Circular RNAs: diversity of form and function

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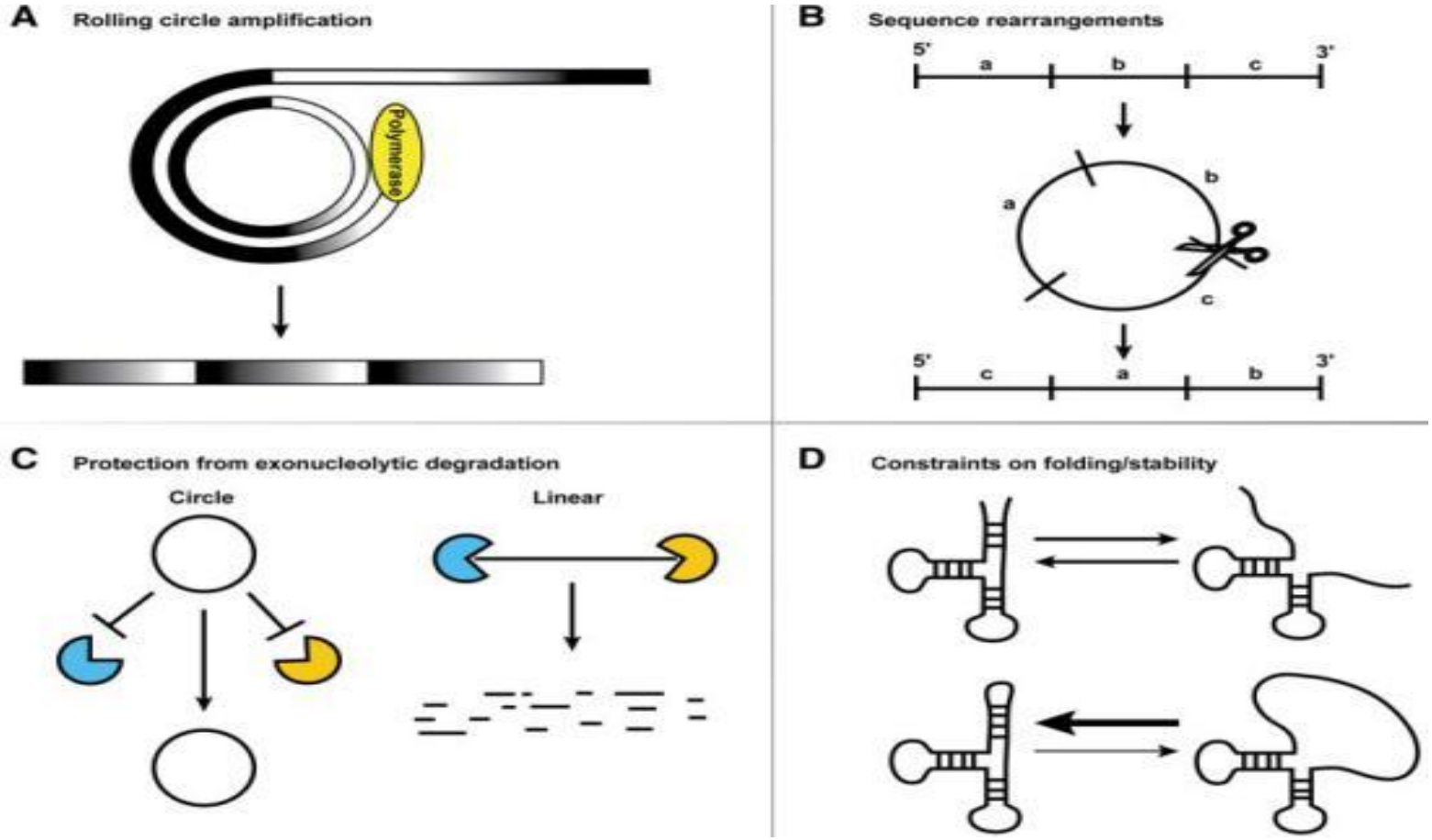
Background

- 除了传统的tRNA, mRNA, and rRNAs，细胞中还含有miRNAs, lncRNAs, piRNAs, siRNAs, tmRNAs, sRNAs, tiRNAs, eRNAs, snoRNAs, snRNAs以及其他的非编码RNA，同时环状RNA也成为了RNA多样性的一个重要种类。
- 目前已经鉴定出来五种常见的环状RNA，包括类病毒、RNA加工过程的中间体、真核生物核pre-mRNA反向剪切产物等。
- 环状RNA有很多有用的性质。例如，可以作为滚环复制到模板、导致DNA的重排、对核酸外切酶的稳定性、环状RNA可以对RNA折叠产生约束---这在某些情况下可能是有益的。



环状RNA的特性 环状RNA可以作为滚环扩增的模板（*A*），提供序列重排的方法（*B*），避免核酸外切酶降解（*C*），限制RNA折叠和使结构稳定性（*D*）

the diversity of circular RNAs

TABLE 1. Types and characteristics of RNA circles

	RNA circle	Type	Organism	Formed by	Possible function (of the circular molecule)	Size
I. Circular RNA genome	Viroids	Genomic and antigenomic	Pathogen of plants	3′–5′ end ligation	Transcription of multimeric copies, stability	~250–400 nt
	Hepatitis delta virus (HDV)	Genomic and antigenomic	Pathogen of humans	3′–5′ end ligation	Transcription of multimeric copies, stability	1.7 kb
II. Circular RNA intron	Excised group I introns	RNA processing byproduct and end product (5′ truncated introns, introns with additional residue at site of circularization, and full-length introns)	Some eukaryotes, some bacteria, some viruses	Ribozyme	Genetic element mobility (?)	250–500 nt
	Group II intron circles and intron lariats	mRNA processing byproduct and end product	Bacteria, some archaea, and some eukaryotic organelles	Ribozyme, 2′–5′ bulged A attack	Genetic element mobility (?)	Up to 3 kb
	Circular intronic RNAs (ciRNAs)	mRNA processing byproduct and end product	Eukaryotes	2′–5′ branchpoint attack (spliceosome mediated) and subsequent degradation of downstream intron sequence	May regulate transcription	<200 nt to >3 kb
	Excised tRNA introns	tRNA processing byproduct and end product	Some archaea	3′–5′ end ligation	Can contain snoRNAs	
III. Circular RNA processing intermediate	rRNA precursors	Intermediate in rRNA processing reaction	Some archaea	3′–5′ end ligation		
	Permuted tRNAs	Intermediate in tRNA processing reaction	Some algae and archaea	3′–5′ end ligation	Rearrange genomic order of sequence	
IV. Circular noncoding RNA	Some snoRNAs		Some archaea	3′–5′ end ligation	Stability	
	RNase P		Some archaea	3′–5′ end ligation	Stability	
V. Circular RNA spliced exons	Exonic circular RNAs (circRNAs)	mRNA processing byproduct and end product	Eukaryotes	Backsplicing (spliceosome mediated)	ceRNAs (sponges), regulators of mRNA levels or translation, other	<100 nt to >4 kb

the diversity of circular RNAs

- Circular RNA genome
- Circular RNA from introns
- Circular RNA intermediates in RNA processing reaction
- Circular ,noncoding RNAs in archaea with snRNP functions
- Circular RNA from eukaryotic ‘backsplicing’

Circular RNA genomes—viroid and hepatitis delta virus circles

- 是环状单链RNAs（ssRNAs），环状允许滚环RNA复制，其中从单个起始事件产生多个基因组拷贝。
- 类病毒或HDV RNA招募宿主DNA依赖性的RNA聚合酶以引发RNA基因组的循环复制。
- 随着线性复合物生成后，这些RNA通过核酶或酶切分离为单体长度，留下5‘羟基和2’，3‘-环磷酸酯末端。
- **关键的一步**是连接这些线性单体分子的5‘和3’末端以产生负链的环状RNA。
- **连接的确切机制尚不清楚**

