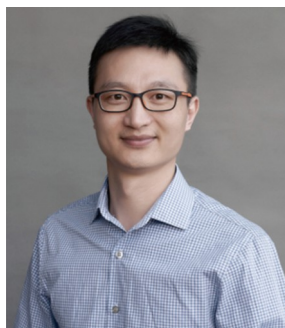


综述



王露, 博士, 中国科学院分子细胞科学卓越创新中心/上海生物化学与细胞生物学研究所研究员、博士生导师、研究组长。实验室主要以模式生物果蝇的卵巢和肠道组织、小鼠肝脏组织以及肿瘤细胞系作为对象研究转座子在基因组水平的转座行为、潜在功能和调控机制。通过研究转座子在这些系统中的调控机制和功能进一步解密转座子对于生殖、发育和疾病的影响。

来源于逆转座子RNA的生物学功能

冯煜[#], 孙昊田[#], 王露^{*}

(中国科学院分子细胞科学卓越创新中心/上海生物化学与细胞生物学研究所,
核糖核酸功能与应用重点实验室, 中国科学院大学, 上海 200031)

摘要: 转座子广泛存在于几乎所有的真核生物基因组中, 并且人类基因组中近一半的DNA是由转座子构成的。转座子在基因组中的转座可以引起DNA断裂、基因突变甚至基因组不稳定, 所以其异常激活不仅会导致动物不育和疾病, 还可能加速衰老进程, 因此转座子通常被认为是对有机体不利的。然而, 也有证据表明, 来源于逆转座子的RNA可以在多种生理过程中发挥重要的生物学功能, 如维持早期胚胎发育、激活天然免疫反应等。本文将对来源于逆转座子RNA的生物学功能进行阐述, 进一步加深对转座子RNA的认识。

关键词: 转座子; 胚胎发育; 天然免疫; 衰老

The biological impact of retrotransposon derived RNA

FENG Yu[#], SUN Haotian[#], WANG Lu^{*}

(Key Laboratory of RNA Science and Engineering, Shanghai Institute of Biochemistry and Cell Biology, Center for Excellence in Molecular Cell Science, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200031, China)

Abstract: Transposons make up a large fraction of the genome in almost all of the eukaryotic organisms, comprising nearly 50% of the human genome. Transposon mobilizations could induce DNA breaks and cause gene mutations and even genomic instability, which can not only lead to animal sterility and disease, but also potentially drive aging, thereby being largely considered detrimental. Nevertheless, increasing evidence also suggests that transposon derived RNA plays very important roles in regulating many biological processes, such

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[#]共同第一作者: 冯煜, E-mail: fengyu2021@sibcb.ac.cn; 孙昊田, E-mail: sunhaotian2022@sibcb.ac.cn

^{*}通信作者: E-mail: lu.wang@sibcb.ac.cn

as maintaining embryogenesis and inducing innate immune responses, etc. In this review, we will further characterize the new discoveries in the field in transposon derived RNA, to understand their biological impacts better.

Key Words: transposon; embryogenesis; innate immunity; aging

1 逆转座子的分类及转座机制

转座子是一段能在基因组中随机跳跃的DNA序列, 又被称为“可移动元件”。自Barbara McClintock在玉米基因组中发现转座子以来, 人们对基因组的认知从静态物质转变为一个能够不断变化自身结构的动态有机质。在人类基因组中, 转座子占比近50%^[1-3]。根据转座方式的差异, 转座子可被分为DNA转座子和RNA转座子。DNA转座子以“剪切-粘贴”的方式实现转座, 而RNA转座子则通过“复制-粘贴”的方式在宿主基因组中增加自身拷贝^[4]。

根据长末端重复序列(long terminal repeat, LTR)的有无, 逆转座子又分为LTR型逆转座子和非LTR型逆转座子。内源性逆转录病毒即LTR型逆转座子往往被认为来源于古老的外源性逆转录病毒^[5]。因此, LTR型逆转座子激活会转录生成mRNA^[6-8]。同正常基因一样, 转座子mRNA也会经历出核、翻译

的过程, 合成转座所需的蛋白质, 包括衣壳蛋白Gag和多聚蛋白Pol, 部分LTR转座子还会编码包膜蛋白Env。这些蛋白质和转座子mRNA结合后在胞质中包裹形成病毒样颗粒(virus-like particle, VLP)^[9,10]。在VLP内, LTR型逆转座子会以tRNA作为引物并且利用自身表达的具有逆转录酶活性的Pol蛋白, 实现其mRNA逆转录成cDNA^[11]。当cDNA进入细胞核并整合进宿主基因组中的新位点时, 就实现了一次完整的转座过程^[12](图1)。而非LTR型转座子则以更原始和古老的形式存在于宿主基因组中, 分为LINEs(long interspersed nuclear elements)和SINEs(short interspersed nuclear elements)两种。LINE为长散在重复序列, 可以编码自身转座所需的蛋白质, 与自身转录出的mRNA形成核糖核蛋白颗粒(ribonucleoproteins, RNPs)进入细胞核内完成转座周期^[13](图1)。SINE为短散在重复序列, 通常以短且非编码RNA的形式借助LINE合成的蛋白质实现转座^[14](图1)。

