综述

程红，中国科学院分子细胞科学卓越创新中心(原上海生物化学与细胞生物学研究所)研究组长、研究员、博士生导师，中国科学院“百人计划”和上海市“浦江人才计划”获得者。1998年毕业于中国医科大学，获医学学士学位；2003年毕业于日本神户大学，获博士学位。2003年至2008年，在美国哈佛大学医学院细胞生物学系从事博士后研究。2008年回国，担任中国科学院上海生物化学与细胞生物学研究所研究员。主要从事RNA转运与降解的机制和功能研究，旨在揭示新生RNA出核转运或核内降解命运决定的机制、调控和生物学意义，重点研究方向包括：mRNA出核与pre-mRNA加工的复杂关联、RNA的质量控制和核内降解及其调控、细胞亚核结构调控RNA出核或降解的生理病理机制。自2008年独立组建以来，实验室获得了一系列前沿性进展，先后在*Mol Cell*、*Genes Dev*、*EMBO J*、*PNAS*、*J Cell Biol*、*Nucleic Acids Res*等国际知名学术期刊上发表多篇具有重要影响力的论文。近期发表论文被F1000 Prime推荐、生物通和BioArt等专评，并被国际知名期刊*Nat Rev Genet*等正面引用和评述。

RNA出核转运及其调控

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摘要：生物体中遗传信息的传递遵循中心法则，即从基因组DNA传递到RNA，再进一步传递到蛋白质。作为遗传信息传递的中间一环，RNA需要在细胞核中生成，并进一步被转运到细胞质中，其中涉及的RNA出核转运过程则是保证遗传信息精确传递的重要步骤，并参与了基因表达的精确调控过程。绝大多数的mRNA通常在细胞核内包装形成mRNP，并在TREX复合体(transcription-export complex，TREX)和出核因子NXF1(nuclear RNA export factor 1)的帮助下转运出核。另有一小部分的mRNA则以CRM1(chromosome region maintenance protein 1)依赖的方式进行出核转运。大量研究表明，mRNA出核过程不仅与上游的转录和加工相偶联，而且能够反向调控上游步骤。此外，细胞核中RNA的出核机器与降解机器相互竞争，共同决定新生RNA的核内命运。尤为重要的是，当mRNA出核受阻时，在细胞和个体层面上会产生不同程度的生理或病理缺陷。最新的研究表明，除mRNA以外，circRNA和lncRNA等其他RNA分子也被认为能够转运出核并翻译产生蛋白质，参与各类生物学过程的调控，其出核过程则涉及一些新的受体因子和调控蛋白。本文将结合最新的研究进展，对已知RNA出核转运通路的相关具体过程和调控机制进行总结，并对领域内后续研究的重难点进行讨论和展望。

关键词：RNA出核转运；TREX复合体；NXF1；mRNP包装；核质运输

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Mechanism and regulation of RNA nuclear export

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Abstract: The transmission of genetic information in organisms usually follows the genetic central dogma, which means the genetic information transfers from genomic DNA to RNA, and then further to protein. As an intermediate link in this transmission, RNA molecules need to be generated in the nucleus and further transported to the cytoplasm. So RNA nuclear export is a key step to ensure the correct transmission of genetic information and the precise regulation of gene expression. The majority of mRNAs are usually packaged to mRNPs in nucleus, which are exported by transcription-export complex (TREX) and nuclear RNA export factor 1 (NXF1). Meanwhile, a small portion of mRNAs are exported in a chromosome region maintenance protein 1 (CRM1)-dependent manner. Numerous studies have shown that mRNA nuclear export is not only coupled to upstream transcription and processing, but also as a new pathway to regulate upstream mRNA processes. Additionally, the RNA nuclear export machinery competes with the degradation machinery and determines nascent mRNAs fate. More importantly, blocking mRNA nuclear export can produce varying degrees of physiological or pathological defects at cellular and animal levels. According to latest research, other RNA molecules like circRNA and lncRNA, which have been found to be exported to cytoplasm and regulated different biological processes by producing proteins through translation, are exported by utilizing several new receptors and adaptors. In this review, we will summarize the known RNA nuclear export pathways about their specific mechanisms and regulations by following the latest scientific progresses, and highlight the key points of subsequent research in related field.

Key Words: RNA nuclear export; TREX complex; NXF1; mRNP packaging; nucleocytoplasmic transport

在真核细胞中，核膜将细胞分隔成细胞核和细胞质两个区室，DNA作为遗传信息的载体存在于细胞核中，而蛋白质作为生命活动的主要承担者，主要在细胞质中进行合成。RNA作为一种传递遗传信息的大分子，往往在细胞核中以DNA为模版转录产生，而后进一步转运到细胞质中，作为翻译机器的模版合成蛋白质。由此可见，RNA作为遗传信息的传递媒介，其出核转运对于遗传信息的精确表达起到了至关重要的作用，因此对于RNA出核转运及其调控机制的研究是一个十分重要的基础科学问题。RNA出核过程的研究始于20世纪末，其中涉及的核心机制已经大致清楚，但对于中间过程的精细调控则还有许多未解之谜，目前仍然是领域内的研究热点[1]。随着技术手段的发展以及研究的逐步深入，一些新的发现也挑战了对传统出核过程及其工作模型的理解。本文将结合最新的科研进展，对此前的RNA出核转运研究进行总结，主要介绍mRNA的核心出核通路及已知的调控机制，并简要概括其他小RNA、环状RNA(circRNA)、长链非编码RNA(lncRNA)等新型转录本的出核过程。