Circular RNA from introns

- **Group I introns**

  autocatalytic ribozyme
- **Group II introns**

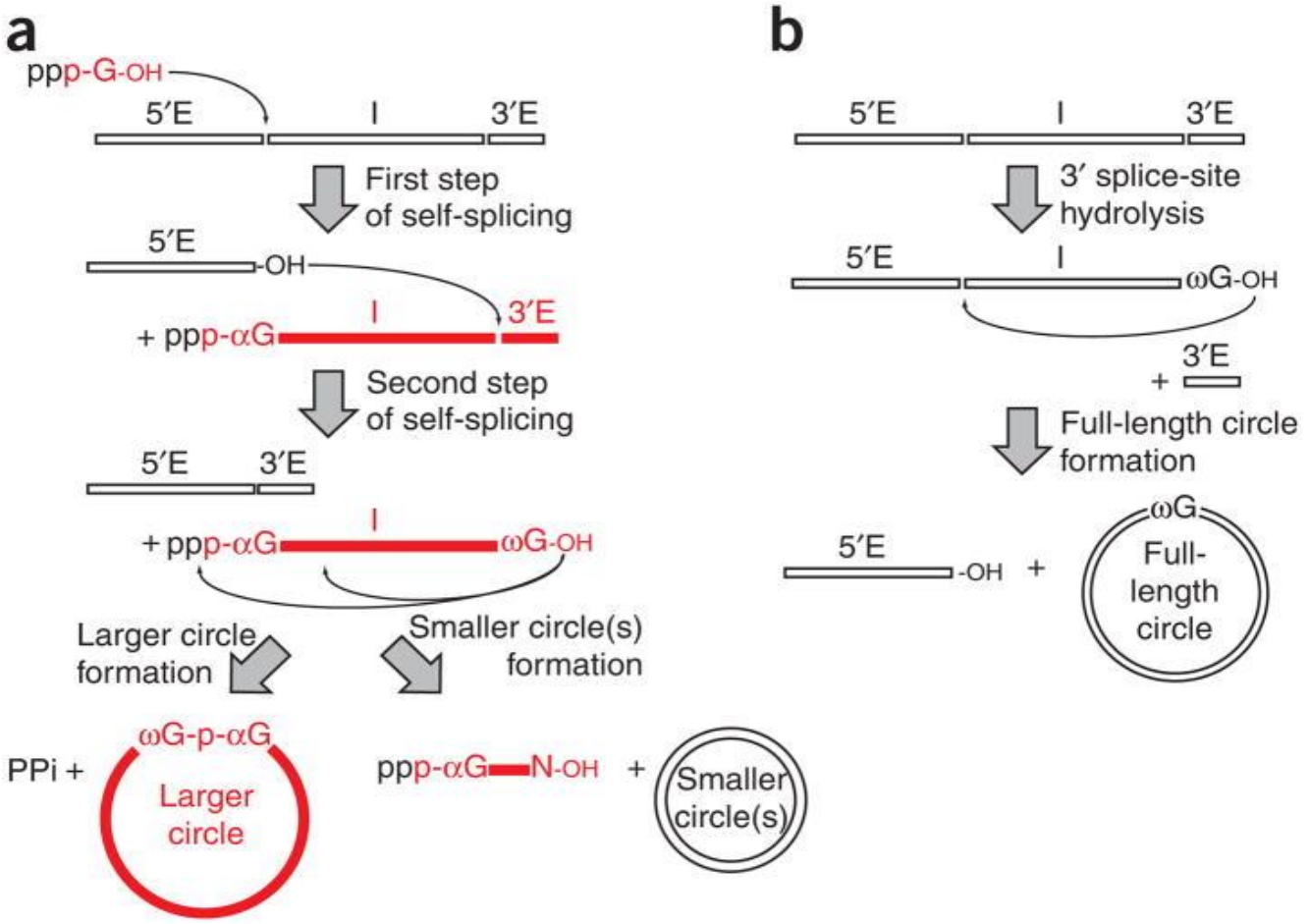
  self-splicing ribozymes
- **Circular intronic RNAs(ciRNAs)**

  intron lariats

Group I introns

- 3’剪接位点处的水解作用连同5’剪接位点的酯基转移作用形成时，这些环可以包含全长的内含子.
- 但是更常见的是当切除的线性内含子经历进一步的内部酯交换反应时，内含子的5‘端被截短。最近，在环化位点发现了含有额外残基的环状产物，源于辅因子。
- 内含子的环状形式是否具有任何功能上的意义仍有待确定。