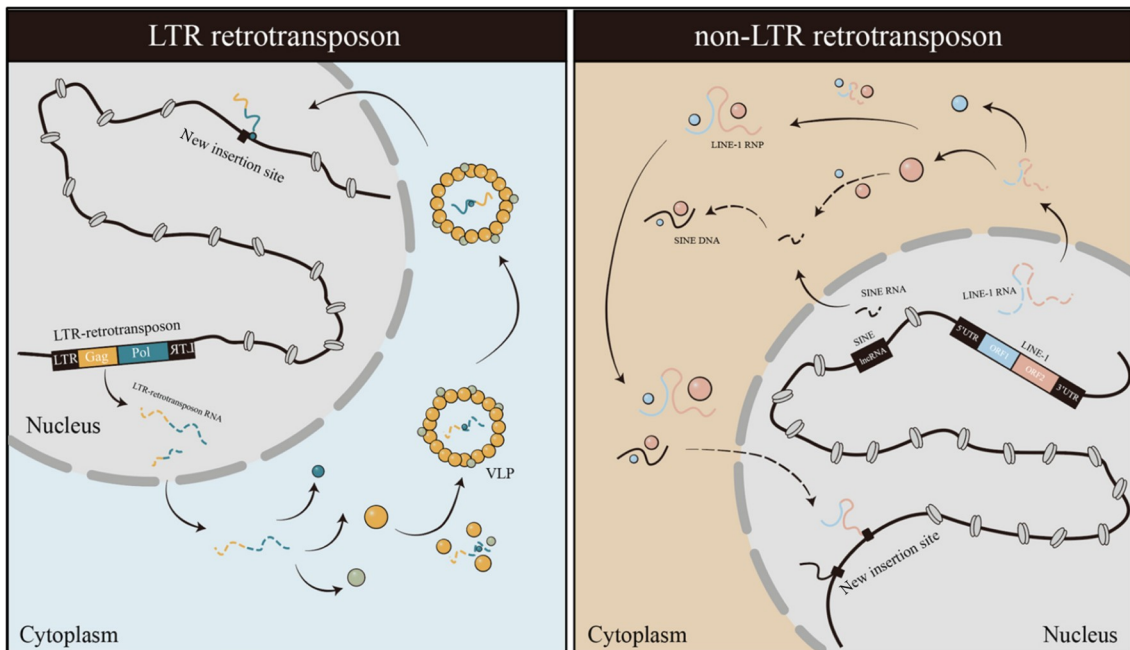


图1 逆转座子在基因组中扩增的机制

2 逆转座子RNA在胚胎发育过程中的功能

转座子的异常激活往往会给宿主带来一系列不利的影响,包括血友病、神经退行性疾病以及各类癌症^[3,15,16]。因此,在长期进化中宿主产生了一系列措施来抑制转座子的异常激活,包括组蛋白修饰、DNA甲基化、siRNA沉默途径等^[17-19]。很长一段时间,人们普遍认为,宿主与转座子之间仅存在界限鲜明的对立与冲突关系。但是随着测序技术的不断进步和对转座子基因结构和功能的深入了解,人们渐渐发现,转座子的正向功能同样不容忽视。

在小鼠和人类胚胎着床前,转座子已被证实具有高水平的转录活性^[20,21]。这期间异染色质标志物的重塑、较为开放的染色质结构以及受精后染色质组装和DNA合成的暂时解偶联都为转座子转录激活提供了绝佳的机会。作为小鼠基因组中最丰富的转座元件,LINE-1占其基因组的18%。近年来,研究者们发现,小鼠胚胎发育的正常进行与LINE-1的时期特异性激活密不可分。在胚胎发育的过程中,来源于LINE-1的长链非编码RNA(long non-coding RNA, lncRNA)通过结合依赖性的方式调控染色质的可及性。这似乎已经构成了一种微妙的平衡,过早地沉默LINE-1会降低染色质可及性,而LINE-1的过度激活则会抑制发育过程中的

渐进式染色质压缩^[20,22]。同时,Meng等^[23]发现,LINE-1 5'UTR可作为增强子可调控相邻基因的活性,从而促进早期胚胎全能性的建立。此外,Perchaarde等^[24]发现,当胚胎中LINE-1 RNA缺失时,会使小鼠胚胎停滞在二细胞期。通过进一步研究,他们发现,这是由于LINE-1 RNA会招募Nucleolin/Kap1至特定染色质区域,抑制二细胞相关启动元件*Dux*,激活小鼠胚胎干细胞rRNA的合成,从而使小鼠胚胎顺利通过二细胞期(图2)。

2012年,Macfarlan等^[25]发现,小鼠胚胎干细胞以及诱导性多能干细胞中存在一类罕见的瞬息态细胞群,这类细胞会表达高水平的逆转座子MERVL(murine endogenous retrovirus-L)以及二细胞期基因,但不表达其他常见多能干细胞标志基因如*Pou5f1*、*Sox2*和*Nanog12*。研究者们将这类细胞称为二细胞胚胎样细胞(2-cell-like cells, 2CLC)。至此,MERVL被视为常见的多功能干细胞的标志基因^[25-27];在Sakashita等^[28]的发现之前,MERVL的重激活对小鼠胚胎植入前发育的确切功能仍然未知。研究表明,MERVL转录本最初在细胞核中积累,直到二细胞期后期,它们才被释放并限制在细胞质中。用反义寡核苷酸(antisense oligonucleotide, ASO)限制细胞核和细胞质中MERVL的

