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INTAC复合体的功能研究与机制探索新进展

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摘要 基因表达的精确时空调控对生物体的生存和发育至关重要. Integrator作为一种后生动物特异性的多亚基复合物, 能够与蛋白磷酸酶PP2A核心酶(PP2A-AC)形成稳定的复合体, 被命名为INTAC(Integrator-PP2A-AC). INTAC复合体是RNA聚合酶Ⅱ启动子近端暂停和提前终止的关键调节因子, 还对多种非编码RNA进行3′末端加工. INTAC复合体在转录调控中发挥重要作用, 其功能缺失与多种生理过程异常及疾病发生密切相关. 本文系统梳理了INTAC复合体的发现历程、结构特征及功能进展, 重点解析了其在转录调控过程中的多重作用, 并总结了INTAC复合体在生理和疾病中的关键功能.

关键词 INTAC, Integrator, PP2A, RNA聚合酶Ⅱ, 转录终止

基因表达的多层级精密调控网络, 对生物体的发育以及各种生物学功能稳态的维持至关重要. 当基因表达发生异常时会导致多种疾病(包括癌症、代谢性疾病、神经退行性疾病等)的发生, 而基因的转录是基因表达的核心环节, 作为遗传信息传递的关键节点, 转录不仅通过RNA聚合酶对基因的精准识别实现遗传信息的读取, 更通过动态调控塑造细胞命运.

RNA聚合酶Ⅱ(Pol Ⅱ)介导的转录是一个复杂且精密的过程, 包括转录起始、启动子近端暂停和释放、有效延伸及转录终止[1~5]. 启动子近端暂停是后生动物所特有的转录过程, 它是指Pol II在转录起始后延伸到20~100 bp后暂停的现象. 在停留不同的时间后, Pol II将走向两个命运: 继续延伸或启动子近端转录终止[4]. 众所周知, 基因的转录是动态且高度活跃的生物学过程, 常伴随DNA双链解旋引发的不稳定性. 为了维持遗传信息调控的精确性和基因组的稳定性, 整个转录过程都依赖严密的调控机制, 包括染色质重塑与修饰因子[6]、多种转录因子[7,8]、Mediator复合体[9]、INTAC复合体[10,11]等. 其中, INTAC(Integrator-PP2A-AC)复合体是近年来新发现的转录调控因子[12], 其作为一种非经典的PP2A全酶, 在转录调控中发挥着重要的作用. INTAC复合体的蛋白磷酸酶与核酸内切酶的活性分别调控转录的不同过程, 磷酸酶模块主要抑制暂停Pol Ⅱ的释放和转录延伸以限制转录的激活, 而核酸内切酶模块主要切割新生RNA, 介导暂停Pol II的启动子近端转录终止, 并减弱增强子的无效转录[13~16]. 此外, 越来越多的研究表明, INTAC复合体发育异常或功能失调可导致多种疾病, 尤其在胚胎发育、神经功能及肿瘤发生等方面[17~19], 因此亟待深入了解INTAC复合体的具体功能和作用机制.

