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# miRNA: 开启基因表达调控新纪元——浅析2024年度诺贝尔生理学或医学奖

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基因表达调控是生物体内决定细胞类型和功能, 确保生物体维持正常生理功能并适应环境变化的关键机制, 涉及DNA转录成RNA、RNA翻译成蛋白质以及蛋白质修饰、复合体组装、降解等过程. 微小核糖核酸(microRNA, miRNA)是真核生物中普遍存在的一类非编码小RNA, 通过序列互补与特定mRNA结合来精准调控靶基因表达, 对细胞分化、发育、免疫反应和疾病发生具有重要作用. 2024年诺贝尔生理学或医学奖授予了美国科学家Victor Ambros和Gary Ruvkun, 以表彰他们"发现miRNA及其在转录后基因调控中的作用"的卓越贡献. 本文将探讨miRNA的发现历程、功能执行的方式以及对现代医药和先进农业的影响, 揭示miRNA的奥秘和科学对人类的贡献.

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## 1 miRNA的发现

1993年, Victor Ambros和Gary Ruvkun在模式生物秀丽隐杆线虫中发现了第一个miRNA——lin-4及其基因调控作用. 他们发现, 敲除*lin-4*基因和过表达*lin-14*基因的线虫表现出相同的发育缺陷, 表明两个基因的功能是互补的. Ambros确定了*lin-4*基因的序列, 发现它不编码蛋白, 而是表达一种长度为22个核苷酸的RNA分子[1]. Gary Ruvkun则将受lin-4负调控的靶序列定位到了*lin-14* mRNA的3′非翻译区(3′-untranslated region, 3′-UTR)[2]. 他们共同意识到*lin-4*产生的小RNA可能会抑制*lin-14*基因的表达. 随后, 他们在*Cell*杂志上同期发表了论文, 提出了一种对中心法则"DNA→RNA→蛋白质"所阐述的基因表达模式的全新的调控机制: *lin-4*产生的这种小RNA能够与*lin-14* mRNA的3′-UTR互补, 从而抑制*lin-14*的翻译. 然而, 由于lin-4序列并不保守, 这一发现被认为是线虫特有的, 并未受到科学界的广泛关注. 直至2000年, Ruvkun实验室在线虫中发现了第二个具有类似功能的基因*let-7*, 其编码的21个核苷酸的RNA也能通过结合靶基因(例如*lin-14*、*lin-28*、*lin-41*、*lin-42*以及*daf-12*)mRNA的3′-UTR来调节线虫的发育[3,4]. 与lin-4不同, let-7在动物中高度保守[4], 因此科学界开始认识到这种小RNA可能在多个物种中普遍存在并具有普适性的基因表达调控作用. 2001年10月, Ambros实验室通过生物信息学和cDNA克隆技术在线虫中又发现了15个编码这种小RNA的基因[5]. 与此同时, Thomas Tuschl[6]和David Bartel[7]团队也在线虫、果蝇和人类细胞中发现了多个小RNA并鉴定了它们的序列. 他们在*Science*杂志上同期发文, 将这种小RNA命名为microRNA(miRNA).

2002年是植物miRNA研究的开端, David Bartel[8]、James C Carrington[9]与Xuemei Chen[10]领导的团队分别在模式植物拟南芥中发现了miRNA, 他们还发现植物miRNA与靶基因mRNA序列具有高度互补配对的特性. 2006年之后, 随着二代测序技术的发展, 生命科学领域进入了高通量时代, 在人类、小鼠、大鼠、斑马鱼、果蝇、水稻、拟南芥等多种物种中陆续发现了很多miRNA, 包括一些低丰度的miRNA[11~13]. 至今, miRNA基因数据库miRBase已收集了271种生物中38000多个miRNA前体(pre-miRNA)和48860个成熟miRNA, 这反映了miRNA研究领域的快速发展.