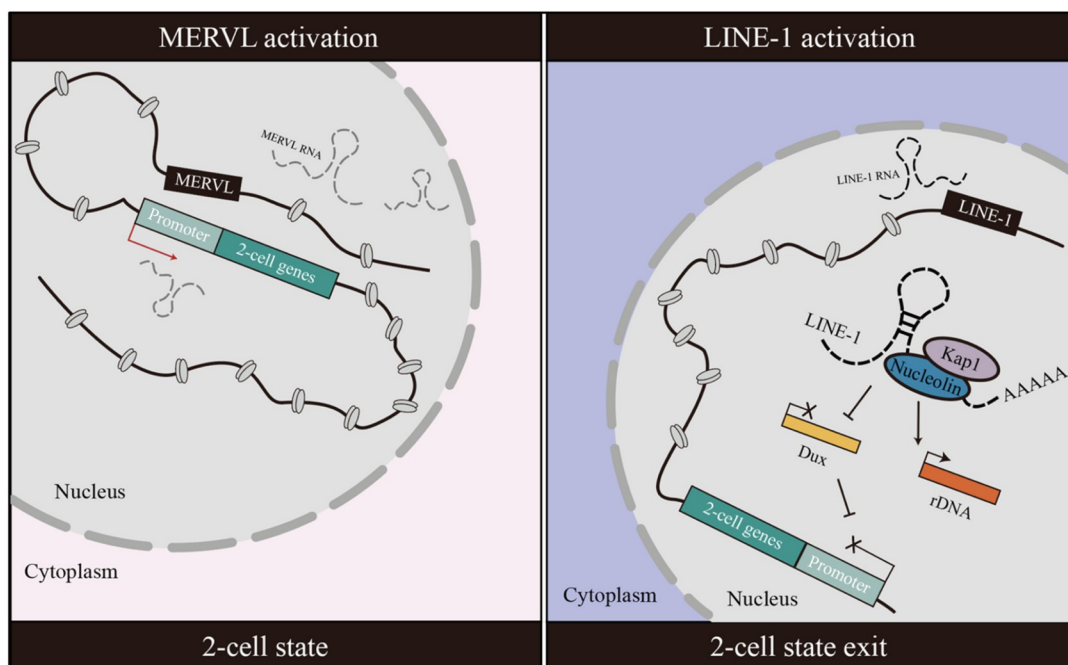


图2 逆转座子在胚胎发育过程中的功能

RNA水平会影响胚胎分化以及基因组稳定性,进而导致胚胎死亡^[28](图2)。有趣的是,较低活性的MERVL在着床前胚胎中维持了二细胞期转录水平和染色质状态,显示了其在胚胎由全能性向多能性转变中的作用^[28]。因此,受MERVL在早期小鼠胚胎发育中的调控作用及其在维持细胞全能性中重要性的启发,几个研究小组通过操纵MERVL转录建立了全能性干细胞系,为研究细胞全能性提供了有价值的体外模型^[29-31]。

在人类多能干细胞中,内源性逆转录病毒HERV-H(human endogenous retrovirus H)的转录激活能够建立拓扑结构域(topologically associating domains, TADs),敲除特异位点的HERV-H后会剔除相应的拓扑结构域边界并降低上游基因的表达,HERV-H这种建立拓扑结构域边界的能力完全依赖于自身高转录出来的RNA^[32]。在人类胚胎干细胞中,HERV-H还可以形成lncRNA,与OCT4相互作用,共同维持胚胎干细胞的特性^[33]。

综上所述,在胚胎发育过程中,转座子会以lncRNA的形式影响胚胎染色质可及性,调控胚胎发育特殊时期的基因表达。因此,转座子与宿主胚胎细胞之间的共生进化关系是转座子在被驯化之后以另一种方式精细调控胚胎发育中的特异性基因,以确保早期胚胎发育顺利且稳步地进行。

3 逆转座子RNA可以激活天然免疫反应

天然免疫系统是存在于绝大多数生物中的一种古老的防御形式,是抵御病原微生物入侵的第一道防线。与适应性免疫不同,天然免疫系统功能的发挥依赖进化过程中形成的模式识别受体(pattern recognition receptors, PRRs)感知微生物病原体所携带的保守性的分子特征——病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)。活化后的模式识别受体能激活宿主的一系列天然免疫通路,从而调控多种免疫反应相关基因的表达,包括I型干扰素(type I interferons, IFN-I)、细胞因子和趋化因子等^[34]。这一过程对于维持机体的免疫防御至关重要。RNA作为一种极其重要的病原体相关分子模式存在于转座子生命周期的诸多环节,来源于转座子的不同RNA形式可能被不同的模式识别受体识别,进而触发天

然免疫系统的激活(图3)。

Toll样受体(Toll like receptor, TLR)家族的单链RNA(single-stranded RNA, ssRNA)识别受体TLR7和TLR8能够监测来自ERV的RNA信号。这种RNA信号激活了小胶质细胞和巨噬细胞内的TLR信号通路,进而诱发了细胞的炎症反应^[35,36]。在传统的观念中,细胞质中双链RNA(double-stranded RNA, dsRNA)的存在往往被视为病毒感染和复制活跃的标志^[37]。然而,有研究证据显示,ERV、LINE-1和SINE也具有生成dsRNA的能力^[38-40]。dsRNA可以通过单一逆转座子位点的双向转录或通过来自不同位点的相同或相似转座子RNA的不完全碱基配对形成,也可以通过单个转录本的倒置重复序列经碱基配对形成具有dsRNA的茎环结构^[41]。RLRs(RIG-I-like receptors)和TLR3作为天然免疫通路中两类经典的dsRNA识别蛋白都被证实能够参与转座子来源的dsRNA的识别。RLRs家族包含三个成员,RIG-I(retinoic acid-inducible gene I)、MDA5(melanoma differentiation-associated protein 5)和LGP2(laboratory of genetics and physiology 2)。三种蛋白质都具备保守的DEXD/H解旋酶结构域,但只有包含信号转导所需的N端CARDs(caspase activation and recruitment domains)的RIG-I和MDA5能够直接参与信号转导。相反,由于CARD的缺乏,LGP2则更多地被认为可以参与RIG-I和MDA5的反馈调节^[42-46]。当受到来源于转座子dsRNA的激活后,RIG-I或MDA5会发生构象变化,暴露二者的CARD结构域并促使自身与线粒体抗病毒信号蛋白(mitochondrial antiviral signaling protein, MAVS)的CARD结构域结合。这种CARD-CARD域相互作用导致MAVS的聚集和下游信号分子的招募,包括TNF受体相关因子(tumor necrosis factor receptor associated factors, TRAFs)、TANK结合激酶1(TANK-binding kinase 1, TBK1)和干扰素调节因子3/7(IFN regulatory factor 3/7, IRF3/7),这些分子共同作用诱导I型干扰素和其他炎症细胞因子的表达^[47-50]。Chiappinelli等^[51]证明,使用DNA甲基转移酶抑制剂Aza(5-azacytidine)或Dac(5-aza-2'-deoxycytidine)可以在多种细胞类型中诱导HERV的显著上调,导致dsRNA积累并激活RLRs和TLR3所在的天然免疫通路。同样,Mikhailkevich