1 mRNA出核转运的分子机制

DNA经转录首先产生前体mRNA(pri-mRNA)，并伴随着一系列的共转录和转录后加工步骤，形成成熟的mRNA分子，进而被转运出核[2]。Pri-mRNA的核内加工通常包括5′端加帽、内含子剪接以及3′端切割加尾等步骤，因此成熟的

mRNA通常仅含有编码序列，并具有5′端的帽子以及3′端的多聚腺苷酸尾等特征。一般认为，只有正常加工成熟的mRNA分子，才会进一步被包装成mRNP，经核孔转运出核，而加工异常的mRNA则会被核内RNA降解机器识别并降解，防止出核并翻译产生异常的蛋白质[3-5]。

mRNA出核因子往往以转录或核内加工偶联的方式结合到pri-mRNA上，与其他RNA结合蛋白一起包装形成mRNP，并运输到核膜周围，最后经核孔转运出核(图1)[6]。因此mRNA的出核过程根据发生的先后顺序，可以大致分成RNA出核蛋白的招募、mRNP的包装、出核受体的结合、mRNP的核内转运、以及核孔处mRNP的解聚和mRNA的释放等几个步骤。其中，不同的步骤分别会涉及不同类型的mRNA出核因子，下文将分别介绍mRNA出核途径中的重要出核因子，以及ATP水解介导的mRNP包装、运输、解聚过程。

1.1 出核受体

mRNA出核过程主要由出核受体介导，其中最主要的出核受体是NXF1-NXT1二聚体[7-9]。研究发现，NXF1蛋白由于含有RRM(RNA recognition motif)序列，具有直接结合RNA的能力[10-12]，但其本身往往形成一个闭合的构象，导致结合RNA的能力较弱，与辅助蛋白NXT1或TREX复合体的结合会使NXF1本身的构象打开，并暴露内部的RNA结合域，使其结合RNA的能力大大提升[13,14]。另外，有研究表明，一些病毒的入侵会导致宿主mRNA出核受阻，其主要的原理是病毒NS蛋白(nonstructural protein)通过结合NXF1，从而抑制了NXF1-NXT1二聚体与TREX复合体或核孔复合物(nuclear pore complex，NPC)的结合，使得宿主本身的mRNA出核途径受阻，进而影响宿主的基因表达[15,16]。

NXF1-NXT1二聚体作为最主要的出核受体，介导了绝大多数mRNA的出核转运过程，且在真核生物中高度保守[9]，但仍有一小部分mRNA是不依赖于NXF1-NXT1二聚体出核的[17-19]。CRM1本身其实是一种蛋白质出核因子，通过识别蛋白质序列中的出核信号(nuclear export signal，NES)，主要是亮氨酸基序，从而辅助蛋白质的出核转运[20,21]。一部分AU-rich的mRNA通常结合一些富含亮氨酸基序的RNA结合蛋白，如HuR[22,23]等，并能够进一步招募CRM1，进而以CRM1依赖的方式转运出核。此外，mRNA帽结合蛋白eIF4E也能通过招募CRM1从而帮助一部分mRNA出核转运[24-26]。