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## 2 miRNA的生物合成及作用方式

### 2.1 miRNA的生物合成

miRNA是一类长20~24个核苷酸的内源性非编码小RNA[14], 在基因表达调控中扮演着关键角色. miRNA的生物合成过程涉及多个精细调控的步骤: *MIR*基因首先被RNA聚合酶II(少数情况下为RNA聚合酶III)转录, 产生初级转录本(pri-miRNA), 其长度大约为300~1000个核苷酸. 在动物细胞核中, RNase III家族核酸内切酶Drosha将pri-miRNA加工成约65个核苷酸的pre-miRNA[15]. pre-miRNA被转运蛋白exportin 5转运到细胞质中[16], 被核酸内切酶Dicer进一步切割, 产生约22个核苷酸的miRNA:miRNA*二聚体[17]. 随后, miRNA:miRNA*二聚体中的miRNA链通常被装载到ARGONAUTE (AGO)蛋白中, 形成RNA介导的沉默复合体(RNA-induced silencing complex, RISC)来抑制靶基因的表达. miRNA*链通常会被降解[18], 但少数miRNA*链也可与AGO蛋白结合并调控基因表达.

植物miRNA的合成过程与动物有所不同. 首先, 植物中pri-miRNA到成熟miRNA的两步切割过程完全发生在细胞核内[19], 并且大多数植物miRNA在细胞核内装载到AGO蛋白上[20]. 其次, 植物中没有Drosha的同源蛋白, 两步切割主要由同一个内切酶DICER-LIKE 1完成[21]. 再次, 动物中一个pri-miRNA可以产生多个pre-miRNA 以及相应的成熟miRNA[22], 而植物中一般只产生一个成熟的miRNA. 最后, 植物miRNA的3′端会被HUA ENHANCER 1甲基化, 而动物中的大多数miRNA则不发生这种修饰[23].

### 2.2 miRNA的作用方式

在动物中, miRNA通过其种子序列(5′端第2~8位核苷酸)识别并结合到靶基因mRNA的3′-UTR区域, 主要通过两种机制发挥作用: 促进mRNA降解或抑制其翻译[24,25]. miRNA主要通过与AGO蛋白形成的RISC来发挥对mRNA的降解作用, AGO蛋白可以与GW182蛋白互作, 随后GW182招募一系列脱腺苷化酶复合物, 使mRNA末端失去保护, 进而通过5′-3′ RNA核酸外切酶和3′-5′ RNA核酸外切酶实现mRNA降解, 以抑制该基因的表达[26]. 此外, 有证据表明, RISC通过从mRNA上移除真核细胞翻译起始因子4F(eukaryotic translation initiation factor 4F, eIF4F)的组分(如eIF4A)来阻止eIF4F复合物的形成, 进而抑制翻译起始, 导致靶mRNA的翻译受到阻碍[27].

在植物中, miRNA与靶标mRNA序列高度互补, 可以通过剪切靶mRNA来发挥沉默效应[28]. 此外, 植物中也广泛存在miRNA介导的翻译抑制现象, 例如拟南芥miR172靶向*APETALA 2*基因, 导致其编码蛋白水平下降, 而mRNA水平没有明显变化, 揭示了植物miRNA可以抑制靶mRNA的翻译, 并且翻译抑制独立于mRNA降解[20]. 这些发现揭示了miRNA在动植物中不同的调控机制, 以及它们在基因表达调控中的复杂作用.