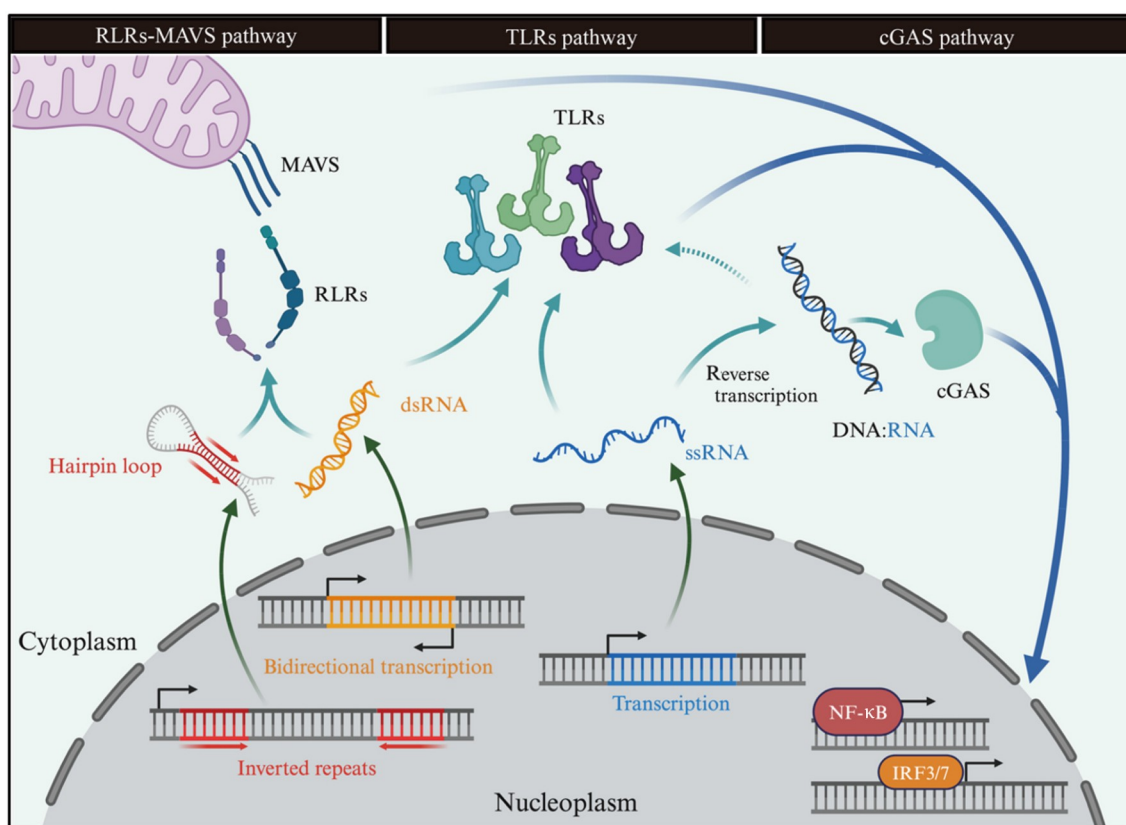


图3 逆转座子RNAs激活天然免疫的分子机制

等^[52]也在电离辐射处理后的THP-1人类单核细胞中发现了HERV表达显著上升, 并进一步验证了MDA5与TLR3、HERV dsRNA的结合能力。

某些特定的逆转座子如HERV-K和LINE-1, 在转座周期中可能会通过RNA逆转录过程形成DNA:RNA杂合体(DNA:RNA hybrid)。一项研究成果表明, 来源于转座子的DNA:RNA可以被盲鼯鼠增生性癌变前细胞中的cGAS(cyclic GMP-AMP synthase)识别并进一步诱导下游适配蛋白STING(stimulator of interferon genes)的活化而激活天然免疫系统, 诱导类型 I 干扰素依赖的细胞坏死信号通路从而阻止癌症的发生^[53]。也有证据表明, TLR9也可以与来自病毒衍生序列的DNA:RNA杂合体相互作用, 通过下游Myd88信号传递诱导抗病毒反应^[54]。尽管缺乏直接证据, 研究者推测, 转座子的逆转录过程中形成的DNA:RNA杂合体可能充当TLR9信号传导的激活剂, 从而调节免疫反应^[55]。

4 逆转座子与衰老

在衰老过程中, 表观遗传学的重塑是广泛而复

杂的, 并且具有明显的细胞特异性。然而, 从酵母到人类的研究表明, 衰老过程中一个普遍的趋势是异染色质的减少, 以及与此相关的、原本受到抑制的基因组区域发生转录激活^[56-58]。研究表明, 异染色质或者调控异染色质建立的相关因子的缺失会激活逆转座子而促进衰老进程^[59,60]。通过对果蝇模式生物的研究发现, 其基因组precentromeric区域富含转座子和piRNA cluster, 伴随着衰老的进程, 与异染色质建立和维持直接相关的H3K9me3和HP1在precentromeric区域的富集会下降的趋势^[61,62]。同时, 多项研究表明, 在果蝇中, 逆转座子会在衰老的组织中激活, 如脂肪组织和神经组织, 而抑制逆转座子的活性则可以延长果蝇的寿命^[63-67]。一项对线虫的研究同样表明, 生命发育过程中逆转座子的激活可以加速衰老和死亡, 通过利用特异性的RNAi抑制逆转座子的活性可以有效延长线虫的生命周期^[68]。同时, 在年老的猴子和人类的多种组织和血液样品中可以检测到逆转座子的活化现象, 表明逆转座子的激活可能是细胞和组织衰老的一大特征^[59]。

