Molecular Cell Weekly Update (2022-11-01 - 2022-12-05)

# Bacterial origins of cyclic nucleotide-activated antiviral immune signaling(循环核苷酸激活的抗病毒免疫信号的细菌起源)

日期：2022-12-01

## Summary

Second-messenger-mediated signaling by cyclic oligonucleotides (cOs) composed of distinct base, ring size, and 3′-5′/2′-5′ linkage combinations constitutes the initial trigger resulting in activation of signaling pathways that have an impact on immune-mediated antiviral defense against invading viruses and phages. Bacteria and archaea have evolved CRISPR, CBASS, Pycsar, and Thoeris surveillance complexes that involve cO-mediated activation of effectors resulting in antiviral defense through either targeted nuclease activity, effector oligomerization-mediated depletion of essential cellular metabolites or disruption of host cell membrane functions. Notably, antiviral defense capitalizes on an abortive infection mechanism, whereby infected cells die prior to completion of the phage replication cycle. In turn, phages have evolved small proteins that target and degrade/sequester cOs, thereby suppressing host immunity. This review presents a structure-based mechanistic perspective of recent advances in the field of cO-mediated antiviral defense, in particular highlighting the ancient evolutionary adaptation by metazoans of bacterial cell-autonomous innate immune mechanisms.

由循环寡核苷酸（COS）（COS）的第二消息介导的信号传导，由不同的碱基，环尺寸和3'-5'/2'-5'连接组合组成，构成了初始触发，从而激活了对免疫产生影响的信号传导途径 - 针对入侵病毒和噬菌体介导的抗病毒防御。细菌和古细菌已经进化了CRISPR，CBASS，PYCSAR和THOERIS监测复合物，涉及效应子的共激活，从而通过靶向的核酸酶活性，效应子寡聚介导的基本细胞代谢物或宿主宿主细胞膜束功能的破坏。值得注意的是，抗病毒防御能够利用流产的感染机制，在噬菌体复制周期完成之前，感染细胞死亡。反过来，噬菌体进化了靶向和降解/隔离COS的小蛋白质，从而抑制了宿主的免疫力。这篇综述介绍了基于结构的机理观点，即在共同介导的抗病毒防御领域的最新进展，尤其强调了通过细菌细胞自主的先天免疫机制的后生动物的古代进化适应。

## Keywords

cyclic nucleotides, signaling pathways, antiviral defense, CRISPR, CBASS, Pycsar, Thoeris

环状核苷酸，信号通路，抗病毒防御，CRISPR，CBASS，PYCSAR，THOERIS

# POLQ seals post-replicative ssDNA gaps to maintain genome stability in BRCA-deficient cancer cells(POLQ密封后复制后的ssDNA间隙，以维持BRCA缺陷癌细胞中的基因组稳定性)

日期：2022-11-30

## Summary

POLQ is a key effector of DSB repair by microhomology-mediated end-joining (MMEJ) and is overexpressed in many cancers. POLQ inhibitors confer synthetic lethality in HR and Shieldin-deficient cancer cells, which has been proposed to reflect a critical dependence on the DSB repair pathway by MMEJ. Whether POLQ also operates independent of MMEJ remains unexplored. Here, we show that POLQ-deficient cells accumulate post-replicative ssDNA gaps upon BRCA1/2 loss or PARP inhibitor treatment. Biochemically, cooperation between POLQ helicase and polymerase activities promotes RPA displacement and ssDNA-gap fill-in, respectively. POLQ is also capable of microhomology-mediated gap skipping (MMGS), which generates deletions during gap repair that resemble the genomic scars prevalent in POLQ overexpressing cancers. Our findings implicate POLQ in mutagenic post-replicative gap sealing, which could drive genome evolution in cancer and whose loss places a critical dependency on HR for gap protection and repair and cellular viability.

POLQ是微学介导的最终结合（MMEJ）的DSB修复的关键效应子，并且在许多癌症中都过表达。POLQ抑制剂赋予HR和SHIELDIN缺陷癌细胞中的合成致死性，该细胞已提出反映MMEJ对DSB修复途径的关键依赖性。POLQ是否也独立于MMEJ运行仍然未开发。在这里，我们表明缺陷的细胞在BRCA1/2损失或PARP抑制剂治疗后积累了复制后的ssDNA间隙。从生化上，POLQ解旋酶和聚合酶活性之间的合作分别促进RPA位移和ssDNA-GAP填充。POLQ还能够进行微学介导的间隙跳过（MMG），该间隙在间隙修复过程中产生缺失，类似于POLQ过表达的癌症中普遍存在的基因组疤痕。我们的发现暗示了POLQ在诱变后的缝隙缝隙密封中，这可能会驱动癌症中的基因组进化，并且其损失对HR对HR的间隙保护和修复以及细胞生存能力的关键依赖。

## Keywords

POLQ, homologous recombination, BRCA genes, PARP inhibitors, replication stress, post-replicative gap repair, BRCA, PARP

POLQ，同源重组，BRCA基因，PARP抑制剂，复制应力，复制后间隙修复，BRCA，PARP

# Profiling lariat intermediates reveals genetic determinants of early and late co-transcriptional splicing(分析幼虫中间体揭示了早期和晚期剪接的遗传决定因素)

日期：2022-11-25

## Summary

Long introns with short exons in vertebrate genes are thought to require spliceosome assembly across exons (exon definition), rather than introns, thereby requiring transcription of an exon to splice an upstream intron. Here, we developed CoLa-seq (co-transcriptional lariat sequencing) to investigate the timing and determinants of co-transcriptional splicing genome wide. Unexpectedly, 90% of all introns, including long introns, can splice before transcription of a downstream exon, indicating that exon definition is not obligatory for most human introns. Still, splicing timing varies dramatically across introns, and various genetic elements determine this variation. Strong U2AF2 binding to the polypyrimidine tract predicts early splicing, explaining exon definition-independent splicing. Together, our findings question the essentiality of exon definition and reveal features beyond intron and exon length that are determinative for splicing timing.