## 3 miRNA的重要性及应用前景

miRNA的发现标志着基因表达调控领域的一个新纪元, 这一突破性成果终于在31年后登榜诺贝尔生理学或医学奖. Ambros和Ruvkun对miRNA及其转录后调控作用的研究, 揭示了生命过程中一个全新的调控层面, 颠覆了人们对基因调控的认知. 虽然lin-4的研究最初并未被重视, 但是随着let-7的发现和二代测序技术的进步, 非编码RNA的研究逐渐成为热点, miRNA的重要性也随之被广泛认可. 对于现代研究人员而言, miRNA的发现本身已不再是研究的核心, 更关键的挑战在于如何将miRNA的应用扩展到生产和生活实践中, 这要求我们深入理解miRNA的作用机制.

miRNA参与调控动物发育和各种生理病理过程, 其临床应用能力巨大且不局限于特定疾病. 截至目前, 约有十几款miRNA药物进入I期和II期临床试验, 适应症包括亨廷顿病、小细胞肺癌、慢性丙型肝炎等(表1)[29]. miRNA治疗目前主要有两种方法: miRNA模拟物(miRNA mimics)和抗miRNA (antimiRs). miRNA mimics通常通过模拟内源miRNA, 从而弥补在疾病过程中丧失功能的miRNA; antimiRs则通过结合并抑制内源过表达的miRNA的功能, 起到相反的作用[30]. 然而, miRNA靶向基因的特异性相对较低, 容易产生脱靶效应, 导致药物副作用, 其弊端显而易见[30]. 迄今为止, 尚无miRNA药物进入III期临床试验或获得FDA批准上市[29], 因此, miRNA药物开发与应用仍面临巨大挑战.

miRNA药物的开发主要面临以下两点问题: (1) 一个miRNA可能同时靶向多个基因, 对于下游靶基因的调控成网络形式. 鉴于miRNA是内源的、对生理过程起调控功能的元件, 其在疾病诊断方面具有巨大潜能. 但其巨大潜能的反面就是问题的根源, 目前miRNA的生物学功能并未达到完全明晰, 这使得miRNA靶点的选择与验证遇到极大困难. (2) miRNA的递送同样是一大难点. 目前miRNA的递送方式包括基于病毒载体的递送系统与基于纳米载体的递送系统(比如脂质纳米颗粒、仿生纳米载体等)[31], 但这些方法均未能达到非常良好的效果, miRNA的递送方式仍有待改进. 尽管miRNA药物的开发仍存在诸多问题, 但其前景依然光明, 我们相信在不远的将来, miRNA治疗可以成为临床中的重要医疗手段.

在农业领域, miRNA的应用前景同样广阔. miRNA可作为靶点进行农作物农艺性状改良. 例如, 基于水稻中miR156及其靶基因*Ideal Plant Architecture 1*的研究, 已开发出高产抗病的水稻新品系[32]. 此外, 人工miRNA(artificial miRNA, amiRNA)技术已成功应用于动植物中, 通过设计特定序列的amiRNA来调控靶基因的表达[33,34], 这进一步展示了miRNA在临床实践和农业发展中的潜力.

**表 1** 目前进入临床试验阶段的miRNA药物

**Table 1** miRNA-based drugs in clinical trials

| 药物名称 | miRNA | 适应证 | 临床试验阶段 |
|---|---|---|---|
| miR-10b | miR-10b | 星形细胞瘤、少突胶质细胞瘤、少突星形细胞瘤、间变性星形细胞瘤、间变性少突胶质细胞瘤、间变性少突星形细胞瘤、胶质母细胞瘤、脑肿瘤等 | 观察性试验 |
| RG-101 | miR-122 | 慢性丙型肝炎 | 观察性试验 |
| Serum MicroRNA-25 | miR-25 | 胰腺肿瘤 | 观察性试验 |
| INT-1B3 | miR-193a-3p模拟物 | 晚期实体瘤 | I期 |
| AMT-130 | 人工miRNA | 亨廷顿病 | I期 |
| RGLS4326 | miR-17 | 常染色体显性遗传多囊肾病 | I期 |
| MesomiR 1 | miR-16 | 恶性胸膜间皮瘤、非小细胞肺癌 | I期 |
| CDR132L | miR-132 | 心力衰竭 | I期 |
| RG-012/lademirsen/SAR339375 | miR-21 | 奥尔波特综合征 | II期 |
| Remlarsen/MRG-201 | miR-29 | 瘤样瘢痕 | II期 |
| Miravirsen/SPC3649 | miR-122 | 慢性丙型肝炎 | II期 |
| RG-101 | miR-122 | 慢性丙型肝炎 | II期 |
| MRX34 | miR-34a | 实体瘤(肝细胞癌、黑色素瘤、小细胞肺癌、非小细胞肺癌、淋巴瘤、多发性骨髓瘤、肾细胞癌等) | II期 |
| Cobomarsen/MRG-106 | miR-155 | 蕈样肉芽肿、皮肤T细胞淋巴瘤、慢性淋巴细胞白血病、弥漫性大B细胞淋巴瘤、成人T细胞白血病/淋巴瘤 | II期 |