研究表明,在衰老的小鼠组织中,尽管衰老细胞所占的比例较低,但是逆转座子在这些组织中依然被激活了,这种不依赖于衰老细胞的机制可能与SIRT6相关^[69,70]。SIRT6可以通过结合逆转座子LINE-1的5'UTR招募KAP1蛋白,从而通过进一步招募HP1和MeCP2来沉默LINE-1的活性^[70]。在衰老小鼠的组织中,原本与LINE-1结合的SIRT6会丢失,导致LINE-1的抑制效果减弱而出现激活现象^[69]。对SIRT6缺陷的小鼠进行逆转录酶抑制剂(reverse transcriptase inhibitor, NRTI)处理会使小鼠的寿命延长一倍,并且会显著提高SIRT6缺陷小鼠的骨密度、肌肉量以及肠道功能和运动能力^[69]。同样,对中年小鼠进行逆转录酶抑制剂处理也会有效延缓衰老相关的生物标志物的出现进程^[69]。这些结果表明,逆转座子的激活可能会促进衰老进程,而抑制逆转座子的活性可能促进健康长寿。

LINE-1编码的ORF2蛋白具备逆转录酶的活性,可以将LINE-1的RNA逆转录成cDNA。研究表明,在衰老细胞和组织中都会检测到来源于LINE-1的cDNA,这些cDNA可以和DNA识别受体cGAS结合而激活天然免疫反应^[69,71]。在上述的SIRT6缺陷的小鼠、衰老的细胞以及自然衰老的组织中,细胞质中出现的LINE-1的cDNA与IFN- β 的激活表现出了高度的一致性。通过使用逆转录酶抑制剂或者利用RNAi去沉默LINE-1的活性能够有效改善因cGAS而引起的IFN- β 的激活^[69,71,72]。

在衰老相关的疾病或者疾病模型如阿尔兹海默症中,逆转座子HERV和LINE-1的表达与疾病的发生都有一定的相关性^[73]。研究表明,与正常人相比,阿尔兹海默症患者的大脑皮层中逆转座子HERV-K、HERV-L、HERV-H都表现出高表达的现象^[74-76]。为了在小鼠模型中研究逆转座子激活导致神经炎症的分子机制,研究人员通过在神经前体细胞中敲除抑制逆转座子的关键蛋白TRIM28而激活逆转座子的表达,结果发现,逆转座子ERV表达的蛋白质形成了聚集样的结构并且导致神经胶质细胞活化^[77,78]。除此之外,一些研究表明,在利用小鼠建立的阿尔兹海默症模型中,逆转座子来源的RNA会通过结合RNA识别受体如TLR8,激活天然免疫反应并导致神经退行性病变和神经炎症^[36,79]。

5 来源于逆转座子的嵌合RNA

嵌合RNA(chimeric RNA)是一种由来自不同基因的外显子片段通过转录剪接或者染色体重排联接而成的RNA分子,对于来源于逆转座子的嵌合RNA我们更倾向将其定义为:具有基因和逆转座子衍生序列的成熟RNA片段^[80]。根据转座子在基因中的插入片段,转座子-基因嵌合RNA可以被分为三种类型:(1)具有转座子转录起始位点的嵌合转录本;(2)具有转座子转录终止位点的嵌合转录本;(3)具有转座子部分或者全长的嵌合转录本^[81-84]。不同类型的嵌合RNA具备不同的翻译潜力,如(1)和(2)可以产生原有蛋白质的截断异构体,(3)造成的外显子序列拼接可以产生新的融合蛋白。

LINE1的反义启动子(antisense promoter, ASP)可将相反方向的转录驱动到相邻的基因序列,产生带有人类基因的嵌合转录物。这种反义启动有助于近4%的人类基因的转录,并被认为可能对健康和疾病产生广泛的影响^[85,86]。在小鼠中,ERV的LTR以组织特异性或时期特异性的方式驱动嵌合RNA的产生,其蛋白产物促进了胚胎发育的正常进行^[87,88]。在果蝇*CHKov1*基因的编码序列中,由于Doc插入导致原基因的转录本被截断,编码出更短的异构体,提高了果蝇对杀虫剂和病毒的耐受程度,促进了种群的适应性进化^[89]。在癌细胞中,异常激活的转座子会触发onco-exaptation效应,在此过程中产生的嵌合产物可能会促进肿瘤的发展^[90-92]。Lock等^[92]在弥漫性大B细胞淋巴瘤(DLBCL)中发现,LTR与脂肪酸结合蛋白7基因(*Fabp7*)的嵌合RNA可转录一种新型蛋白异构体,参与细胞的异常增殖。鉴于大多数逆转座子在正常细胞中受到严格控制,相较于癌细胞来说,由基因嵌合产生的蛋白质在良性组织中几乎不表达,因此这种具有肿瘤特异性的转座子嵌合肽段有望成为肿瘤治疗靶点的宝贵来源^[84]。

参考文献

- [1] Wells JN, Feschotte C. A field guide to eukaryotic transposable elements. *Annu Rev Genet*, 2020, 54(1): 539-561
- [2] Fueyo R, Judd J, Feschotte C, et al. Roles of transposable elements in the regulation of mammalian transcription. *Nat Rev Mol Cell Biol*, 2022, 23(7): 481-497