脊椎动物基因中具有短外显子的长长内含子被认为需要跨外显子的剪接组装（外显子定义），而不是内含子，从而需要外显子的转录才能拼写上游内含子。在这里，我们开发了COLA-SEQ（共转录套索测序），以研究共同剪接基因组宽的时间和决定因素。出乎意料的是，在下游外显子转录之前，所有内含子中有90％的内含子可以剪接，表明外显子的定义对于大多数人体内含子来说不是必需的。尽管如此，剪接时序在内含子上却有很大的变化，各种遗传元素决定了这种变化。强大的U2AF2与息肉嘧啶道的结合预测了早期剪接，从而解释了外显子定义与无关的剪接。我们的发现共同质疑外显子定义的重要性，并揭示了内含子和外显子长度的特征，这些特征是剪接时机的决定性的。

## Keywords

CoLa-seq, co-transcriptional splicing, lariat RNAs, branch point, modeling, polypyrimidine tract, GC content, U2AF, exon definition, intron definition

Cola-seq，共转录剪接，套索RNA，分支点，建模，多吡啶胺段，GC含量，U2AF，外显子定义，内含子定义

# Structural insights into caspase ADPR deacylization catalyzed by a bacterial effector and host calmodulin(细菌效应子和宿主钙调蛋白催化caspase adpr脱酰化的结构见解)

日期：2022-11-23

## Summary

Programmed cell death and caspase proteins play a pivotal role in host innate immune response combating pathogen infections. Blocking cell death is employed by many bacterial pathogens as a universal virulence strategy. CopC family type III effectors, including CopC from an environmental pathogen Chromobacterium violaceum, utilize calmodulin (CaM) as a co-factor to inactivate caspases by arginine ADPR deacylization. However, the molecular basis of the catalytic and substrate/co-factor binding mechanism is unknown. Here, we determine successive cryo-EM structures of CaM-CopC-caspase-3 ternary complex in pre-reaction, transition, and post-reaction states, which elucidate a multistep enzymatic mechanism of CopC-catalyzed ADPR deacylization. Moreover, we capture a snapshot of the detachment of modified caspase-3 from CopC. These structural insights are validated by mutagenesis analyses of CopC-mediated ADPR deacylization in vitro and animal infection in vivo. Our study offers a structural framework for understanding the molecular basis of arginine ADPR deacylization catalyzed by the CopC family.

程序性细胞死亡和胱天蛋白酶蛋白在宿主先天免疫反应打击病原体感染中起关键作用。阻断细胞死亡是许多细菌病原体用作普遍毒力策略的。COPC家族III型效应子，包括来自环境病原体紫杉醇的COPC，利用钙调蛋白（CAM）作为通过精氨酸ADPR脱酰化的cocactor来灭活caspase。然而，催化和底物/co因子结合机制的分子基础尚不清楚。在这里，我们确定了在反应，过渡和反应后状态下凸轮 - copc-Caspase-3三元复合物的连续冷冻EM结构，这些状态阐明了COPC催化的ADPR脱环化的多步酶机制。此外，我们捕获了从COPC的修改后CASPASE-3脱离的快照。这些结构见解通过体内的COPC介导的ADPR脱酰化的诱变分析来验证。我们的研究提供了一个结构框架，用于理解COPC家族催化的精氨酸ADPR脱酰化的分子基础。

## Keywords

caspase, Chromobacterium violaceum, ADPR-deacylization, post-translational modification, type III secretion system, effector, programmed cell death

caspase，紫cas菌，紫外线，ADPR二核化，翻译后修饰，III型分泌系统，效应子，程序性细胞死亡

# Translation—A tug of war during viral infection(翻译 - 病毒感染期间的战争)

日期：2022-11-04

## Summary

Viral reproduction is contingent on viral protein synthesis that relies on the host ribosomes. As such, viruses have evolved remarkable strategies to hijack the host translational apparatus in order to favor viral protein production and to interfere with cellular innate defenses. Here, we describe the approaches viruses use to exploit the translation machinery, focusing on commonalities across diverse viral families, and discuss the functional relevance of this process. We illustrate the complementary strategies host cells utilize to block viral protein production and consider how cells ensure an efficient antiviral response that relies on translation during this tug of war over the ribosome. Finally, we highlight potential roles mRNA modifications and ribosome quality control play in translational regulation and innate immunity. We address these topics in the context of the COVID-19 pandemic and focus on the gaps in our current knowledge of these mechanisms, specifically in viruses with pandemic potential.

病毒繁殖取决于依赖宿主核糖体的病毒蛋白质合成。因此，病毒已经发展出了显着的策略来劫持宿主翻译装置，以促进病毒蛋白的产生并干扰细胞先天的防御。在这里，我们描述了病毒用来开发翻译机制的方法，重点关注各种病毒家族的共同点，并讨论此过程的功能相关性。我们说明了互补策略宿主细胞用于阻断病毒蛋白产生的宿主细胞，并考虑细胞如何确保在核糖体上进行战争中依赖于翻译的有效抗病毒反应。最后，我们强调了潜在的角色mRNA修饰和核糖体质量控制在翻译调节和先天免疫中。我们在Covid-19大流行的背景下解决了这些主题，并关注当前对这些机制的知识的差距，特别是在具有大流行潜力的病毒中。

## Keywords

host shutoff, translation regulation, RNA modifications, innate immunity

宿主关闭，翻译法规，RNA修改，先天免疫力