Group I introns

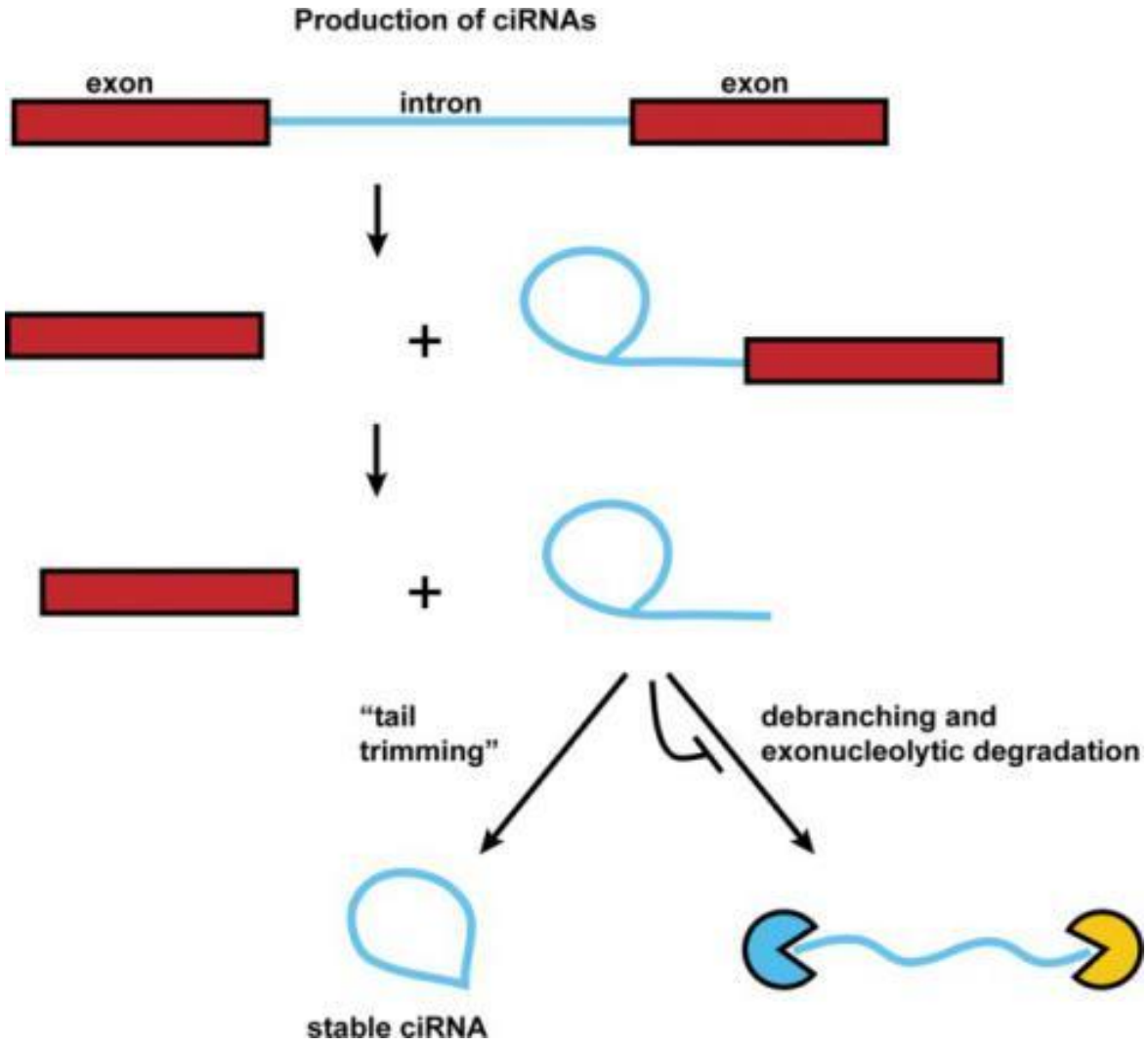


图片来源：**A natural ribozyme with 3′,5′ RNA ligase activity**

Group II introns

- **细菌和一些真核细胞器基因**中发现II组内含子是**自剪接核酶。**
- 酯交换反应导致通过2'-5'连接环化形成的内含子**套索产物**
- 这些套索RNA可以进行**反向剪接**，插入到DNA和RNA中，这可能有助于其**遗传迁移**
- 组II内含子还可以在体内产生**全长**的环，其中可能是通过涉及**两个内含子**的**反式**反应引发的**可变剪接途径，**以首先释放3'剪接位点用于随后的5'剪接位点的酯交换

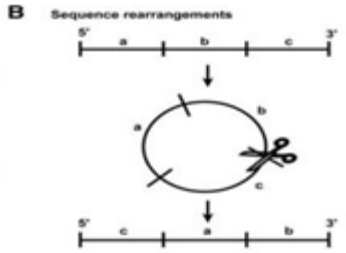
Circular intronic RNAs (ciRNAs)



环状内含子RNA通过真核剪接体介导的剪接产生。从拼接反应产生的套索内含子避免了正常的脱支和降解，而是修剪了从分支点下游的3'“尾”导致稳定的ciRNA。

Circular RNA intermediates in RNA processing reactions

- 可以在RNA加工反应中产生环状RNA作为中间体
- 在一些古细菌中，16S和23S rRNA作为线性分子从前体切除，然后通过连接酶进行环化，非常类似于tRNA内含子，随后进一步的RNA加工反应可以产生成熟的rRNA。（图3）
- 在一些藻类和古细菌中，环状RNA是重组的tRNA基因的生物发生中的关键中间体，其基因的“5”和“3”“区域的顺序在基因组中颠倒（图 1B）



Circular RNA intermediates in RNA processing reactions

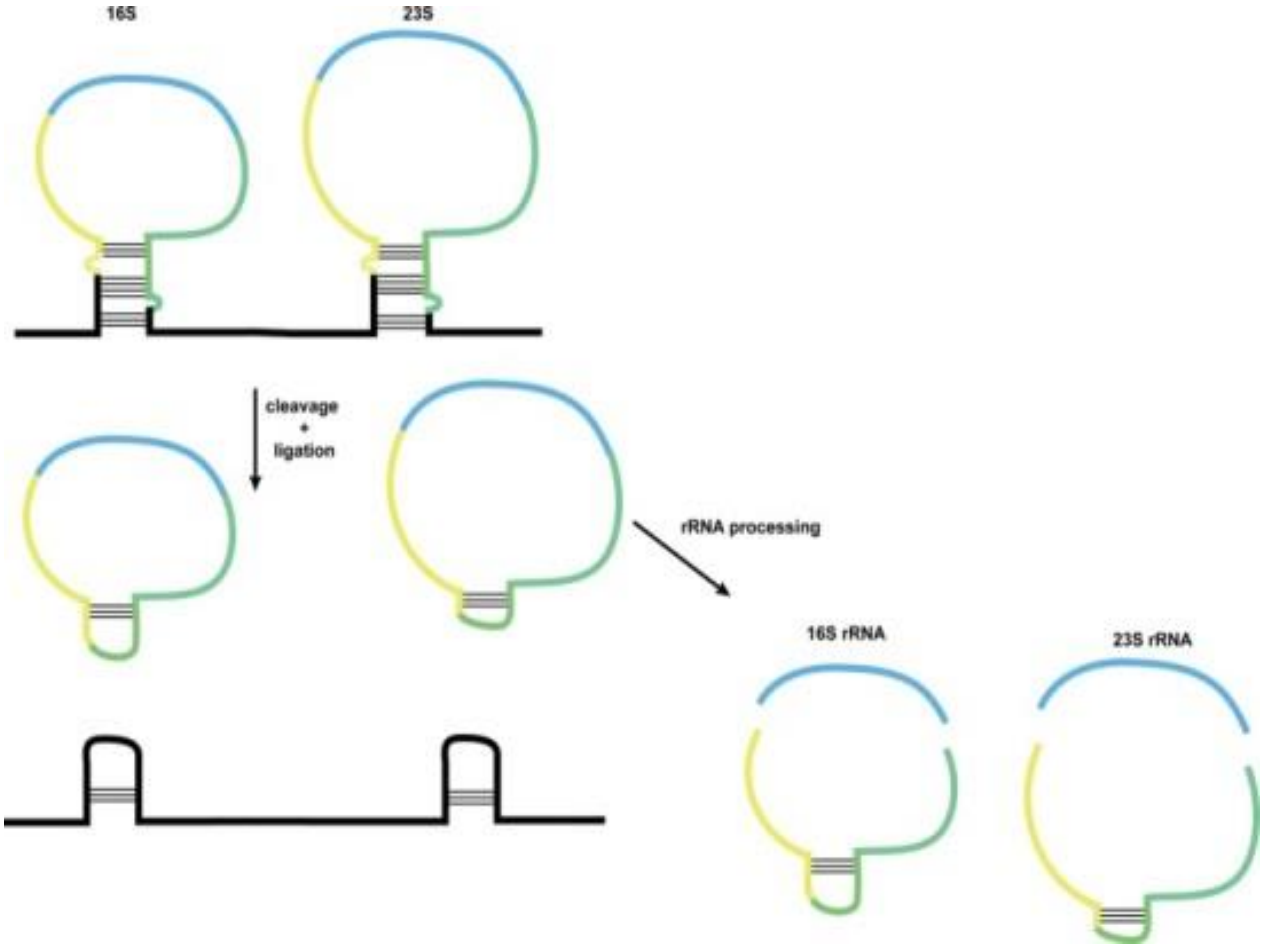
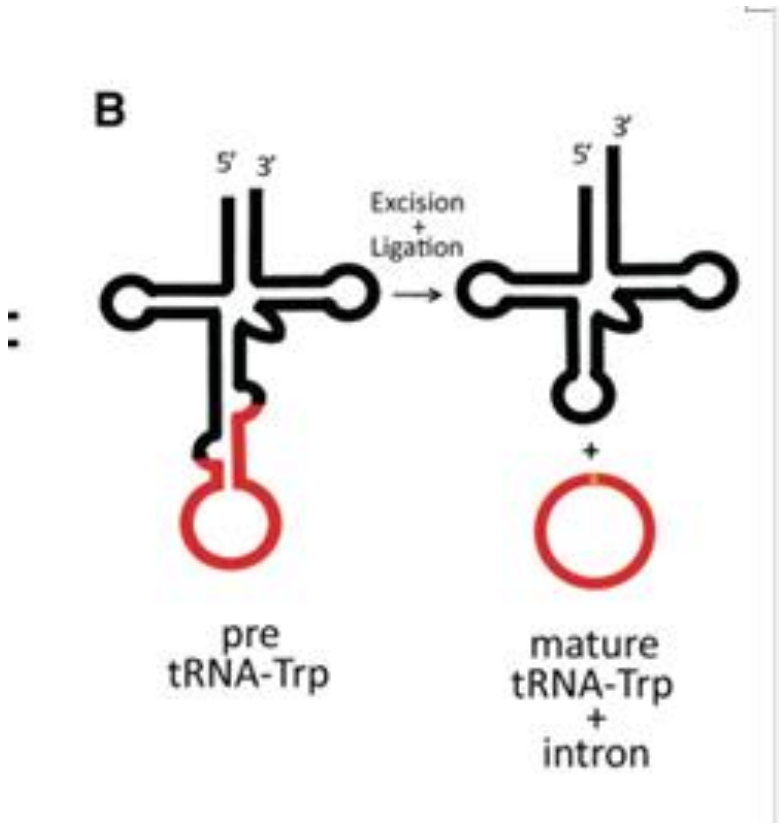