1 INTAC(Integrator-PP2A-AC)复合体的发现

1.1 Integrator的发现

Integrator复合体是一类分子量约1.5 MDa的多亚基转录调控复合体, 于2005年在人类细胞中被首次鉴

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定, 该复合物因能够特异性结合RNA聚合酶Ⅱ(Pol Ⅱ)的C端结构域(CTD)而引起广泛关注[12]. 基于质谱的蛋白质组学分析揭示了其由12个未表征的亚基(INTS1-INTS12)组成, 这些亚基与Pol Ⅱ多个组分存在直接的相互作用(图1). 值得注意的是, Integrator复合体在高等生物中高度保守, 但在酵母等低等真核生物中完全缺失, 暗示其在高等生物中进化出独特的转录调控功能[12]. 功能研究表明, Integrator复合体通过与Pol Ⅱ CTD结合被特异性招募到小核RNA(small nuclear RNA, snRNA)基因位点, 当snRNA的3′末端加工信号(3′box)被转录识别后, Integrator复合体的内切酶活性亚基INTS11切割新生RNA前体的3′端, 触发转录终止并释放成熟的snRNA到细胞核质中, 参与剪接体的组装并发挥下一步功能[10,12,20]. 后续研究通过全基因组的RNA干扰(RNAi)筛选, 进一步鉴定了INTS13和INTS14两个辅助亚基的存在[21], 并通过生物化学的手段确认C7orf26为Integrator复合体的第15个核心组分, 后被命名为INTS15[22]. 尽管已知Integrator复合体通过剪切暂停状态下Pol Ⅱ所合成的RNA以促进转录终止, 但其剪切的具体分子机制及其与Pol Ⅱ CTD磷酸化调控的协同关系仍亟待阐明.

1.2 INTAC复合体的发现

蛋白磷酸酶2A(PP2A)作为真核生物中高度保守的丝氨酸/苏氨酸磷酸酶, 负责调控细胞内约50%的蛋白去磷酸化事件, 是信号转导与转录调控的核心执行者[23], 然而, PP2A是否可以通过发挥去磷酸化活性直接参与转录调控仍待进一步的研究. 近年来, 研究者通过核内PP2A功能分析发现, Integrator复合体能够与PP2A的核心酶(由支架亚基PP2A-A和催化亚基PP2A-C组成)形成稳定互作. 基于冷冻电子显微镜(cryo-EM)的结构解析与染色质免疫沉淀测序(ChIP-seq)定位研究证实, 绝大多数Integrator复合体亚基均可与PP2A核心酶(PP2A-AC)共定位, 并共同组装为功能性超分子复合体——INTAC(Integrator-PP2A-AC)[11]. 图1展示了INTAC复合体的模块化结构特征: Integrator复合体作为支架平台, 招募PP2A-AC形成非经典PP2A全酶. 与传统PP2A全酶(由PP2A-AC与调节亚基PP2A-B组成)不同, INTAC复合体通过Integrator亚基实现底物特异性识别, 从而直接参与Pol II的去磷酸化与转录终止调控. 这一发现不仅拓展了PP2A的生物学功能范畴, 更为理解转录-表观遗传交叉调控提供了全新视角.

2 INTAC复合体的组成

INTAC复合体的核心模块包括骨架和肩部模块, 骨架模块由INTS1、INTS2和INTS7组成, INTS5和INTS8也被称为INTAC复合体的“肩膀”, 与骨架模块一起作为复合体其他模块交互的脚手架. 磷酸酶模块(INTS6、PP2A-AC)与核心模块结合, 可使Pol Ⅱ的CTD去磷酸化[16]. 核酸内切酶模块由INTS4、INTS9和INTS11组成[24]. 辅助模块因其结构形态类似于蝎子的尾巴, 也被称为“尾部”模块, INTS13和INTS14紧密相连, 并通过INTS13直接连接到内切酶模块[25,26]. INTS15与INTS10-INTS13-INTS14亚基结合并与INTS5相连, 将辅助模块定位到INTAC复合体的核心位置[27](图1). 迄今为止, 研究者们已经鉴定了INTAC复合体所包含的18个亚基, 包括INTS1-INTS15[12,21,22]、PP2AC[10,11]、SOSS[28]和DSS1[29].

2.1 INTAC复合体的蛋白磷酸酶模块: 转录暂停的“刹车系统”——INTS6/PP2A-A/PP2A-C

在INTAC复合体的磷酸酶模块中, PP2A磷酸酶被招募至INTAC骨架, 此过程依赖于INTS5/8“肩膀”模块和INTS6亚基的存在[30], INTS8亚基可直接接触PP2A结构亚基(PP2A-A)[10](图1).