- [3] Phimister EG, Kazazian Jr. HH, Moran JV. Mobile DNA in health and disease. *N Engl J Med*, 2017, 377(4): 361-370
- [4] Huang CRL, Burns KH, Boeke JD. Active transposition in genomes. *Annu Rev Genet*, 2012, 46(1): 651-675
- [5] Johnson WE. Origins and evolutionary consequences of ancient endogenous retroviruses. *Nat Rev Microbiol*, 2019, 17(6): 355-370
- [6] Boeke JD, Garfinkel DJ, Styles CA, et al. Ty elements transpose through an RNA intermediate. *Cell*, 1985, 40(3): 491-500
- [7] Lauerma V. Plus strand strong-stop DNA transfer in yeast Ty retrotransposons. *EMBO J*, 1997, 16(21): 6603-6612
- [8] Heyman T, Agoutin B, Friant S, et al. Plus-strand DNA synthesis of the yeast retrotransposon Ty1 is initiated at two sites, PPT1 next to the 3' LTR and PPT2 within the pol gene. PPT1 is sufficient for Ty1 transposition. *J Mol Biol*, 1995, 253(2): 291-303
- [9] Pachulska-Wieczorek K, Le Grice S, Purzycka K. Determinants of genomic RNA encapsidation in the *Saccharomyces cerevisiae* long terminal repeat retrotransposons Ty1 and Ty3. *Viruses*, 2016, 8(7): 193
- [10] Peterson-Burch BD, Voytas DF. Genes of the pseudoviridae (Ty1/copia retrotransposons). *Mol Biol Evol*, 2002, 19(11): 1832-1845
- [11] Finston WI, Champoux JJ. RNA-primed initiation of Moloney murine leukemia virus plus strands by reverse transcriptase *in vitro*. *J Virol*, 1984, 51(1): 26-33
- [12] Schorn AJ, Martienssen R. Tie-break: host and retrotransposons play tRNA. *Trends Cell Biol*, 2018, 28(10): 793-806
- [13] Kulpa DA, Moran JV. Cis-preferential LINE-1 reverse transcriptase activity in ribonucleoprotein particles. *Nat Struct Mol Biol*, 2006, 13(7): 655-660
- [14] Luan DD, Korman MH, Jakubczak JL, et al. Reverse transcription of R2Bm RNA is primed by a nick at the chromosomal target site: a mechanism for non-LTR retrotransposition. *Cell*, 1993, 72(4): 595-605
- [15] Burns KH. Transposable elements in cancer. *Nat Rev Cancer*, 2017, 17(7): 415-424
- [16] Küry P, Nath A, Créange A, et al. Human endogenous retroviruses in neurological diseases. *Trends Mol Med*, 2018, 24(4): 379-394
- [17] Deniz Ö, Frost JM, Branco MR. Regulation of transposable elements by DNA modifications. *Nat Rev Genet*, 2019, 20(7): 417-431
- [18] Cosby RL, Chang NC, Feschotte C. Host-transposon interactions: conflict, cooperation, and cooption. *Genes Dev*, 2019, 33(17-18): 1098-1116
- [19] Bruno M, Mahgoub M, Macfarlan TS. The arms race between KRAB-Zinc finger proteins and endogenous retroelements and its impact on mammals. *Annu Rev Genet*, 2019, 53(1): 393-416
- [20] Fadloun A, Le Gras S, Jost B, et al. Chromatin signatures and retrotransposon profiling in mouse embryos reveal regulation of LINE-1 by RNA. *Nat Struct Mol Biol*, 2013, 20(3): 332-338
- [21] Göke J, Lu X, Chan YS, et al. Dynamic transcription of distinct classes of endogenous retroviral elements marks specific populations of early human embryonic cells. *Cell Stem Cell*, 2015, 16(2): 135-141
- [22] Jachowicz JW, Bing X, Pontabry J, et al. LINE-1 activation after fertilization regulates global chromatin accessibility in the early mouse embryo. *Nat Genet*, 2017, 49(10): 1502-1510
- [23] Meng S, Liu X, Zhu S, et al. Young LINE-1 transposon 5' UTRs marked by elongation factor ELL3 function as enhancers to regulate naïve pluripotency in embryonic stem cells. *Nat Cell Biol*, 2023, 25(9): 1319-1331
- [24] Percharde M, Lin CJ, Yin Y, et al. A LINE1-nucleolin partnership regulates early development and ESC identity. *Cell*, 2018, 174(2): 391-405.e19
- [25] Macfarlan TS, Gifford WD, Driscoll S, et al. Embryonic stem cell potency fluctuates with endogenous retrovirus activity. *Nature*, 2012, 487(7405): 57-63
- [26] Yang F, Huang X, Zang R, et al. DUX-miR-344-ZMYM2-mediated activation of MERVL LTRs induces a totipotent 2C-like state. *Cell Stem Cell*, 2020, 26(2): 234-250.e7
- [27] Choi YJ, Lin CP, Risso D, et al. Deficiency of microRNA miR-34a expands cell fate potential in pluripotent stem cells. *Science*, 2017, 355(6325): eaag1927
- [28] Sakashita A, Kitano T, Ishizu H, et al. Transcription of MERVL retrotransposons is required for preimplantation embryo development. *Nat Genet*, 2023, 55(3): 484-495
- [29] Yang M, Yu H, Yu X, et al. Chemical-induced chromatin remodeling reprograms mouse ESCs to totipotent-like stem cells. *Cell Stem Cell*, 2022, 29(3): 400-418.e13
- [30] Xu Y, Zhao J, Ren Y, et al. Derivation of totipotent-like stem cells with blastocyst-like structure forming potential. *Cell Res*, 2022, 32(6): 513-529
- [31] Shen H, Yang M, Li S, et al. Mouse totipotent stem cells captured and maintained through spliceosomal repression. *Cell*, 2021, 184(11): 2843-2859.e20
- [32] Zhang Y, Li T, Preissl S, et al. Transcriptionally active HERV-H retrotransposons demarcate topologically associating domains in human pluripotent stem cells. *Nat Genet*, 2019, 51(9): 1380-1388
- [33] Lu X, Sachs F, Ramsay LA, et al. The retrovirus HERVH is a long noncoding RNA required for human embryonic