图3：在一些古细菌中，在核糖体RNA加工中形成环状RNA作为中间体。含有隆起-螺旋-隆起motif的核糖体RNA前体被切割并连接，形成进一步处理以释放16S和23S rRNA的环状中间体。rRNA区域用浅蓝色表示，上游和下游区域分别是黄色和绿色。

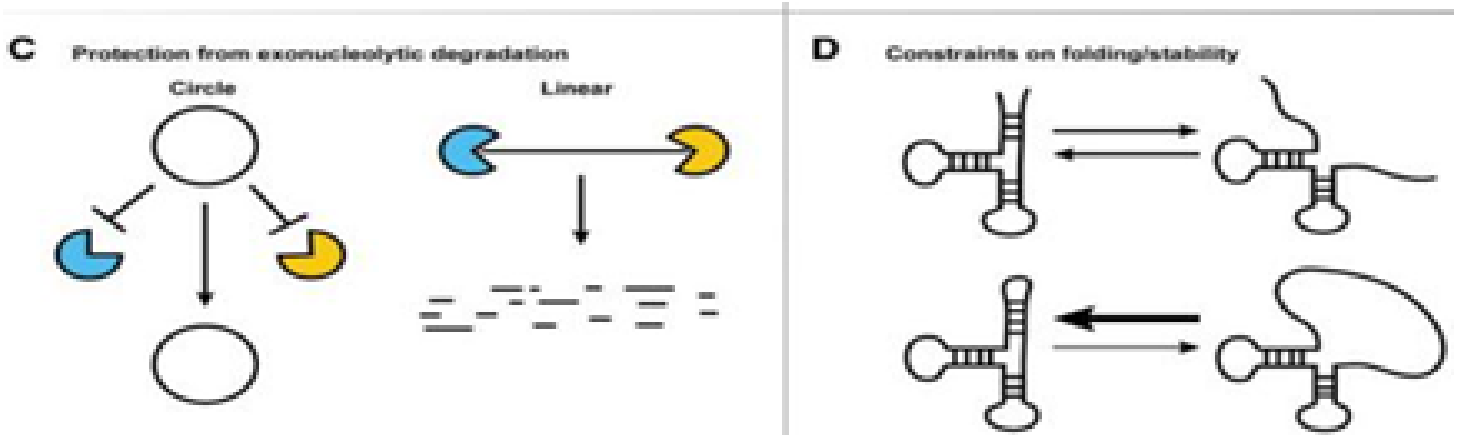
Circular, noncoding RNAs in archaea with snRNP functions



在一些古细菌中，已经描述了用于RNase P RNA和一些snoRNA的环状RNA，其可以从切除的环化的tRNA内含子产生。

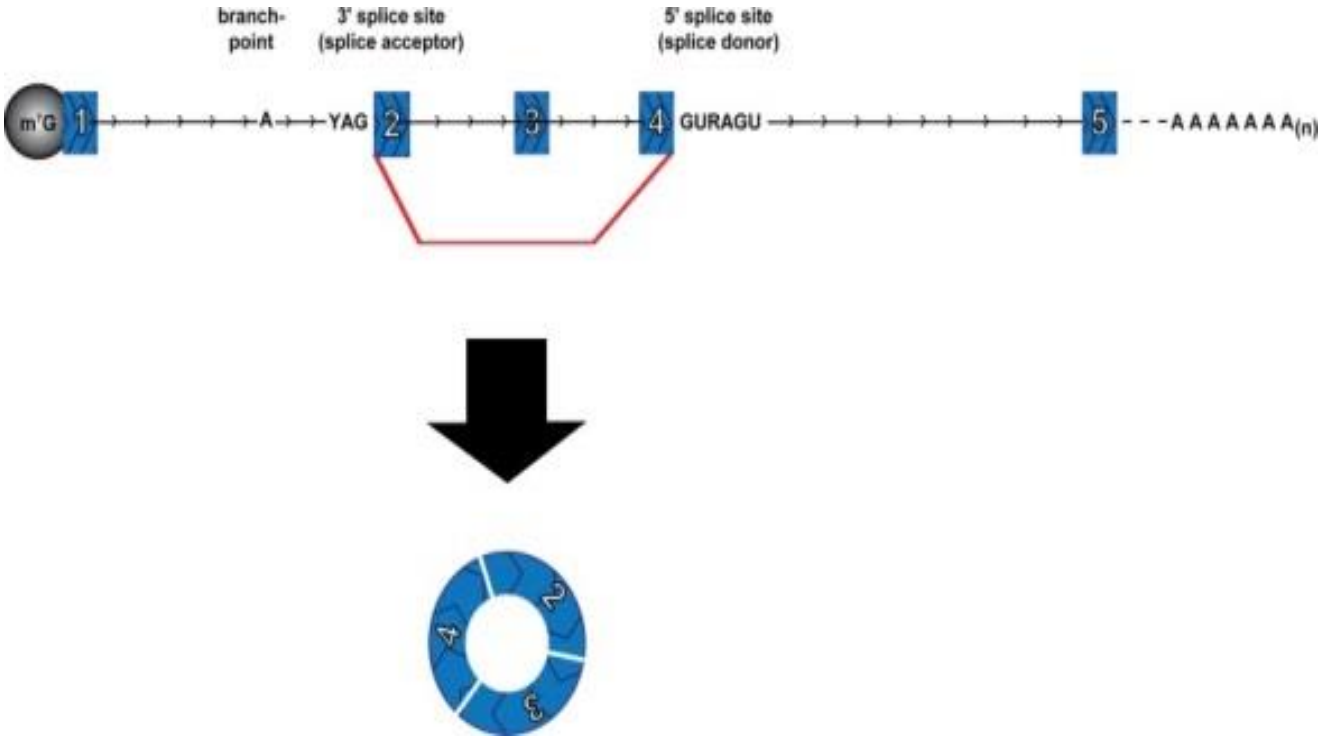
图片来源：Transcriptome-wide discovery of circular RNAs

Circular, noncoding RNAs in archaea with snRNP functions



功能非编码RNA的环状可能是有益的，因为它可以保护它们免受外切核酸酶的侵害，也可能通过对RNA施加结构限制来增加恰当的折叠。

Circular RNA from eukaryotic ‘backsplicing’



真核生物中另一种类型的环状RNA来自剪接体介导的前体mRNA剪接，其中下游5‘剪接位点（剪接供体）连接到上游3’剪接位点（剪接受体），从而产生环状产物（circRNA）。这个过程被称为**反向剪切**。