INTAC复合体的磷酸酶模块通过去磷酸化Pol Ⅱ的C端结构域(CTD), 在转录动态平衡与基因组稳定性的维持中发挥核心作用. 该模块可特异性去除Pol II CTD的Ser2/5/7位点磷酸化, 拮抗转录延伸促进因子b(The positive transcription elongation factor b, P-TEFb)的激酶活性, 稳定启动子近端暂停的Pol II, 确保基因表达快速响应外界刺激. 研究表明, INTS8或PP2A核心酶的整体耗竭会导致Pol II CTD在Ser5和Ser2位点的磷酸化水平及新生转录RNA水平的升高[10,11,13]. 此外, 研究发现, INTS6、INTS8和PP2A磷酸酶(Int-PP2A)形成了一个独特的INTAC功能模块, 通过控制P-TEFb催化亚基CDK9的关键底物, 包括Pol II CTD和DRB敏感性诱导因子(DRB sensitivity-inducing factor, DSIF)等的磷酸化, 拮抗CDK9活性, 维持转录平衡[30].

2.2 INTAC复合体的内切酶模块: 转录终止的“分子剪刀”——INTS4/9/11

在所有INTAC复合体的亚基中, 内切酶模块的结构和功能是最为深入研究的[11,31~33]. INTS9和INTS11

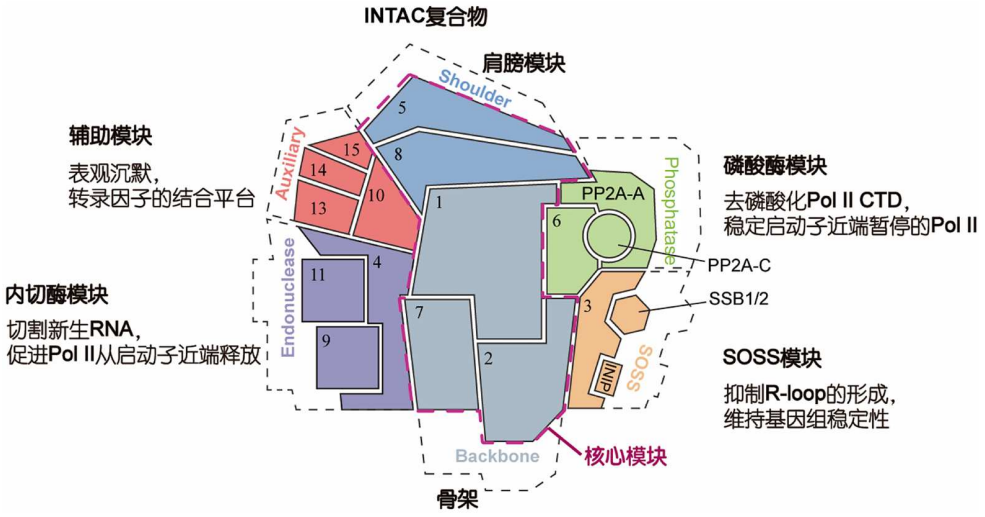

图 1 INTAC复合体的结构组成示意图. INTAC复合体的结构可划分为骨架模块、肩膀模块、内切酶模块、磷酸酶模块、辅助模块以及SOSS模块. 其中, 内切酶模块和磷酸酶模块分别切割RNA和去除Pol II磷酸化, 促进启动子近端转录终止; 辅助模块可提供转录因子的结合平台, 促进表观沉默; SOSS模块则抑制R-loop的形成, 维持基因组稳定

Figure 1 Schematic diagram of the structural composition of the INTAC complex. The INTAC complex comprises six structural modules: backbone, shoulder, endonuclease, phosphatase, auxiliary and SOSS module. Endonuclease module: Cleaves RNA to mediate promoter-proximal transcription termination; Phosphatase module: Dephosphorylates Pol II to release paused transcription; Auxilary module: Provides docking sites for transcription factors, enabling epigenetic silencing; SOSS module: Prevents R-loop accumulation to maintain genome stability

是两个核酸内切酶亚基，分别类似于CPSF100和CPSF73(经典多聚腺苷酸化复合体的RNA切割酶), INTS11的大部分N端MBL结构域和β-CASP结构域与CPSF73高度保守[34]. INTS9和INTS11以“头对头”的方式排列, 形成一种伪对称异二聚体, 共同构成一个保守的酶活催化口袋，发挥底物识别与切割RNA的酶活功能. INTS4作为支架蛋白, 是INTAC复合体介导RNA切割的关键组分，可将核酸酶二聚体整合进完整的INTAC复合体中[35].