1.2 TREX复合体

在NXF1-NXT1依赖的mRNA出核途径中，TREX复合体的结合是必不可少的一个步骤，其通过共转录的方式结合到pri-mRNA上，帮助mRNA

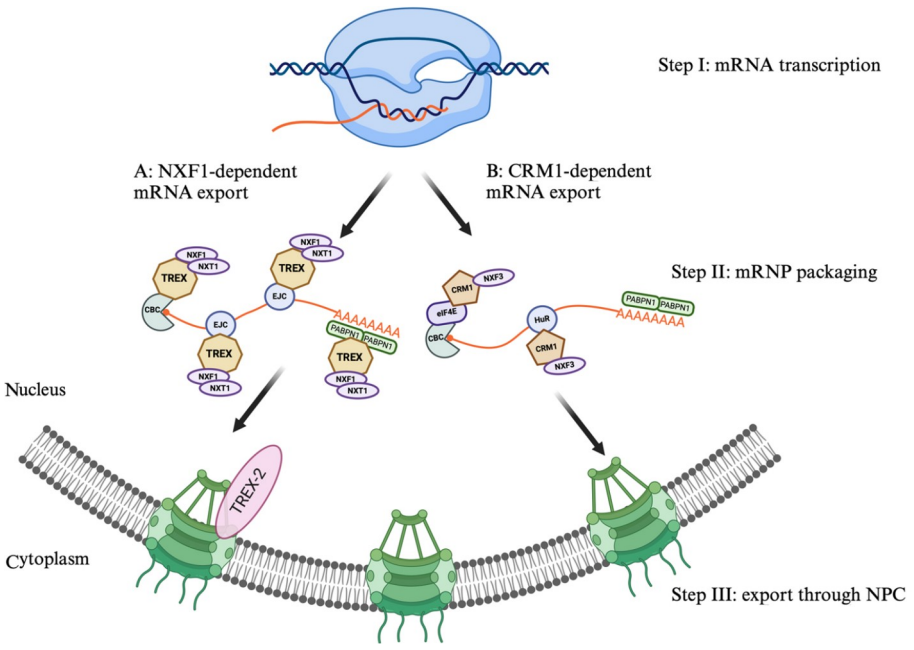

图1 mRNA经典出核通路

包裹形成mRNP，并介导了后续mRNP与NXF1-NXT1二聚体的结合，从而完成出核转运的步骤[11,14,27-31]。TREX复合体由七亚基的THO复合体、RNA结合蛋白ALYREF以及RNA解旋酶UAP56组成[29,32,33]，其中ALYREF和THO能够通过与帽结合复合体(cap-binding complex，CBC)和外显子拼接复合体(exon-junction complex，EJC)的相互作用，以共转录的方式结合到mRNA上，进而促进整个TREX复合体的招募和mRNP的组装[11,27-31,34-36]。有研究表明，作为RNA解旋酶的UAP56[37-39]，其水解ATP的活性直接促进了TREX复合体的组装和构象变化，使得TREX复合体包裹在mRNA分子的外侧形成类似球形的mRNP复合物，并在核孔处水解ATP产生能量使mRNP外壳解聚，mRNA通过与TREX-2复合体以及核孔蛋白的相互作用，转运到细胞质中[40-45]。

此外，UAP56的同源蛋白URH49，同样具有ATP水解酶和RNA解旋酶的活性，被发现在某些情况下，替代UAP56形成新的AREX(alternative TREX)复合体，参与mRNA的出核转运过程[46-49]。另外，一些研究显示，TREX复合体还涉及其他几个不同的蛋白，如CHTOP[11,50]、CIP29[42]、PDIP3[51]、ZC3H11A[51]、UIF[52]等，它们也同样参与了mRNA的出核调控。

1.3 其他mRNA出核相关蛋白

在mRNA出核步骤的最下游，mRNP在NXF1-NXT1的帮助下，依次结合TREX-2复合体以及核孔复合物NPC，来完成最后的出核转运[5]。TREX-2复合体由5个亚基组成，其中GANP亚基作为整个TREX-2复合体的骨架，能够与出核受体NXF1以及核孔蛋白TPR相互作用，使得mRNP锚定在核膜内侧，靠近核孔，并在该处完成mRNP的解聚过程[53-61]。后续NXF1介导mRNA分子和富含FG基序(phenylalanine and glycine motif，FG motif)的核孔蛋白相互作用，从而使mRNA分子逐步穿越核孔到达细胞质中[62,63]。

核孔复合物作为细胞核膜上唯一的大分子通道，是所有RNA出核和蛋白质入核的唯一通道。单个独立的核孔复合物由约30种不同的核孔蛋白构成。每种核孔蛋白在复合物中又含有8~24个不等的拷贝，使得单个核孔复合物整体的相对分子质量达到了100 MDa以上[64-66]。核孔复合物形成的中空运输通道直径约40 nm，满足了所有生物大分子或复合体的运输需要，并且有研究发现，核孔复合物的结构天然会发生一定的动态性改变，使得其中空的通道直径最高可达约60 nm，以满足不同状态下的物质运输需要[67,68]。而核质运输的选择性主要由核孔复合物中间富含FG基序的核孔蛋白(FG nucleoporins，FG-Nups)提供，经NXF1-NXT1介导出核的mRNP需要通过NXF1与不同的FG-Nups相互作用，逐步从核膜内侧转移至核膜外侧，进而在细胞质一侧完成释放[69]。

在CRM1依赖的出核途径中，TREX复合体被其他RNA结合蛋白所取代，如HuR、eIF4E、SR蛋白等[22-26]。真核翻译起始因子eIF4E往往结合在mRNA的5′端，并招募CRM1在该mRNA上的结合，从而参与此类mRNA的出核转运过程，并被认为对于此类mRNA的出核后翻译也具有重要的调控意义[70]。另外，作为NXF1家族的成员，NXF3在CRM1出核途径中替代NXF1成为主要的出核受体，协助CRM1结合的mRNA与核孔复合物的相互作用，对该出核途径也起到了关键的调控作用[71]。

1.4 mRNP的包装与释放

在所有的mRNA出核通路中，mRNA都必须和RNA结合蛋白相互作用，并进一步包装形成mRNP，才能进行后续以蛋白动态相互作用介导的核内转运。mRNP的包装被认为开始于TREX复合体的共转录招募[11,27,28,30,34]。新转录产生的mRNA通过结合TREX复合体逐步形成mRNP。这一过程通常需要TREX复合体中的RNA解旋酶UAP56水解ATP产生能量，从而完成mRNP的核内组装[37,40-42,44]。最新的结构生物学研究表明，mRNP会形成一个RNA在内部、TREX复合体组分THOC在外部的类球状结构，TREX复合体中的ALYREF由于具有柔性的非结构性基序(intrinsic disorder region，IDR)，从而能够帮助TREX复合体结合到mRNA上[41]。同时，研究发现，TREX复合体中的RNA解旋酶UAP56在mRNP的组装和解聚过程中发挥了关键作用，其水解ATP的能量直接促进了TREX复合体和mRNP的构象变化，并促进了mRNP从TREX复合体转移到TREX-2复合体，乃至帮助介导了NXF1与核孔复合