IDENTIFICATION AND VALIDATION OF BACKSPLICED CIRCLES

TABLE 2. Evidence for human circRNAs (transcriptome-wide)

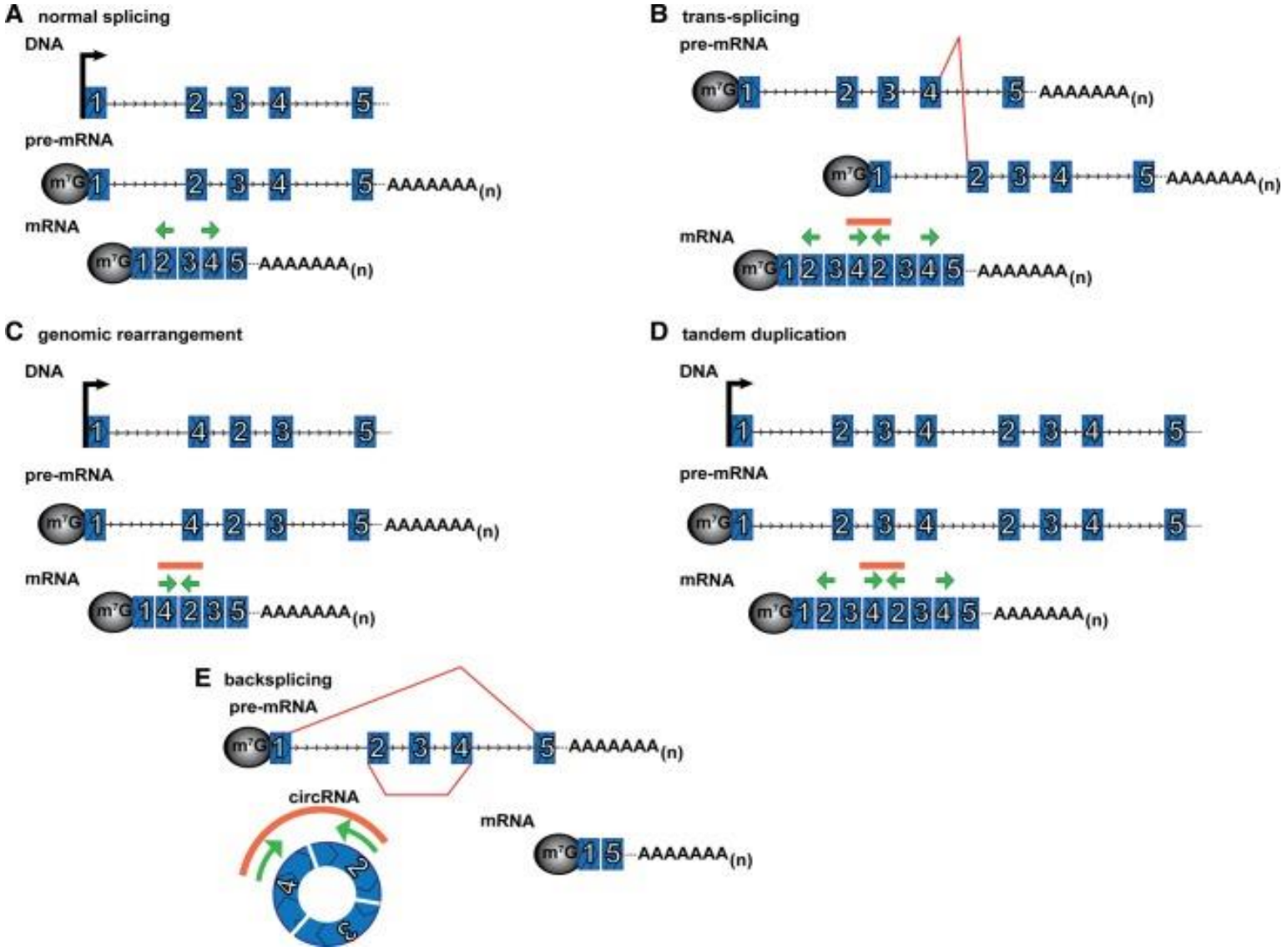
Organism	Sample	circRNA/gene	Support for exon scrambling	Support for circularization	References
Human	39 ENCODE data sets	7112 predicted circRNAs (circRNA fraction ≥10%)	RNA-seq		Guo et al. (2014)
	Cell line (HS68)	25,166 high-confidence circRNAs	RNA-seq	RNA-seq enriched in RNaseR samples in two biological replicates	Jeck et al. (2013)
	Cell line, cells (HEK293, CD19+ leukocytes, CD34+ leukocytes, neutrophils)	1950 predicted circRNAs	RNA-seq		Memczak et al. (2013)
	15 Cell lines (ENCODE data sets)	46,866 predicted circRNAs	RNA-seq		Salzman et al. (2013)
	Cell lines, cells (HeLa, H9, CD19+ leukocytes, CD34+ leukocytes, neutrophils)	2748 predicted circRNAs	RNA-seq	Statistical approach inferred linear tandem duplication for only 23 of these	Salzman et al. (2012)

因为**反向剪切**产生的大多数环都是基于RNA-seq读数的解释来确定的，所以一个重要的问题是这些“环”中有多少是真正的环状RNA。 如表2和表3,3中详述的，使用多种不同的测定法来鉴定和验证环状RNA。

Scrambled exons

- circRNA的一个标准是存在加扰的外显子，其中由于下游和上游剪接位点的连接，RNA序列相对于相应的基因组是无序的。
- 对于单个基因，通过RT-PCR使用针对特定基因的Outward-facing primers（外显子两端向外的引物，在cricRNA 检测中，如果能产生pcr产物，则说明其是环化的）（图5）或通过使用跨越外显子连接的探针的Northern blot来检测加扰的外显子。

Scrambled exons



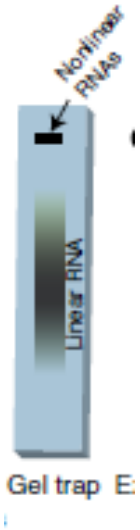
Scrambled exons

Scrambled exon–exon junctions can also originate by alternative mechanisms including DNA rearrangements, tandem duplications in the DNA, and *trans*-splicing.

加扰外显子与外显子的连接也可以来源于替代机制，包括DNA重排，DNA中的串联重复和反式剪切。

Additional criteria for circularity

- 由于不存在5’和3’末端，外切核酸酶抗性已经成为富集circRNAs的常用方法。
- 没有线性mRNA特征---线性mRNA，但不是circRNA，转录本通常是加帽和聚腺苷酸化的……
- TRAP电泳
- 通过凝胶相对于其相应的线性分子的移动性的特征差异来区分环。



PROPERTIES OF EUKARYOTIC circRNAS

- diversity of circRNAs produced by backsplicing
  反式剪切产生的circRNA具有多样性
- the existence of circRNAs is a widespread phenomenon
  circRNA的存在是一个普遍存在的现象
- conserved between different species
  不同的物种之间存在保守性
- circRNAs are expressed at a variety of different levels, and at altered levels in different cell types.

  circRNAs以各种不同的水平表达，并且在不同细胞类型中被改变

PROPERTIES OF EUKARYOTIC circRNAS

- diversity of circRNAs produced by backsplicing

1. Comprise a single exon or multiple exons

2. The size of the spliced circle molecule can range from under 100 nt to over 4 kb

3. A gene that gives rise to a circRNA could encode a single isoform,or many

4. (Some,but not all) Be associated with exon skipping alternative splicing of the corresponding linear transcript

5. Some circRNAs contain some of the same exons as annotated mRNAs, and some are from noncoding RNAs.Some are antisense to annotated genes.