研究发现，INTAC复合体的核酸内切酶模块的成熟与激活受到严格的时间-空间控制，其分子机制涉及多层次的伴侣蛋白介导的组装与活性位点屏蔽[33], 主要包含WDR73(WD Repeat Domain 73) 和BRAT1 (BRCA1-associated ATM activator 1). WDR73是一种属于WD重复蛋白家族的分子伴侣蛋白，通过与INTS11亚基结合，可直接覆盖INTS11的金属离子依赖性内切酶活性位点，形成物理屏障以阻止底物RNA的过早结合，有助于稳定INTS11并在异二聚化过程中阻断其活性位点；BRAT1是一种多功能支架蛋白，有助于将INTS9/11异二聚体从细胞质导入细胞核；在细胞核内可与INTS4亚基互作, 确保INTS9/11在核内精准对接至INTAC复合体骨架, 避免游离亚基的异常聚集[33].

INTAC内切酶通过切割新生RNA, 促进Pol II从启动子近端释放, 可防止无效转录延伸. 研究发现, 体内将INTS11快速降解，破坏INTAC的核酸内切酶模块的功能时, 可诱导Pol Ⅱ在启动子近端的积累, 并阻止Pol Ⅱ的启动子近端提前终止[13]; 在基因远端, INTAC复合体通过磷酸酶模块切割异常延伸的RNA(如反义转录本或未成熟的RNA)，可防止转录通读和基因组不稳定性的发生[28].

2.3 INTAC复合体的辅助模块: 表观沉默和转录因子的“神秘调控者”——INTS10/13/14/15

INTAC的辅助模块由INTS10、INTS13、INTS14和INTS15形成的四聚体构成，也被称为“臂”模块，是INTAC复合体中科学家了解最少的模块，虽不直接参与RNA切割或磷酸酶催化的功能，却在整个INTAC复合体组装、染色质重塑、转录因子的结合与招募及疾病调控中发挥着不可或缺的“幕后调控者”角色(图1). INTS13和INTS14以异二聚体的构象相互连接[26]. INTS15与INTS5和INTS10相互作用，可通过INTS10将INTS13/INTS14异二聚体与INTAC核心连接, 是辅助模块组装至INTAC的关键因子[27]. INTS15直接作用于INTS10，参与调节蛋白质编码基因上的Pol Ⅱ的暂停

释放, INTS13/14/10可以被独立募集到顺式作用元件上并调控它们的激活[36].

尽管辅助模块在INTAC复合体核酸内切酶模块介导的snRNA加工中发挥辅助作用, 但其缺失仅会导致轻微的snRNA终止缺陷, 因此该模块可能具有独立于INTAC复合体的功能[26,36~38]. INTS13可识别增强子区域的非编码RNA转录本, 辅助INTS11亚基切割增强子RNA(enhancer RNA, eRNA), 防止染色质的过度开放及邻近基因的异常激活[39]. 当INTAC复合体被招募到暂停的Pol II时, INTS13和INTS14亚基上的保守位点, 可作为枢纽来促进序列特异性转录因子与INTAC复合体的结合, 从而通过整合不同信号调控转录进程[27,40].

与此同时, 最新研究发现, INTAC复合体的辅助模块具有独特的非酶活依赖功能, 其能够招募组蛋白去甲基化酶复合物RACK7/ZMYND8-KDM5C到染色质的启动子区域, 通过降低染色质上组蛋白H3K4甲基化修饰, 从而介导转录沉默并抑制肿瘤细胞的生长[41]. 此外, 辅助模块对人类多能性神经干细胞的分化命运也具有重要调控作用[42].