物的相互作用[40,41]。

mRNP的释放发生在核孔复合物的胞质侧，该过程中有三个蛋白质发挥了重要作用，分别是核孔蛋白NUP214和GLE1，以及RNA解旋酶DDX19[72-77]。具体来说，DDX19首先在GLE1的帮助下结合ATP，而后DDX19/ATP/GLE1复合体与胞质一侧的mRNP结合，在GLE1和IP_6(inositol hexakisphosphate)的介导下，DDX19的ATP水解酶活性被激活，水解ATP并释放能量，重塑mRNP并使蛋白质和mRNA解离，mRNA从而释放到细胞质中。帮助完成mRNA释放的DDX19分子还能够被胞质侧的核孔蛋白NUP214结合并回收进核内，从而继续参与更多mRNP的出核转运过程[78,79]。

mRNP在核内的运输一直以来都是领域内研究的难点。之前有一些工作通过电子显微镜以及超高分辨率成像的方法，研究了mRNP在核内的运输过程，认为mRNP在核内的转运以及与核孔的对接是mRNA出核途径中最关键的限速步骤[80-85]。随着研究的逐步深入，目前认为mRNP在核内的转运通常是依靠液液相分离(liquid-liquid phase separation，LLPS)过程，核内的DEAD-box蛋白通过其水解ATP的酶活性，促进了核内亚细胞结构的动态变化，以及染色质状态的动态转变，导致mRNP伴随各类亚核结构的动态形成及解聚，逐步转移到核膜边缘，进而结合核孔复合物进行最后的出核转运[72,86-92]。

2 mRNA出核转运的相关调控

mRNA出核转运是一个连续、多步骤的过程，有若干种不同类型的蛋白质参与其中，因此通常受到多方面的严密调控。处于下游的mRNA出核转运不仅受到上游转录和加工过程的影响，还能作为一种新的调控因子来反向调控上游过程。也有研究发现，染色质状态和RNA修饰能够调控mRNA出核转运，进而参与基因选择性表达的控制。而RNA降解机器与出核通路的竞争，共同决定了mRNA的核内命运。上述不同的调控方式往往也具有不同的分子调控机制，多种调控手段相互影响、共同作用，从而保证了遗传信息的精确传递。

2.1 mRNA的上游转录和加工调控出核

在转录的起始阶段，RNA聚合酶Ⅱ(RNA polymeraseⅡ，Pol Ⅱ)在转录合成一段20~30 nt的pri-mRNA片段之后，一个m7G帽子会被添加到pri-mRNA的5′端，并结合一个帽结合复合体CBC[93,94]。通常认为，一个m7G帽子能够增强mRNA的稳定性，防止被错误降解，而缺乏m7G帽子的mRNA往往出核效率很低[30,94]。有研究发现，出核因子ALYREF与CBC有直接的相互作用，从而能够将TREX复合体招募到mRNA的5′端，帮助mRNA的出核转运[30,34,36]。

在mRNA的核内剪接加工步骤中，出核因子也会被mRNA加工机器逐步招募到新生的转录本上，从而完成mRNP的共转录组装。Pri-mRNA的剪接会在外显子连接处招募EJC复合体，研究发现，EJC复合体也能结合TREX复合体中的UAP56和ALYREF，从而促进整个TREX复合体的招募和mRNP的组装[27-29,34,35]。某些在pri-mRNA剪接过程中发挥重要作用的SR蛋白，如SRSF1、SRSF3等，也参与了出核因子的招募过程，敲低这些SR蛋白能够在不影响全局剪接效率的前提下，造成RNA的核内异常累积[95-98]。

在转录终止阶段，mRNA的3′端加工因子PCF11，通过结合Pol Ⅱ CTD(C-terminal domain)，并以CTD依赖的方式招募ALYREF和TREX复合体，从而偶联了mRNA的3′端加工和出核过程[99,100]。另有研究发现，3′端加工因子CSTF2也能够结合ALYREF并将其招募到mRNA的3′末端[36]。此外，另一3′端加工因子CPSF6还能够以非Pol Ⅱ CTD依赖的方式直接结合出核受体NXF1，从而参与mRNA的出核调控[101]。

对于包含polyA尾的mRNA，其加尾步骤及polyA尾的长度调控也会对出核过程产生影响。研究发现，敲低polyA尾结合蛋白PABPN1会导致一些mRNA的出核效率降低，进一步的实验证明，PABPN1能够招募TREX复合体并使之结合到mRNA的3′末端，从而帮助mRNA的出核转运[36]。一项对酵母的研究还发现，控制polyA尾长的蛋白Nab2p同样也参与了mRNA的出核调控，敲低*Nab2p*会导致广泛性的核内mRNA尾长降低，并伴随出核抑制和核内polyA mRNA累积的现象[102-104]。而对于不含有polyA尾的histone mRNA，其3′末端的茎环结合蛋白SLBP(stem loop binding protein)，通过

与3′端切割因子CPSF3和出核因子ALYREF的结合，从而偶联了histone mRNA的3′端加工和出核过程，促进了不含polyA尾修饰的histone mRNA的出核转运[105]。

