细胞

对NHEJ修复途径的重要调节因子,其在染色质中的募集成为当前的研究热点。多项研究证实53BP1与染色质的结合主要受组蛋白修饰的调节,凸显了进一步研究组蛋白与53BP1作用机制的重要性。现有的研究大多关注修复调节因子对53BP1募集的影响。然而,组蛋白修饰在53BP1募集中发挥的作用也同样值得关注与进一步探索。本文综述了53BP1结构、53BP1募集分子机制以及组蛋白修饰在53BP1募集中的作用机制,但仍有许多问题和重要的研究方向需要继续探索。组蛋白H3K18、H3K56如何与53BP1相互作用以及它们是否影响53BP1识别K2AK15ub、H4K20me2,尚有待深入研究。随着组蛋白修饰与53BP1募集的深度开发,可为癌症治疗提供更多选择。

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