## 4 结语

在今年的诺贝尔生理学或医学奖颁奖典礼上，miRNA研究以其在基因表达调控领域的革命性贡献获得殊荣，开启了该领域的新纪元. 这一荣誉实至名归. 正如所有科学研究领域一样，人工智能(AI)在miRNA研究中的应用，特别是在RNA和蛋白质结构预测以及深度学习领域，将极大地推动我们对miRNA生物合成和功能深层机制的理解，加速科学发现的步伐. 为了进一步推进miRNA研究的发展，我们需要开发更高精度的时间和空间分辨率技术，以实现对miRNA的检测、定量、可视化和操控. 这些技术的进步将为miRNA研究提供更深入的洞察，为人类健康带来福祉，并为该领域描绘一个更加辉煌的未来.

未来miRNA研究有几个关键方向值得关注. 首先是miRNA在癌症诊断与治疗中的应用, 特别是作为肿瘤标志物的潜力. 其次是miRNA在神经退行性疾病中的作用，如阿尔茨海默病和帕金森病的研究. 此外，miRNA在代谢性疾病和感染性疾病中的调控作用，以及新的miRNA生物标志物的开发也是重要领域. 最后, 改进miRNA递送技术, 将进一步推动miRNA在临床中的应用. 我们满怀期待，相信这些重大科学进展将为人类健康事业带来革命性的变革.

## 推荐阅读文献


1 Lee R C, Feinbaum R L, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. Cell, 1993, 75: 843–854

2 Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene *lin-14* by *lin-4* mediates temporal pattern formation in *C. elegans*. Cell, 1993, 75: 855–862

3 Reinhart B J, Slack F J, Basson M, et al. The 21-nucleotide *let-7* RNA regulates developmental timing in *Caenorhabditis elegans*. Nature, 2000, 403: 901–906

4 Pasquinelli A E, Reinhart B J, Slack F, et al. Conservation of the sequence and temporal expression of *let-7* heterochronic regulatory RNA. Nature, 2000, 408: 86–89

5 Lee R C, Ambros V. An Extensive Class of Small RNAs in *Caenorhabditis elegans*. Science, 2001, 294: 862–864

6 Lagos-Quintana M, Rauhut R, Lendeckel W, et al. Identification of novel genes coding for small expressed RNAs. Science, 2001, 294: 853–858

7 Lau N C, Lim L P, Weinstein E G, et al. An abundant class of tiny RNAs with probable regulatory roles in *Caenorhabditis elegans*. Science, 2001, 294: 858–862

8 Reinhart B J, Weinstein E G, Rhoades M W, et al. MicroRNAs in plants. Genes Dev, 2002, 16: 1616–1626

9 Llave C, Xie Z, Kasschau K D, et al. Cleavage of *Scarecrow-like* mRNA targets directed by a class of *Arabidopsis* miRNA. Science, 2002, 297: 2053–2056

10 Park W, Li J, Song R, et al. CARPEL FACTORY, a dicer homolog, and HEN1, a novel protein, act in microRNA metabolism in *Arabidopsis thaliana*. Curr Biol, 2002, 12: 1484–1495