2.2 RNA修饰和染色质状态对出核的影响

RNA修饰作为一种重要的转录后调控手段，被认为参与了众多的生物学过程，包括但不限于转录和翻译调控、基因的选择性表达、胚胎发育等[106]。近年来一些研究发现，RNA修饰也能够参与RNA核内加工和出核转运的调控。目前，有研究发现，RNA上的核苷酸修饰多达一百余种，主要位于tRNA上，而在mRNA中丰度较高的修饰有m6A、m5C、m1A以及假尿苷修饰等，其通过调控mRNA的稳定性、翻译效率等多个方面共同参与基因的转录后调控过程[106,107]。研究发现，m6A结合蛋白YTHDC1通常定位于细胞核中，能够结合TREX复合体并将其招募到含有m6A修饰的mRNA上，帮助这类mRNA的出核转运[108,109]。此外，敲低去甲基化酶ALKBH5也能够促进mRNA出核转运，提示m6A修饰本身可能作为一种mRNA出核的正反馈因子，从而参与mRNA出核转运的调控[110]。此外，TREX复合物的组分ALYREF也被鉴定为一种新的m5C结合蛋白，能够结合被m5C修饰的mRNA并进一步招募TREX复合体，从而促进含m5C修饰的mRNA的出核转运[111]。

染色质状态和组蛋白修饰现已被发现能够参与基因的转录调控和新生RNA的合成，通常认为，异染色质区域较少发生转录事件，而常染色质则与基因的活跃转录相关[112-114]。细胞核内染色质的不均匀动态分布造成了亚核结构的动态变化，也间接影响了mRNA的出核转运[115]。组蛋白修饰作为一种染色质状态的指标，在一些针对酵母的研究中被发现参与了mRNA的出核调控过程，如组蛋白H2B的乙酰化或去乙酰化被报道以转录依赖或非转录依赖的方式调控mRNP的包装和出核转运[116-118]。一些与组蛋白修饰或染色质状态变化相关的蛋白质，如SPT6，也被发现参与了mRNA的加工和出核转运[119,120]。

2.3 mRNA出核因子调控上游过程

通常认为，mRNA的出核转运作为信息传递的最后一步，往往受上游的mRNA转录和加工所调控，但近年来有研究表明，mRNA出核因子能够通过提前结合新产生的mRNA分子，进而参与调控mRNA的早期转录和加工[121]。TREX复合体由于能以共转录加工的方式被招募到新生转录本上，也被认为参与了mRNA转录和加工过程的调控[11]。有研究发现，TREX复合体中的THO能够调控Pol Ⅱ的转录延伸和终止过程，敲低THO会导致Pol Ⅱ转录活性下降，并使Pol Ⅱ的转录终止受阻，产生更多的通读或融合转录本[122-128]。此外，TREX复合体还被发现能调控mRNA的3′端可变加尾过程，敲低TREX复合体的组分ALYREF、UAP56或者THO，都能够诱导产生更多具有短3′UTR的可变加尾转录本[128-130]。一项针对mRNA出核受体NXF1的研究还表明，NXF1也能够参与调控Pol Ⅱ的转录延伸和mRNA的3′端可变加尾[101]，提示mRNA的出核转运过程可能深度参与了更为广泛的上游调控，新生mRNA转录本的核内加工和出核转运之间可能存在更为复杂的内在相互影响。

除了TREX复合体与出核受体NXF1以外，mRNA出核相关的其他蛋白也被发现在mRNA早期的转录和加工过程中发挥功能。如在酵母和果蝇等一些低等真核生物中，TREX-2复合体被发现能够和SAGA复合体相互作用，参与SAGA复合体介导的转录调控，敲低TREX-2复合体的组分也能够导致不同程度的转录活性抑制[61,131-134]。而位于RNA出核转运过程中最末端的核孔复合物，也被广泛认为参与了对异染色质和亚核结构的调控[64,135,136]，部分核孔蛋白还被证明能够结合Pol Ⅱ从而直接调控转录的活性[137]。

2.4 mRNA出核和降解机器对转录本的分选

mRNA的出核转运除了被细胞核中的RNA转录和加工机器调控以外，还面临RNA核内降解机器的竞争。一般来说，被正确加工成熟的mRNA会被出核因子结合从而具有较强的出核能力，而加工异常或者错误的mRNA则会被核内RNA降解机器识别并降解，因此核内新生mRNA转录本会面临出核和降解机器的竞争和分选，两者共同决定了mRNA的核内命运[138,139]。通常认为，仅有加工异常或者错误的mRNA才会被RNA核内降解机器识别。但我们早期的研究发现，正常加工的mRNA也能够作为核内降解机器的底物而被识别并降

解[140]。这可能代表了一种重要的转录后调控机制，能够保证基因的精确表达，避免某些异常过量的mRNA占据翻译机器，从而影响其他重要蛋白质的翻译。

RNA的核内降解主要由RNA外切体(exosome)发挥功能，其具有RNA内切酶以及3′-5′外切酶活性，负责核内绝大多数RNA的降解[141-143]。Exosome由多个亚基组成，其发挥作用需要诸多辅助因子的参与，而RNA解旋酶MTR4作为必不可少的辅助因子，对于exosome的激活具有重要作用[144,145]。MTR4或exosome组分的敲除会导致大量RNA的核内累积，进一步影响亚核结构和染色质分布的变化，从而抑制上游的RNA转录过程[140,146,147]。Exosome对于不同RNA降解底物的识别是通过其他不同的辅助因子结合不同种类的RNA实现的，这些辅助因子能与MTR4或者exosome的核心组分相互作用，进而招募整个exosome来降解不同种类的RNA[148-150]。