PROPERTIES OF EUKARYOTIC circRNAS

- the existence of circRNAs is a widespread phenomenon

1.Nearly 2000 circ-RNAs have been predicted in mouse sequences, and over 700 in C. elegans

2.Drosophila has RNA sequencing evidence for over 800 scrambled exon spliced junctions

3.in plants (Arabidopsis thaliana), yeast (Schizosaccharomyces pombe and Saccharomyces cerevisiae)（粟酒裂殖酵母和酿酒酵母）, and protists (Plasmodium falciparum and Dictyostelium discoideum)（恶性疟原虫和盘基网柄菌）

PROPERTIES OF EUKARYOTIC circRNAS

- (Some)conserved between different species

genes encoding circles in one species are more likely to also encode circles in the other

Jeck等人（2013）确定了69个包含在小鼠和人之间精确保守的后缀连接的circRNA。

但是特异性circRNAs的其他保守性功能作用，或者促进circRNA形成的pre-mRNA的保守特征仍有待确定。

PROPERTIES OF EUKARYOTIC circRNAS

- circRNAs are expressed at a variety of different levels, and at altered levels in different cell types

1. For most genes with both linear and circular RNA species, the amount of circRNAs is between 0.1% and 10% of the linear amounts,with most <1%.

2.For at least 50 genes the circular form is thought to be more abundant that the linear RNAs

Biogenesis, transport, and degradation of circRNAs

- **circRNA biogenesis**

  环状RNA的生物合成

- **cellular localization of circRNAs**

  环状RNA的细胞定位

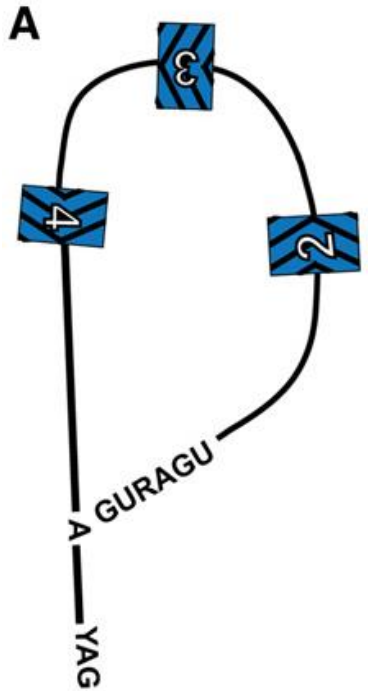
- **circRNA degradation**

  环状RNA的降解

circRNA biogenesis

- **Two features enhance the formation of circRNAs by spliceosomal backsplicing**

1.An intron lariat generated by skipping alternative exons may also bring nonlinear splice sites together

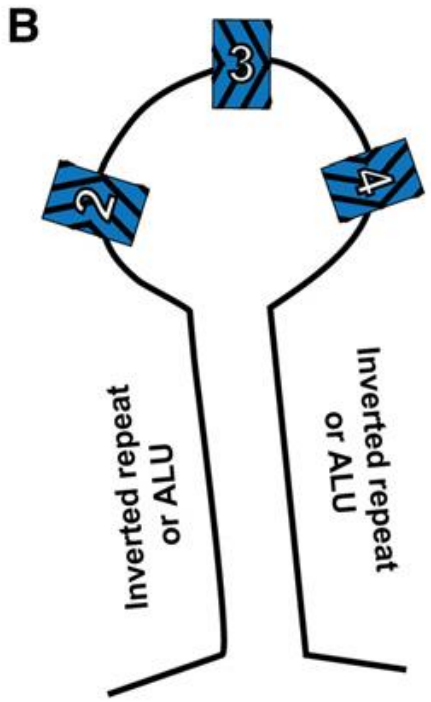


A:

由外显子跳跃而产生的内含子套索

circRNA biogenesis

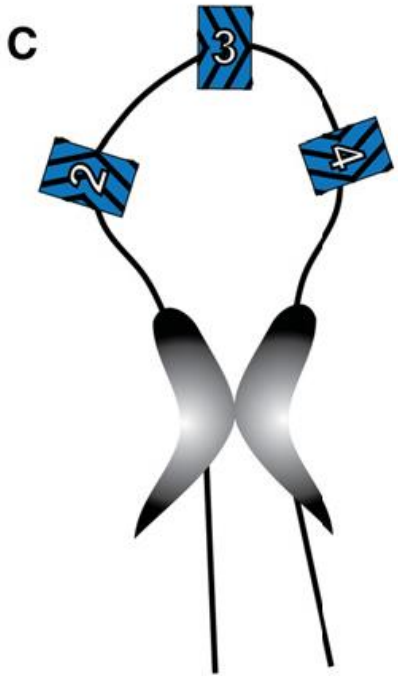
2.structure of the pre-mRNA brings the two splice sites into close proximity



B：
侧链反向重复序列或**ALU**元件形成扩展的碱基配对结构

circRNA biogenesis

- One anticipates that there will be additional mechanisms to facilitate nonlinear splice site pairings, and these may include other cis-acting RNA sequences or trans-acting factors



C:
RNA结合蛋白之间的相互作用形成了侧翼内含子之间的桥梁。

cellular localization of circRNAs

- 已经分析的内源性circRNA大多是属于细胞质的(CircRNAs appear to be efficiently transported to the cytosol since the endogenous circRNAs that have been analyzed are cytoplasmic)

- circRNA标记出核可能涉及剪接过程中外显子复合物的沉积，复合物的沉积可以募集mRNA的出核因子(The manner by which circRNAs are tagged for export is not yet clear but may involve the deposition of an exon-junction complex during splicing, which could then recruit mRNA export factors)

- circRNA通常不被翻译(The circRNAs analyzed are not associated with ribosomes , circRNAs are not generally translated.) (Capel et al. 1993; Jeck et al. 2013;Guo et al. 2014)

circRNA degradation

- 逃避mRNA降解的主要机制 (escape the predominant mechanisms of mRNA degradation)
- 由于circRNA不被翻译，因此不会引发内切核酸酶的切割(quality control systems that trigger endonuclease cleavage on mRNAs with premature nonsense codons, or strong translation stalls, would not be expected to work on circRNAs since they are not translated)
- circRNA具有高稳定性，这表明circRNA可能实际上以非常低的速率产生，但是由于其稳定性高，因此可以累积到可检测的水平。
- 有人预测circRNA的降解大概涉及内切核酸酶裂解

circRNA function

(一) 调节miRNA活性 - **ciRS-7 / CDR1as**

1.circRNA吸附miRNA

由CDR1基因反义的转录物形成的circRNA包含超过70种保守的miR-7配对序列。虽然这个circRNA密集地与Ago蛋白结合，但是配对序列是有限的，从而阻止结合的miR-7引起circRNA的切割。

2. miRNA miR-671可以指导miRNA介导的ciRS-7 / CDR1的切割。新发现的调节miRNA活性的方法，通过隔离特异性miRNA复合物，并且当环状RNA被切割时可能再次释放它们。