2.4 INTAC复合体的SOSS模块: 基因组稳定性的“双重守卫”——INTS3/SOSS-B1/SOSS-B2

INTAC复合体的SOSS模块是由INTS3、SSB1/2和未表征的蛋白INIP(SOSS-C)组成的一种异三聚体, 其可在体内或体外形成稳定的复合物, 可以感应和修复DNA损伤. INTS3是SSB1/2被募集到双链DNA断裂位点(double strand break, DSB)所必需的[43~45].

研究发现, INTAC可和SOSS形成稳定的复合物, 且该复合物靶向活性启动子和增强子区域, 部分依赖于R-loop中单链DNA(ssDNA, single-stranded DNA)处SSB1/2的募集. SOSS模块可以抑制暂停的Pol Ⅱ的异常积累并防止染色质过于开放, 抑制转录相关的R-loop的形成, 从而维持基因组的稳定性[28]. INTAC-SOSS模块的发现可作为连接调控Pol Ⅱ暂停与维持基因组稳定性的桥梁, 为进一步研究调控Pol Ⅱ暂停在除转录外的其他背景下(如DNA复制和损伤修复)的作用奠定了基础.

3 INTAC复合体参与多个转录调控过程

3.1 INTAC复合体参与增强子RNA的生成

增强子是一种参与调节细胞分化类型和特定基因表达的DNA顺式作用元件[46]. 作为远端DNA序列, 增强子通过形成调节染色质环与其近端启动子结合, 将Pol Ⅱ募集到目标启动子, 进而促进特定基因的转录[47,48]. 一些活性增强子元件被Pol Ⅱ转录以产生非编码增强子RNA. 这些eRNA相对较短(小于1 kb)并在染色质上积累[49], 它们可以重编程多个分化特异性基因的转录, 这可能是胚胎发育、细胞分化过程中基因表达的基础. 而eRNA发生异常会导致基因的持续表达, 从而引起癌症的发生[50]. 研究证实, INTAC复合体通过调控Pol II的转录终止和新生RNA的加工, 在eRNA的生成中发挥关键作用. INTAC复合体的INTS11亚基可识别增强子区域新生eRNA的特定终止信号, 切割RNA前体, 触发转录终止, 从而限制eRNA的长度(通常为0.5~2 kb), 并生成成熟eRNA[51]. 在小鼠红白血病细胞中的INTAC复合体耗竭后, Pol Ⅱ无法及时终止, 在eRNA位点过度积累, 从而导致eRNA的过度延伸并侵入邻近基因区域, 引发异常染色质环和原癌基因的异常激活[52]. 研究表明, eRNA的短暂生成可能通过相分离形成转录凝聚体, 招募Mediator和转录因子, 促进增强子与目标启动子的互作[9,53]. 此外, INTAC复合体的磷酸酶模块可通过去磷酸化Pol II CTD的Ser2/5/7位点, 拮抗激酶的活性, 限制Pol II在增强子区域的持续延伸(图2(a)). 这种动态平衡可确保eRNA呈“脉冲式”生成, 防止过度转录消耗调控资源. INTAC复合体可招募组蛋白去乙酰化酶(HDAC1/2)和H3K4me3去甲基化酶(KDM4C), 擦除增强子区域的活跃表观标记, 抑制eRNA的持续性转录[51].