正常加工的mRNA不仅能够被转运出核，也能够被核内降解，因此细胞如何决定这些新生mRNA转录本的核内命运便成了一个重要的基础科学问题。基于本实验室的前期系统性研究以及众多国际同行的发现，目前一种“竞争模型”正在逐步被学界认可并接受，即出核机器和降解机器通过共同竞争结合新生的mRNA转录本，从而决定这些新生转录本的核内命运(图2)[138,139]。具体来说，exosome的辅助因子MTR4能够和TREX复合体的组分ALYREF共同竞争结合mRNA的5′端帽结合复合体CBC的组分ARS2，从而决定mRNA的出核或降解[140,147,151]。而在mRNA的3′末端，exosome的另一个辅助因子ZFC3H1能够和ALYREF共同竞争polyA尾结合蛋白PABPN1，进而决定mRNA的核内命运[36,152]。

3 mRNA出核通路的生理病理功能及缺陷表型

mRNA出核转运作为细胞内最基本的生物学过程之一，在基因的表达调控中发挥了重要作用，因此该通路的功能异常往往会在细胞或者个体水平上导致严重的生理或病理缺陷。由于mRNA出核转运的重要性，相关出核因子的敲除往往会导致细胞和个体水平上的致死效应，导致难以研究出核通路在不同层面上的生理功能，但仍有部分mRNA出核受阻产生生理缺陷的例子被报道[153]。

有研究发现，TREX复合体亚基THOC1不是酵母存活所必需的，但其敲除小鼠却会产生囊胚发育异常和胚胎致死的表型，表明其在小鼠的早期胚胎发育过程中发挥了重要功能[154]，但在小鼠发育成熟后再诱导性敲除*THOC1*却不会对大多数组织和器官发育产生影响[155]。另有研究则认为，

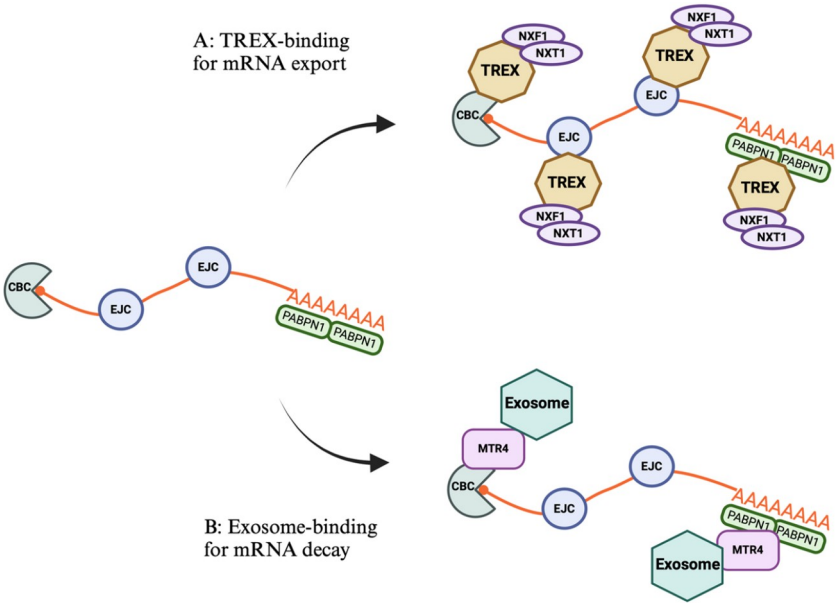

图2 mRNA出核和降解的竞争

THOC1对于睾丸的发育非常重要[156]，提示TREX复合体的生理功能可能因不同的发育过程和组织器官而异。TREX复合体的另一亚基THOC5被发现在维持动物造血系统的正常功能中起到了重要的作用，THOC5的条件性敲除小鼠虽然可以存活但会出现严重的贫血和白细胞减少的症状，提示其对于造血相关基因的出核调控具有重要作用[157,158]。而TREX复合体的THOC2亚基被认为与THOC5一同维持干细胞增殖与分化之间的平衡，相应蛋白的敲除会导致干细胞重编程能力的缺陷，并无法维持正常的囊胚发育[159]。此外，THOC5还被认为与白血病的发展进程相关[160,161]，而THOC2和THOC6的突变或缺陷也被发现会导致神经系统的发育异常[162-165]。

除了TREX复合体的THO亚基外，其他出核相关因子如ALYREF[166,167]、CIP29[168]、CHTOP[169]也被发现与细胞增殖和癌症发生等生理病理过程相关。而eIF4E作为CRM1出核通路中的重要调控蛋白，其过表达往往与癌症发生具有密切的相关性[170,171]。核孔蛋白GLE1的点突变也被发现与神经退行性疾病ALS以及先天性痉挛LCCS1有关[172-174]，说明RNA出核通路在系统和个体层面上具有广泛而重要的生理功能。