- stem cell identity. *Nat Struct Mol Biol*, 2014, 21(4): 423-425
- [34] Medzhitov R. The spectrum of inflammatory responses. *Science*, 2021, 374(6571): 1070-1075
- [35] Heil F, Hemmi H, Hochrein H, et al. Species-Specific Recognition of Single-Stranded RNA via Toll-like Receptor 7 and 8. *Science*, 2004, 303(5663): 1526-1529
- [36] Dembny P, Newman AG, Singh M, et al. Human endogenous retrovirus HERV-K(HML-2) RNA causes neurodegeneration through Toll-like receptors. *JCI Insight*, 2020, 5(7): e131093
- [37] Kumar M, Carmichael GG. Antisense RNA: function and fate of duplex RNA in cells of higher eukaryotes. *Microbiol Mol Biol Rev*, 1998, 62(4): 1415-1434
- [38] Tunbak H, Enriquez-Gasca R, Tie CHC, et al. The HUSH complex is a gatekeeper of type I interferon through epigenetic regulation of LINE-1s. *Nat Commun*, 2020, 11(1): 5387
- [39] Chen R, Ishak CA, De Carvalho DD. Endogenous retroelements and the viral mimicry response in cancer therapy and cellular homeostasis. *Cancer Discov*, 2021, 11(11): 2707-2725
- [40] Reid Cahn A, Bhardwaj N, Vabret N. Dark genome, bright ideas: recent approaches to harness transposable elements in immunotherapies. *Cancer Cell*, 2022, 40(8): 792-797
- [41] Dumetier B, Sauter C, Hajmirza A, et al. Repeat element activation-driven inflammation: role of NF κ B and implications in normal development and cancer? *Biomedicines*, 2022, 10(12): 3101
- [42] Kato H, Takahashi K, Fujita T. RIG-I-like receptors: cytoplasmic sensors for non-self RNA. *Immunol Rev*, 2011, 243(1): 91-98
- [43] Rothenfusser S, Goutagny N, DiPerna G, et al. The RNA helicase Lgp2 inhibits TLR-independent sensing of viral replication by retinoic acid-inducible gene-I. *J Immunol*, 2005, 175(8): 5260-5268
- [44] Venkataraman T, Valdes M, Elsby R, et al. Loss of DEXD/H box RNA helicase LGP2 manifests disparate antiviral responses. *J Immunol*, 2007, 178(10): 6444-6455
- [45] Bruns AM, Leser GP, Lamb RA, et al. The innate immune sensor LGP2 activates antiviral signaling by regulating MDA5-RNA interaction and filament assembly. *Mol Cell*, 2014, 55(5): 771-781
- [46] Uchikawa E, Lethier M, Malet H, et al. Structural analysis of dsRNA binding to anti-viral pattern recognition receptors LGP2 and MDA5. *Mol Cell*, 2016, 62(4): 586-602
- [47] Rehwinkel J, Gack MU. RIG-I-like receptors: their regulation and roles in RNA sensing. *Nat Rev Immunol*, 2020, 20(9): 537-551
- [48] Binder M, Eberle F, Seitz S, et al. Molecular mechanism of signal perception and integration by the innate immune sensor retinoic acid-inducible gene-I (RIG-I). *J Biol Chem*, 2011, 286(31): 27278-27287
- [49] Jiang F, Ramanathan A, Miller MT, et al. Structural basis of RNA recognition and activation by innate immune receptor RIG-I. *Nature*, 2011, 479(7373): 423-427
- [50] Goubau D, Deddouche S, Reis e Sousa C. Cytosolic sensing of viruses. *Immunity*, 2013, 38(5): 855-869
- [51] Chiappinelli KB, Strissel PL, Desrichard A, et al. Inhibiting DNA methylation causes an interferon response in cancer via dsRNA including endogenous retroviruses. *Cell*, 2015, 162(5): 974-986
- [52] Mikhalkovich N, O'Carroll IP, Tkavc R, et al. Response of human macrophages to gamma radiation is mediated via expression of endogenous retroviruses. *PLoS Pathog*, 2021, 17(2): e1009305
- [53] Zhao Y, Oreskovic E, Zhang Q, et al. Transposon-triggered innate immune response confers cancer resistance to the blind mole rat. *Nat Immunol*, 2021, 22(10): 1219-1230
- [54] Rigby RE, Webb LM, Mackenzie KJ, et al. RNA: DNA hybrids are a novel molecular pattern sensed by TLR9. *EMBO J*, 2014, 33(6): 542-558
- [55] Grandi N, Tramontano E. Human endogenous retroviruses are ancient acquired elements still shaping innate immune responses. *Front Immunol*, 2018, 9: 2039
- [56] Sen P, Shah PP, Nativio R, et al. Epigenetic mechanisms of longevity and aging. *Cell*, 2016, 166(4): 822-839
- [57] Booth LN, Brunet A. The aging epigenome. *Mol Cell*, 2016, 62(5): 728-744
- [58] López-Otín C, Blasco MA, Partridge L, et al. The hallmarks of aging. *Cell*, 2013, 153(6): 1194-1217
- [59] Liu X, Liu Z, Wu Z, et al. Resurrection of endogenous retroviruses during aging reinforces senescence. *Cell*, 2023, 186(2): 287-304
- [60] Gorbunova V, Seluanov A, Mita P, et al. The role of retrotransposable elements in ageing and age-associated diseases. *Nature*, 2021, 596(7870): 43-53
- [61] Wood JG, Hillenmeyer S, Lawrence C, et al. Chromatin remodeling in the aging genome of *Drosophila*. *Aging Cell*, 2010, 9(6): 971-978
- [62] Brennecke J, Aravin AA, Stark A, et al. Discrete small RNA-generating loci as master regulators of transposon activity in *Drosophila*. *Cell*, 2007, 128(6): 1089-1103
- [63] Wood JG, Jones BC, Jiang N, et al. Chromatin-modifying genetic interventions suppress age-associated transposable element activation and extend life span in *Drosophila*. *Proc Natl Acad Sci USA*, 2016, 113(40): 11277-11282
- [64] Jones BC, Wood JG, Chang C, et al. A somatic piRNA