3.2 INTAC复合体参与小核RNA加工

小核RNA(snRNA)是一种主要由Pol Ⅱ转录的非编码RNA. 在mRNA前体剪切中发挥关键作用, 其中U1、U2、U4和U5小核RNA直接整合于剪切体中, 而U3和U7 snRNA分别参与rRNA的加工和组蛋白mRNA的转录终止[54~57]. INTAC复合体在snRNA基因转录终止过程中发挥核心功能, 其功能类似于在蛋白质编码基因中起作用的剪切多聚腺苷酸化因子(CPSF). 当延伸过程中的Pol II接近snRNA基因的3′端时, 会遇到富含腺嘌呤的多聚腺苷酸尾(poly A)信号, 从而触发依赖于Pol II CTD的CPSF和剪切刺激因子(CstF)复合体聚集[58]. snRNA基因座具有独特的结构特征, 包括招募Pol II所需的特定DNA基序: 相对于转录起始位点的远端序列元件(DSE)和近端序列元件(PSE)[59](图2(b)). 此

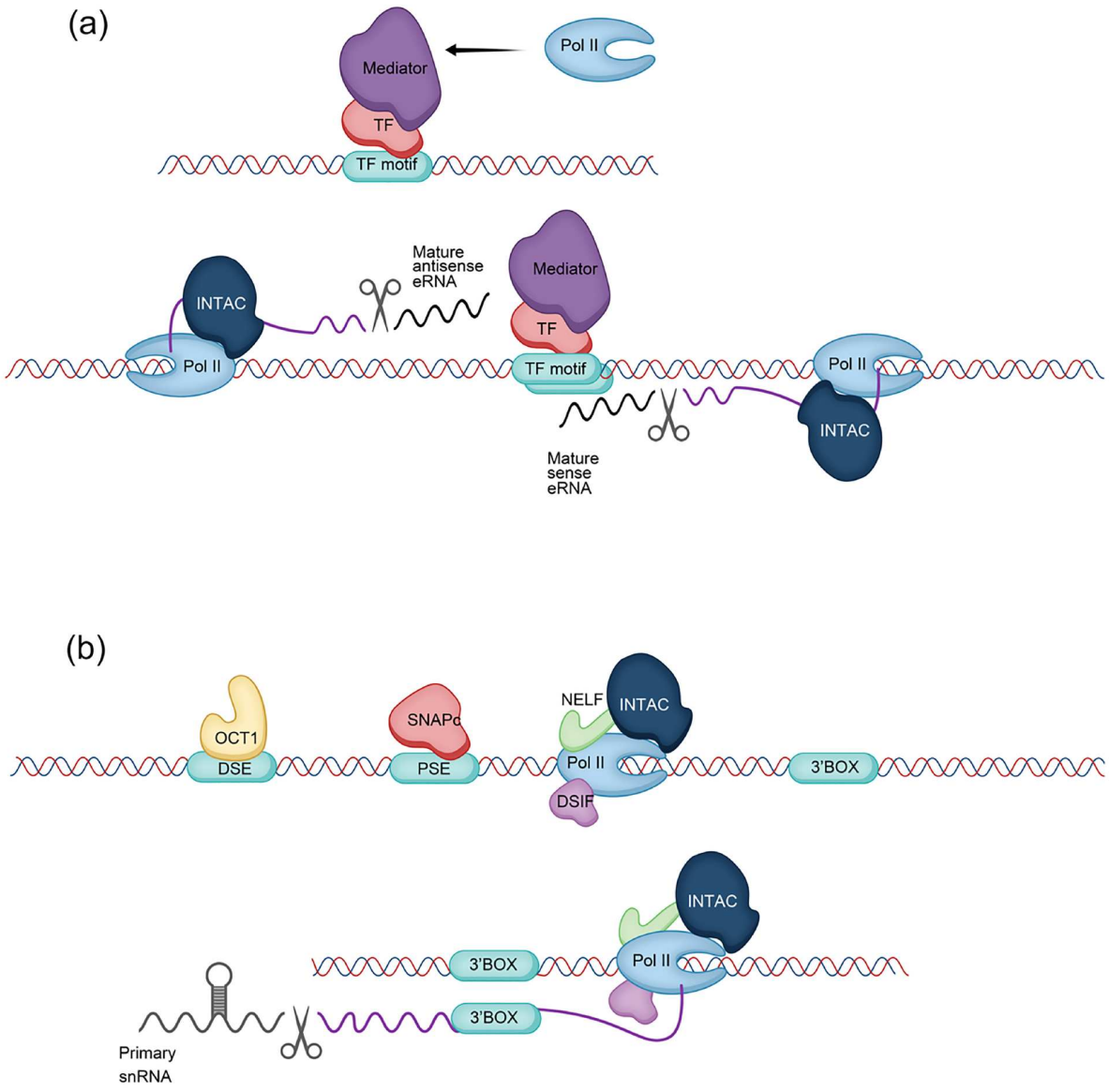

图 2 INTAC复合体参与增强子RNA的生成及小核RNA加工作用机制示意图. (a) 增强子位点通过序列特异性转录因子激活, 这些因子招募共激活因子中介体复合物(Mediator). 在Mediator被募集且转录前起始复合体组装完成后(未图示), 增强子位点发生双向转录, 产生长度超过200 bp的正向和反向转录本(称为增强子RNA, eRNA). 无论是正向还是反向转录的Pol II全酶, 均通过招募INTAC复合体终止转录并释放eRNA, 但不会引发其多聚腺苷酸化. (b) 小核RNA(snRNA)基因座具有独特的启动子元件——远端序列元件(DSE)和近端序列元件(PSE), 它们分别结合OCT1(POU2F1)转录因子和小核RNA激活蛋白复合物(SNAPc). OCT1与SNAPc共同促进募集具有转录起始能力的RNA聚合酶II(Pol II)全酶, 其中包括DRB敏感性诱导因子(DSIF)、负延伸因子(NELF)以及INTAC复合体. Pol II的最大亚基(RBP1)C端结构域(CTD)的Ser7位点磷酸化(P)触发INTAC复合体在转录通过"3′ box"(所有snRNA终止位点的高度保守基序)后, 切割新生的小RNA

Figure 2 Schematic diagram illustrating the mechanism by which the INTAC complex mediates enhancer RNA production and small nuclear RNA processing. (a) Enhancer loci are activated by sequence-specific transcription factors that recruit the coactivator Mediator complex. Following Mediator recruitment and assembly of the transcription preinitiation complex (not