在一些流感病毒[175,176]和疱疹病毒[177-180]感染宿主细胞及自我复制的病理过程中，劫持宿主mRNA出核通路是一种很重要且保守的入侵手段。其主要原理是病毒本身编码的蛋白能够招募ALYREF[177,179,180]、UAP56[181]或NXF1[175,176]，从而使得TREX复合体和NXF1-NXT1二聚体结合在病毒mRNA上，帮助病毒mRNA的出核和蛋白质翻译，并对宿主本身正常的mRNA出核转运和翻译造成干扰，从而诱发细胞凋亡。

4 其他RNA转录本的出核转运及调控

细胞中的RNA转录本种类丰富，除了熟知的mRNA、rRNA和tRNA以外，还包含许多非编码RNA或其他小RNA转录本，其中一些也经由出核过程转运到细胞质中，发挥各种各样的调控功能。这些不同类型的RNA转录本，其出核转运的受体也不尽相同，除了一些lncRNA同样以NXF1-NXT1二聚体介导出核转运以外，其他不同类型的RNA分子也有其对应的出核受体(图3)。这些非经典出核通路和受体因子的存在，也从侧面反映了RNA出核转运途径的丰富性和多样性，暗示RNA出核转运过程作为一种重要的表达调控手段，深度参与了细胞不同的生物学过程。

4.1 miRNA和piRNA的出核

除了携带编码信息的mRNA以外，细胞还会产生一系列长度只有20~30 nt的小RNA来调控基因表达，这些小RNA往往在细胞质中发挥功能，因此也会涉及出核转运的过程[1]。miRNA自转录产生后，在细胞核内先被Drosha结合进行初步加工，再与XPO-5结合，以前体miRNA的形式被转运出核，并在细胞质中进一步被Dicer切割形成成熟的miRNA，从而结合AGO蛋白发挥基因沉默的功能[182]。研究表明，前体miRNA的出核除了依赖于XPO-5以外，还需要Ran-GTP的结合[183-185]。还有一些研究发现，前体miRNA也可以以非XPO-5依赖的方式被转运出核[186-188]。

piRNA作为另一种重要的小RNA分子，通常认为在生殖系统发育过程中具有重要的调控功能，其往往在细胞质中与PIWI家族蛋白结合并经乒乓循环(ping-pong cycle)成熟[189]。piRNA前体的出核转运主要依赖于NXF3-CRM1通路[190,191]，但另有一类piRNA由于具有正常的剪接事件，从而可以直接招募NXF1-NXT1二聚体帮助其出核转运[192]。

4.2 CircRNA的出核

CircRNA是一种新发现的环状RNA分子，被认为是一种反向剪接(back-splicing)的产物，并在哺乳动物细胞中广泛存在，甚至能够被转运到细胞质中，作为核糖体的识别底物翻译产生蛋白质[193,194]。大量的研究发现，circRNA在各种细胞或个体发育中具有重要的生理功能，但circRNA不具有普通mRNA的线性结构，也不具有polyA尾巴，它们是如何被转运到细胞质中的一直是未解之谜。此前有研究认为，circRNA的出核与其长度有关[195]。但最近的一项研究发现，circRNA是通过RNA结合蛋白IGF2BP1的帮助而被转运出核的，其不依赖于传统的NXF1-NXT1二聚体或者CRM1通路，IGF2BP1能够直接结合circRNA分子，并进一步招募蛋白出核受体XPO-2和Ran-GTP，从而完成出核转运[196]。还有研究发现，某些特定circRNA的