3. Hansen et al，2013a; Memczak et al，2013 二个小组证实：circRNA ciRS-7 / CDR1as是保守的、稳定的，它可以调节miR-7的相关性

注：AGO蛋白质主要包含两个结构域：PAZ和PIWI两个结构域。PAZ结构域结合到siRNA 的3’的二核苷酸突出端。PAZ和PIWI两个结构域，对于siRNA和目标mRNA相互作用，从而导致目标mRNA的切割或者翻译抑制过程

circRNA function

调节miRNA活性 - **Sry**

1.小鼠Sry是负责哺乳动物性别决定的基因（决定性别的Y染色体），它可以编码一种特异性的circRNA

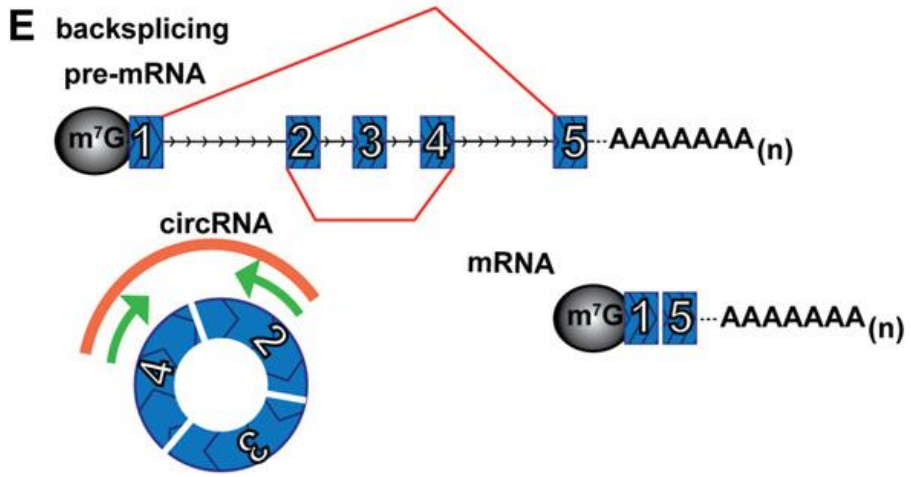
2.1.2-kb单外显子circRNA含有16个miR-138靶位点，所以可能作为miRNA海绵起作用（Hansen等，2013a）

总结：尽管circRNAs ciRS-7 / CDR1as和Sry都作为竞争性内源的RNA（海绵）起作用，但其作用是基于特定的RNA序列和重复序列。因此，这一点是数千个circRNA的一般现象还是基因特异性功能仍然要确定。

circRNA function

(二) circRNA的产生可以对选择性剪切起调节作用

The production of circRNAs is almost certain to also play a role in the regulation of alternative splicing.



circRNA function

(三) circRNA其他可能的功能

前提：鉴于大多数circRNA的丰度低，这可能不会实质上影响靶分子水平

1.circRNA可用于结合和储存组分因子，将因子分类并递送到特定的亚细胞位置，或作为支架其他复合物或反应的装配。

2.虽然一些circRNA具有起始密码子或开放阅读框，并且可以在体外含有IRES因子的人工环状RNA上发生翻译，但是所分析的内源circRNA都没有与核糖体相关联，因此用于翻译circRNA的证据目前还没有

circRNAs in disease

ciRS-7 / CDR1as (the miR-7 circRNA sponge)：其水平的变化会改变 miR-7 靶基因的水平；而miR-7已经被表明具有致癌和肿瘤抑制性质，其功能涉及帕金森病，应激处理，脑发育和细胞增殖（Hansen等人，2013b; Memczak等人2013 ）。

ANRIL：是编码INK4 / ARF基因座附近的lncRNA，ANRIL编码多种RNA同种型，包括圆形变体。 有趣的是，环状ANRIL的表达与atherosclerotic vascular disease（动脉粥样硬化性）的致病风险相关（Burd等，2010）。

Unanswered questions

1. It is not yet apparent what, if any, biological role the majority of circRNAs play;

2.Very little is known about the control of the backsplicing events that generate circRNAs;

3.There is limited information about the localization and degradation of most circRNAs.

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- diversity of circRNAs produced by backsplicing

1. Comprise a single exon or multiple exons

2. The size of the spliced circle molecule can range from under 100 nt to over 4 kb

3. A gene that gives rise to a circRNA could encode a single isoform,or many

4. (Some,but not all) Be associated with exon skipping alternative splicing of the corresponding linear transcript

5. Some circRNAs contain some of the same exons as annotated mRNAs, and some are from noncoding RNAs.Some are antisense to annotated genes.

PROPERTIES OF EUKARYOTIC circRNAS

- the existence of circRNAs is a widespread phenomenon

1.Nearly 2000 circ-RNAs have been predicted in mouse sequences, and over 700 in C. elegans

2.Drosophila has RNA sequencing evidence for over 800 scrambled exon spliced junctions

3.in plants (Arabidopsis thaliana), yeast (Schizosaccharomyces pombe and Saccharomyces cerevisiae)（粟酒裂殖酵母和酿酒酵母）, and protists (Plasmodium falciparum and Dictyostelium discoideum)（恶性疟原虫和盘基网柄菌）

PROPERTIES OF EUKARYOTIC circRNAS

- (Some)conserved between different species

genes encoding circles in one species are more likely to also encode circles in the other

Jeck等人（2013）确定了69个包含在小鼠和人之间精确保守的后缀连接的circRNA。

但是特异性circRNAs的其他保守性功能作用，或者促进circRNA形成的pre-mRNA的保守特征仍有待确定。

PROPERTIES OF EUKARYOTIC circRNAS

- circRNAs are expressed at a variety of different levels, and at altered levels in different cell types

1. For most genes with both linear and circular RNA species, the amount of circRNAs is between 0.1% and 10% of the linear amounts,with most <1%.

2.For at least 50 genes the circular form is thought to be more abundant that the linear RNAs

Biogenesis, transport, and degradation of circRNAs

- **circRNA biogenesis**

  环状RNA的生物合成

- **cellular localization of circRNAs**

  环状RNA的细胞定位

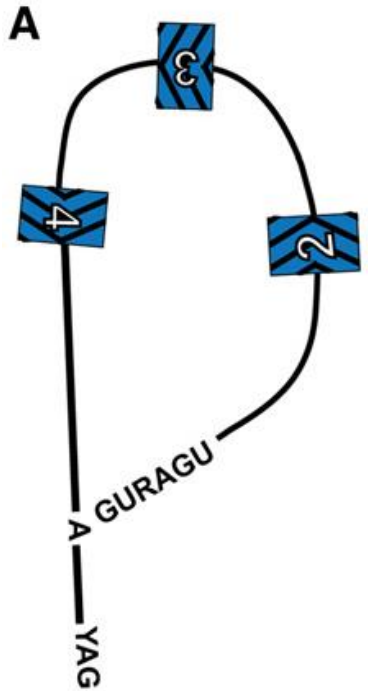
- **circRNA degradation**

  环状RNA的降解

circRNA biogenesis

- **Two features enhance the formation of circRNAs by spliceosomal backsplicing**

1.An intron lariat generated by skipping alternative exons may also bring nonlinear splice sites together

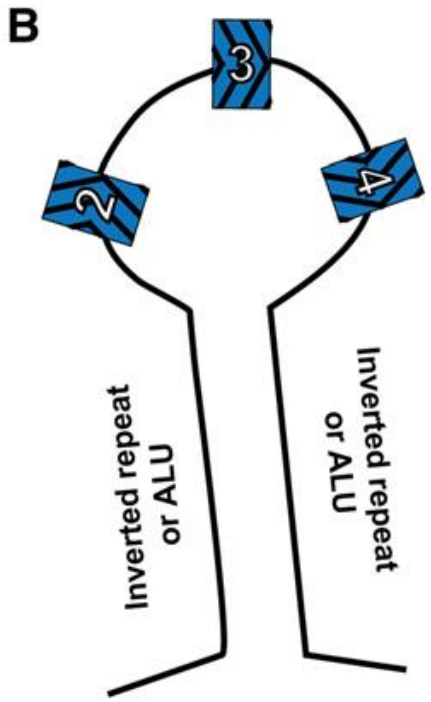


A:

由外显子跳越而产生的内含子套索

circRNA biogenesis

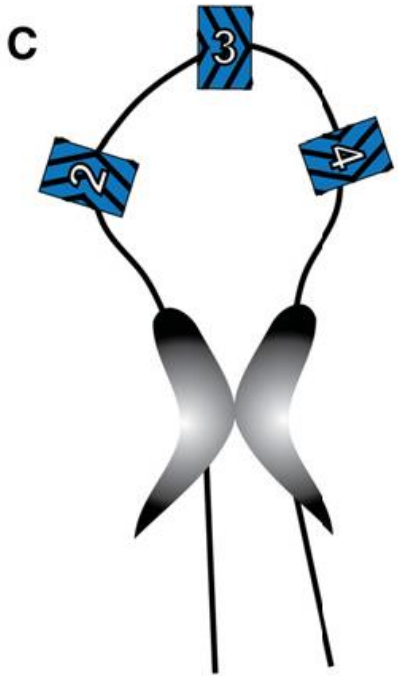
2.structure of the pre-mRNA brings the two splice sites into close proximity



B：
侧链反向重复序列或**ALU**元件形成扩展的碱基配对结构

circRNA biogenesis

- One anticipates that there will be additional mechanisms to facilitate nonlinear splice site pairings, and these may include other cis-acting RNA sequences or trans-acting factors



C:
RNA结合蛋白之间的相互作用形成了侧翼内含子之间的桥梁。

cellular localization of circRNAs

- 已经分析的内源性circRNA大多是属于细胞质的(CircRNAs appear to be efficiently transported to the cytosol since the endogenous circRNAs that have been analyzed are cytoplasmic)

- circRNA标记出核可能涉及剪接过程中外显子复合物的沉积，其可以募集mRNA的出核因子(The manner by which circRNAs are tagged for export is not yet clear but may involve the deposition of an exon-junction complex during splicing, which could then recruit mRNA export factors)

- circRNA通常不被翻译(The circRNAs analyzed are not associated with ribosomes , circRNAs are not generally translated.) (Capel et al. 1993; Jeck et al. 2013;Guo et al. 2014)

circRNA degradation

- 逃避mRNA降解的主要机制 (escape the predominant mechanisms of mRNA degradation)
- 由于circRNA不被翻译，因此不会引发内切核酸酶的切割(quality control systems that trigger endonuclease cleavage on mRNAs with premature nonsense codons, or strong translation stalls, would not be expected to work on circRNAs since they are not translated)
- circRNA具有高稳定性，这表明circRNA可能实际上以非常低的速率产生，但是由于其稳定性高，因此可以累积到可检测的水平。
- 有人预测circRNA的降解大概涉及内切核酸酶裂解

circRNA function

(一) 调节miRNA活性 - **ciRS-7 / CDR1as**

1.circRNA吸附miRNA

由CDR1基因反义的转录物形成的circRNA包含超过70种保守的miR-7配对序列。虽然这个circRNA密集地与Ago蛋白结合，但是配对序列是有限的，从而阻止结合的miR-7引起circRNA的切割。

2. miRNA miR-671可以指导miRNA介导的ciRS-7 / CDR1的切割。新发现的调节miRNA活性的方法，通过隔离特异性miRNA复合物，并且当环状RNA被切割时可能再次释放它们。

3. Hansen et al，2013a; Memczak et al，2013 二个小组证实：circRNA ciRS-7 / CDR1as是保守的、稳定的，它可以调节miR-7的相关性

注：AGO蛋白质主要包含两个结构域：PAZ和PIWI两个结构域。PAZ结构域结合到siRNA 的3’的二核苷酸突出端。PAZ和PIWI两个结构域，对于siRNA和目标mRNA相互作用，从而导致目标mRNA的切割或者翻译抑制过程

circRNA function

调节miRNA活性 - **Sry**

1.小鼠Sry是负责哺乳动物性别决定的基因（决定性别的Y染色体），它可以编码一种特异性的circRNA

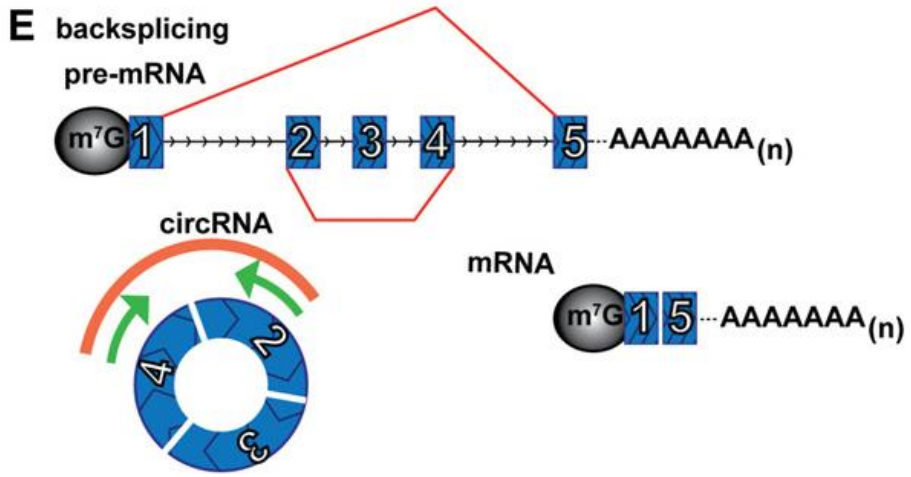
2.1.2-kb单外显子circRNA含有16个miR-138靶位点，所以可能作为miRNA海绵起作用（Hansen等，2013a）

总结：尽管circRNAs ciRS-7 / CDR1as和Sry都作为竞争性内源的RNA（海绵）起作用，但其作用是基于特定的RNA序列和重复序列。因此，这一点是数千个circRNA的一般现象还是基因特异性功能仍然要确定。

circRNA function

(二) circRNA的产生可以对选择性剪切起调节作用

The production of circRNAs is almost certain to also play a role in the regulation of alternative splicing.



circRNA function

(三) circRNA其他可能的功能

前提：鉴于大多数circRNA的丰度低，这可能不会实质上影响靶分子水平

1.circRNA可用于结合和储存组分因子，将因子分类并递送到特定的亚细胞位置，或作为支架其他复合物或反应的装配。

2.虽然一些circRNA具有起始密码子或开放阅读框，并且可以在体外含有IRES因子的人工环状RNA上发生翻译，但是所分析的内源circRNA都没有与核糖体相关联，因此用于翻译circRNA的证据目前还没有

circRNAs in disease

ciRS-7 / CDR1as (the miR-7 circRNA sponge)：其水平的变化会改变 miR-7 靶基因的水平；而miR-7已经被表明具有致癌和肿瘤抑制性质，其功能涉及帕金森病，应激处理，脑发育和细胞增殖（Hansen等人，2013b; Memczak等人2013 ）。

ANRIL：是编码INK4 / ARF基因座附近的lncRNA，ANRIL编码多种RNA同种型，包括圆形变体。 有趣的是，环状ANRIL的表达与atherosclerotic vascular disease（动脉粥样硬化性）的致病风险相关（Burd等，2010）。

Unanswered questions

1. It is not yet apparent what, if any, biological role the majority of circRNAs play;

2.Very little is known about the control of the backsplicing events that generate circRNAs;

3.There is limited information about the localization and degradation of most circRNAs.

相关网址

- circBase website：http://circbase.org/

- 搞懂环状RNA：file:///C:/Users/Administrator/Documents/Tencent%20Files/961372045/FileRecv/circRNA.html

Thank You