depicted), bidirectional transcription initiates at enhancers, generating sense and antisense transcripts exceeding 200 bp in length (termed enhancer RNAs, eRNAs). Both sense- and antisense-oriented RNA polymerase II (Pol II) holoenzymes recruit the INTAC complex to terminate transcription and release eRNAs without triggering polyadenylation. (b) Small nuclear RNA (snRNA) gene loci contain unique promoter elements—the distal sequence element (DSE) and proximal sequence element (PSE)—which bind to the OCT1(POU2F1) transcription factor and the snRNA-activating protein complex (SNAPc), respectively. OCT1 and SNAPc cooperatively recruit transcription-competent Pol II holoenzymes containing DRB sensitivity-inducing factor (DSIF), negative elongation factor (NELF), and the INTAC complex. Phosphorylation (P) of Ser7 residues within the C-terminal domain (CTD) of Pol II's largest subunit (RBP1) triggers INTAC-mediated cleavage of nascent snRNAs after transcription traverses the "3′ box," a highly conserved motif at all snRNA termination sites

外, 人类snRNA基因座中普遍存在一段富含AT的核苷酸序列, 称为3′box, 3′box的存在对U1 snRNA的转录终止至关重要[60], INTAC复合体的内切酶模块可识别3′box并切割RNA, 磷酸酶模块去磷酸化Pol II以促进终止, 切割后的成熟snRNA被快速输出核外, 组装剪切体[12,35]. 当敲低INTS11或INTS1时, 切割活性的缺失会导致跨越3′box位点的未加工转录本异常积累[12]. INTAC复合体功能的缺失将导致Pol II的转录通读以及染色质上Pol II在snRNA基因座3′末端下游数千碱基处的异常滞留[51].