11 Griffiths-Jones S, Grocock R J, van Dongen S, et al. miRBase: microRNA sequences, targets and gene nomenclature. Nucleic Acids Res, 2006, 34: D140–D144

12 Landgraf P, Rusu M, Sheridan R, et al. A mammalian microRNA expression atlas based on small RNA library sequencing. Cell, 2007, 129: 1401–1414

13 Fahlgren N, Howell M D, Kasschau K D, et al. High-throughput sequencing of *Arabidopsis* microRNAs: evidence for frequent birth and death of *MIRNA* genes. PLoS One, 2007, 2: e219

14 Yu Y, Zhang Y, Chen X, et al. Plant noncoding RNAs: hidden players in development and stress responses. Annu Rev Cell Dev Biol, 2019, 35: 407–431

15 Lee Y, Jeon K, Lee J T, et al. MicroRNA maturation: stepwise processing and subcellular localization. EMBO J, 2002, 21: 4663–4670

16 Yi R, Qin Y, Macara I G, et al. Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. Genes Dev, 2003, 17: 3011–3016

17 MacRae I J, Doudna J A. Ribonuclease revisited: structural insights into ribonuclease III family enzymes. Curr Opin Struct Biol, 2007, 17: 138–145

18 Diederichs S, Haber D A. Dual role for argonautes in microRNA processing and posttranscriptional regulation of microRNA expression. Cell, 2007, 131: 1097–1108

19 Wang J, Mei J, Ren G. Plant microRNAs: biogenesis, homeostasis, and degradation. Front Plant Sci, 2019, 10: 360

20 Chen X. A microRNA as a translational repressor of *APETALA2* in *Arabidopsis* flower development. Science, 2004, 303: 2022–2025

21 Kurihara Y, Watanabe Y. *Arabidopsis* micro-RNA biogenesis through Dicer-like 1 protein functions. Proc Natl Acad Sci USA, 2004, 101: 12753–12758

22 Lagos-Quintana M, Rauhut R, Yalcin A, et al. Identification of tissue-specific microRNAs from mouse. Curr Biol, 2002, 12: 735–739

23 Yang Z, Ebright Y W, Yu B, et al. HEN1 recognizes 21-24 nt small RNA duplexes and deposits a methyl group onto the 2′ OH of the 3′ terminal nucleotide. Nucleic Acids Res, 2006, 34: 667–675

24 Zeng Y, Wagner E J, Cullen B R. Both natural and designed micro RNAs can inhibit the expression of cognate mRNAs when expressed in human cells. Mol Cell, 2002, 9: 1327–1333

25 Zeng Y, Yi R, Cullen B R. MicroRNAs and small interfering RNAs can inhibit mRNA expression by similar mechanisms. Proc Natl Acad Sci USA, 2003, 100: 9779–9784

26 Jonas S, Izaurralde E. Towards a molecular understanding of microRNA-mediated gene silencing. Nat Rev Genet, 2015, 16: 421–433

27 Iwakawa H, Tomari Y. Life of RISC: formation, action, and degradation of RNA-induced silencing complex. Mol Cell, 2022, 82: 30–43

28 German M A, Pillay M, Jeong D H, et al. Global identification of microRNA–target RNA pairs by parallel analysis of RNA ends. Nat Biotechnol, 2008, 26: 941–946

29 Seyhan A A. Trials and tribulations of microRNA therapeutics. Int J Mol Sci, 2024, 25: 1469

30 No authors listed. What will it take to get miRNA therapies to market? Nat Biotechnol, 2024, 42: 1623–1624

31 Forterre A, Komuro H, Aminova S, et al. A comprehensive review of cancer microRNA therapeutic delivery strategies. Cancers, 2020, 12: 1852

32 Jiao Y, Wang Y, Xue D, et al. Regulation of *OsSPL14* by OsmiR156 defines ideal plant architecture in rice. Nat Genet, 2010, 42: 541–544