- pathway in the *Drosophila* fat body ensures metabolic homeostasis and normal lifespan. *Nat Commun*, 2016, 7 (1): 13856
- [65] Chen H, Zheng X, Xiao D, et al. Age-associated de-repression of retrotransposons in the *Drosophila* fat body, its potential cause and consequence. *Aging Cell*, 2016, 15 (3): 542-552
- [66] Li W, Prazak L, Chatterjee N, et al. Activation of transposable elements during aging and neuronal decline in *Drosophila*. *Nat Neurosci*, 2013, 16(5): 529-531
- [67] Yang N, Srivastav SP, Rahman R, et al. Transposable element landscapes in aging *Drosophila*. *PLoS Genet*, 2022, 18(3): e1010024
- [68] Sturm Á, Sasköi É, Hotzi B, et al. Downregulation of transposable elements extends lifespan in *Caenorhabditis elegans*. *Nat Commun*, 2023, 14(1): 5278
- [69] Simon M, Van Meter M, Ablaeva J, et al. LINE1 derepression in aged wild-type and SIRT6-deficient mice drives inflammation. *Cell Metab*, 2019, 29(4): 871-885
- [70] Van Meter M, Kashyap M, Rezazadeh S, et al. SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. *Nat Commun*, 2014, 5(1): 5011
- [71] De Cecco M, Ito T, Petrashen AP, et al. L1 drives IFN in senescent cells and promotes age-associated inflammation. *Nature*, 2019, 566(7742): 73-78
- [72] Thomas CA, Tejwani L, Trujillo CA, et al. Modeling of TREX1-dependent autoimmune disease using human stem cells highlights L1 accumulation as a source of neuroinflammation. *Cell Stem Cell*, 2017, 21(3): 319-331.e8
- [73] Evering TH, Marston JL, Gan L, et al. Transposable elements and Alzheimer's disease pathogenesis. *Trends Neurosci*, 2023, 46(3): 170-172
- [74] Sun W, Samimi H, Gamez M, et al. Pathogenic tau-induced piRNA depletion promotes neuronal death through transposable element dysregulation in neurodegenerative tauopathies. *Nat Neurosci*, 2018, 21(8): 1038-1048
- [75] Grundman J, Spencer B, Sarsoza F, et al. Transcriptome analyses reveal tau isoform-driven changes in transposable element and gene expression. *PLoS ONE*, 2021, 16(9): e0251611
- [76] Macciardi F, Giulia Bacalini M, Miramontes R, et al. A retrotransposon storm marks clinical phenocconversion to late-onset Alzheimer's disease. *GeroScience*, 2022, 44(3): 1525-1550
- [77] Jönsson ME, Garza R, Sharma Y, et al. Activation of endogenous retroviruses during brain development causes an inflammatory response. *EMBO J*, 2021, 40(9): e106423
- [78] Ramirez P, Zuniga G, Sun W, et al. Pathogenic tau accelerates aging-associated activation of transposable elements in the mouse central nervous system. *Prog Neurobiol*, 2022, 208: 102181
- [79] Ochoa E, Ramirez P, Gonzalez E, et al. Pathogenic tau-induced transposable element-derived dsRNA drives neuroinflammation. *Sci Adv*, 2023, 9(1): eabq5423
- [80] Lanciano S, Cristofari G. Measuring and interpreting transposable element expression. *Nat Rev Genet*, 2020, 21 (12): 721-736
- [81] McGinnis W, Shermoen AW, Beckendorf SK. A transposable element inserted just 5' to a *Drosophila* glue protein gene alters gene expression and chromatin structure. *Cell*, 1983, 34(1): 75-84
- [82] Lee JY, Ji Z, Tian B. Phylogenetic analysis of mRNA polyadenylation sites reveals a role of transposable elements in evolution of the 3'-end of genes. *Nucleic Acids Res*, 2008, 36(17): 5581-5590
- [83] Reddy ASN, Marquez Y, Kalyna M, et al. Complexity of the alternative splicing landscape in plants. *Plant Cell*, 2013, 25(10): 3657-3683
- [84] Shah NM, Jang HJ, Liang Y, et al. Pan-cancer analysis identifies tumor-specific antigens derived from transposable elements. *Nat Genet*, 2023, 55(4): 631-639
- [85] Nigumann P, Redik K, Mätlik K, et al. Many human genes are transcribed from the antisense promoter of L1 retrotransposon. *Genomics*, 2002, 79(5): 628-634
- [86] Criscione SW, Theodosakis N, Micevic G, et al. Genome-wide characterization of human L1 antisense promoter-driven transcripts. *BMC Genomics*, 2016, 17(1): 463
- [87] Peaston AE, Evsikov AV, Graber JH, et al. Retrotransposons regulate host genes in mouse oocytes and preimplantation embryos. *Dev Cell*, 2004, 7(4): 597-606
- [88] Modzelewski AJ, Shao W, Chen J, et al. A mouse-specific retrotransposon drives a conserved Cdk2ap1 isoform essential for development. *Cell*, 2021, 184(22): 5541-5558.e22
- [89] Magwire MM, Bayer F, Webster CL, et al. Successive increases in the resistance of *Drosophila* to viral infection through a transposon insertion followed by a duplication. *PLoS Genet*, 2011, 7(10): e1002337
- [90] Babaian A, Mager DL. Endogenous retroviral promoter exaptation in human cancer. *Mobile DNA*, 2016, 7(1): 24
- [91] Jang HS, Shah NM, Du AY, et al. Transposable elements drive widespread expression of oncogenes in human cancers. *Nat Genet*, 2019, 51(4): 611-617
- [92] Lock FE, Rebollo R, Miceli-Royer K, et al. Distinct isoform of FABP7 revealed by screening for retroelement-activated genes in diffuse large B-cell lymphoma. *Proc Natl Acad Sci USA*, 2014, 111(34): E3534-E3543