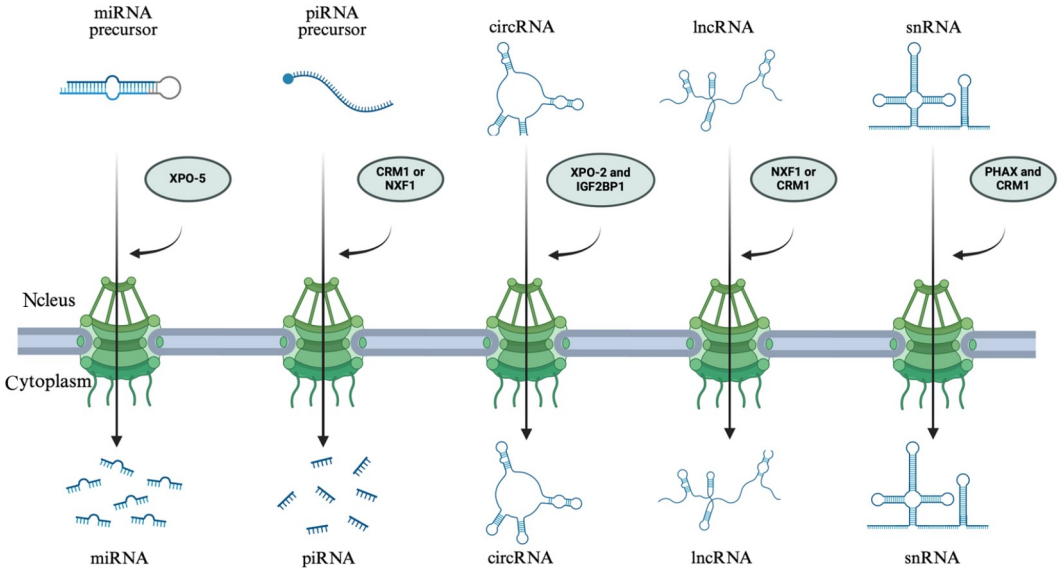

图3 其他RNA转录本的出核转运

定位在神经细胞发育过程中十分重要，随着神经细胞的发育从细胞核逐步定位到细胞质中[197]，暗示circRNA的出核转运可能具有非常重要的生理意义。

4.3 LncRNA及其他转录本的出核

LncRNA由于具有与普通polyA mRNA相同的结构组成，如5′端的帽子和3′端的尾，通常被认为依赖于polyA mRNA相同的TREX复合体以及NXF1-NXT1二聚体进行出核转运。另有一些SR蛋白也能够以序列依赖的方式结合到lncRNA上，并帮助其招募TREX复合体和NXF1[198,199]。但有的研究表明，某些lncRNA是通过招募HuR和GRSF1，从而以CRM1依赖的方式转运出核的[200]。

除上述RNA分子之外，snRNA作为剪接体的重要组分之一，通常会先被转运到细胞核外，在细胞质中结合Sm蛋白后再以snRNP的方式被重新转运入核发挥功能，因此也存在出核转运的过程[1]。研究表明，snRNA的出核往往与CRM1途径有关，蛋白PHAX会结合到snRNA的5′端CBC上，进而招募CRM1对snRNA进行转运[93,201]。

5 讨论与展望

RNA的出核转运作为最基础的生物学过程之一，在基因表达调控中起到重要作用，作为一种重要的转录后调控手段参与了细胞和个体的生长发育、组织和器官分化、环境应激、免疫应答等诸多重要的生理过程[5]。随着研究的逐步深入和测序、成像等相关技术手段的不断革新，很多新的进展也挑战了领域内对RNA出核转运经典模型的认知，如经典的出核受体NXF1，此前被认为在细胞核基质中结合RNA并转运至核孔周围，但亦有研究认为，NXF1在核孔处作为一种类核孔蛋白而与RNA结合[202,203]。还有研究则发现，NXF1在RNA合成的早期先于TREX复合体结合到RNA上[101,204]。因此，还需要更为全面而详尽的研究来进一步加以区分和证明。

作为RNA出核转运的负调控途径，RNA核滞留的相关通路和机制还缺乏深入研究。目前认为，某些特定的RNA序列或未加工完成的内含子序列作为一种RNA核滞留信号，和相关RNA结合蛋白一起参与了RNA核滞留的调控[205]，但其具体的分子机制和调控手段还不是非常清楚，且RNA的出核命运还会受到RNA核降解机器的竞争和调控[139]，提示这可能是一个复杂且多层次的调控网络，也是一种细胞精细转录后调控的强大机制。因此新生RNA的出核命运决定这一重要科学问题仍值得进一步深入研究和探索。

此前诸多研究表明，RNA出核因子也能参与调控上游的RNA转录和加工过程，但其对于细胞内亚核结构和染色质动态变化的贡献还鲜有报道。此前已有的一些研究认为，RNA的合成与运输确实能对亚核结构和染色质的动态变化起调控

作用[86,206,207]，其中涉及液液相分离(LLPS)的调控和本身生物大分子之间的电荷相互作用[208]，而RNA结合蛋白往往具有不同长度的IDR从而具备LLPS的能力，且RNA分子本身就带有强烈负电性等特点，因此进一步阐明RNA核内代谢稳态和亚核结构的相互调控过程，并理清其相互之间的因果关系，也必将成为领域内后续研究的重点之一。

RNA的二级结构和RNA-RNA相互作用已经被证实参与了RNA的转录和加工过程[209-211]，而其对于RNA的出核转运是否存在贡献在此前还是个未知的问题。有研究发现，酵母中双链RNA的形成有助于RNA的出核转运过程[212]，双链RNA与出核因子的结合能力也强于单链RNA，因此可以猜想该机制可能也普遍存在于高等哺乳动物细胞中。RNA二级结构的动态变化和RNA-RNA相互作用也可能在细胞核中形成动态的局部双链，进而作为一种新的手段调控RNA出核转运的偏好性。

mRNP的核内包装和运输一直以来都是领域内研究的难点之一[213]。基于超高分辨率成像和活细胞单分子标记技术的发展与应用，在单分子层面对RNA或RNA结合蛋白进行活细胞标记，进而追踪mRNP自转录起始的包装和核内运输的全过程也是可能的[214]。这将有助于我们理解RNA的转录和加工过程与核内命运决定之间的复杂调控关系，并进一步探索基因的转录后调控和选择性表达在细胞及个体层面的生理功能与意义。

由于RNA出核转运是细胞或个体的底层功能之一，RNA出核因子的敲除或突变往往会导致细胞和个体发育的异常或死亡。随着PROTAC技术[215]的出现和发展，结合AI辅助的计算机模拟，对大量靶标进行PROTAC小分子的设计和筛选也指日可待。在细胞或动物水平上对RNA出核因子或相关蛋白进行PROTAC瞬时降解，研究其在不同组织器官或发育阶段中发挥的作用，也应成为领域内的研究热点，在推动RNA出核缺陷相关的疾病理解和药物研发领域必将有广阔前景和无限可能。

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