33 Niu Q W, Lin S S, Reyes J L, et al. Expression of artificial microRNAs in transgenic *Arabidopsis thaliana* confers virus resistance. Nat Biotechnol, 2006, 24: 1420–1428

34 Schwab R, Ossowski S, Riester M, et al. Highly specific gene silencing by artificial microRNAs in *Arabidopsis*. Plant Cell, 2006, 18: 1121–1133

**Summary for** “miRNA: 开启基因表达调控新纪元——浅析2024年度诺贝尔生理学或医学奖”

# miRNA: starting a new era of understanding gene expression regulation—an introduction of the 2024 Nobel Prize in Physiology or Medicine

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The 2024 Nobel Prize in Physiology or Medicine was awarded to American scientists Victor Ambros and Gary Ruvkun for their groundbreaking discovery of microRNAs (miRNAs) and their pivotal role in post-transcriptional gene regulation. Gene expression regulation is essential for cell fate determination and cellular activities within organisms, ensuring the maintenance of normal physiological functions and adaptability to environmental changes. miRNAs are a class of non-coding small RNAs that precisely regulate target gene expression through sequence complementarity, playing pivotal roles in development, immune responses, and disease progression.

The journey of miRNA discovery began in 1993 when Victor Ambros identified the first miRNA, lin-4, in the model organism *Caenorhabditis elegans*. Meanwhile, Gary Ruvkun’s laboratory localized the target sequence recognized by lin-4 to the 3′ untranslated region (3′-UTR) of the *lin-14* mRNA. In 2000, Gary Ruvkun identified the second miRNA, let-7, a conserved miRNA across animal species. This discovery highlighted the universal regulatory role of these short RNAs and further advanced the field of miRNA research. By 2001, multiple miRNAs were identified in diverse organisms, leading to the formal introduction of the term “microRNA”. The field expanded rapidly with the advent of high-throughput sequencing technologies, resulting in the identification of numerous miRNAs across various species.

miRNAs are endogenous non-coding small RNAs, typically 20-24 nucleotides long, that play key roles in gene expression regulation. Their biogenesis involves several finely regulated steps. In animals, primary miRNA transcripts (pri-miRNAs) are processed in the nucleus by the RNase III enzyme Drosha into precursor miRNAs (pre-miRNAs), which are then exported to the cytoplasm and further processed by Dicer into mature miRNA:miRNA* duplexes. One strand within the duplex is incorporated into the RNA-induced silencing complex (RISC), and guides the RISC to target mRNAs for degradation or translational inhibition. In contrast, in plants, the processing of pri-miRNAs into mature duplexes and the assembly of RISC both take place within the nucleus, after which the RISC is exported to the cytoplasm.

The mechanism of miRNA action differs between animals and plants. In animals, miRNAs recognize target mRNAs via their seed region (the 2nd to 8th nucleotides from the 5′ end) and are thought to predominantly bind to the 3′-UTR of target mRNAs, thereby inhibiting translation or promoting mRNA degradation. In contrast, plant miRNAs exhibit near-perfect complementarity to target mRNAs, leading to mRNA cleavage and translation inhibition.

The discovery of miRNAs has revolutionized our understanding of gene expression regulation. This breakthrough earned Victor Ambros and Gary Ruvkun the Nobel Prize. Their research uncovered a novel layer of gene regulation that occurs at the RNA level in the central dogma of molecular biology. The significance of miRNAs extends beyond basic research into clinical and agricultural applications. Numerous miRNA-based therapeutics are currently under development; however, the progress of miRNA therapeutics faces numerous challenges. In agriculture, miRNAs are being utilized to improve crop traits, such as developing high-yield, disease-resistant rice varieties.

The recognition of miRNA research by the Nobel Prize underscores its transformative impact on the field of gene expression regulation. Future research will likely focus on leveraging miRNAs in clinical and agricultural settings, further realizing their potential to benefit human health and agriculture.

**miRNA, gene expression regulation, non-coding RNAs, RISC, dicer**

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