3.3 INTAC复合体参与编码蛋白质基因的过早转录终止

基因活性的精确时空控制对于生物体在不断变化的环境中的发育、生长和生存至关重要. 基因调控的决定性步骤包括在转录早期时Pol Ⅱ暂停, 以及暂停Pol Ⅱ释放并有效延伸[4]. 在转录早期过程中, Pol Ⅱ与DSIF和转录延伸负向调控因子(Negative elongation factor, NELF)组装形成暂停延伸复合物(paused Pol Ⅱ elongation complex, PEC), 该复合物作为Pol II命运调控的“分子开关”, 可在启动子的转录起始位点下游20-100 bp处发生短暂暂停[61], 之后Pol Ⅱ可以继续有效延伸以合成RNA或者发生转录提前终止. INTAC复合体与Pol Ⅱ复合物结合, 介导启动子附近的转录终止[29,31,62](图3).

染色质的免疫共沉淀实验表明, INTAC复合体不仅存在于小核RNA基因中, 还与启动子近端暂停位点处大多数编码蛋白质基因的Pol Ⅱ共定位[63,64]. INTAC复合体各亚基的敲低或耗竭会影响全基因组的转录水平. 新生RNA分析结果显示, INTAC复合体会优先在许多转录单元(包括蛋白质编码的基因mRNA、长非编码RNA、增强子RNA和反义转录本)的前2 kb区域内终止转录, 这一区域被称为“暂停区”[14,15,61]. 另一INTAC复合体介导的终止位点是R-loop. R-loop是一种由RNA-DNA杂交体和未配对的非模板链DNA组成的结构, R-loop的过度积累会干扰复制叉的形成, 还容易引发

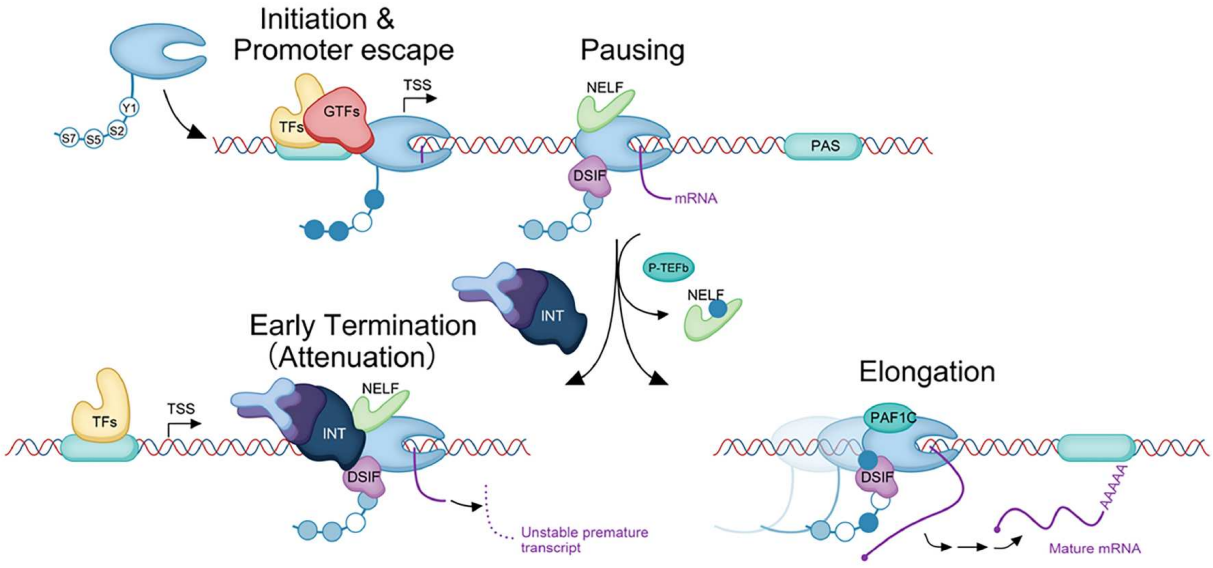

图 3 Pol II命运调控的“分子开关”——INTAC-PEC复合物作用机制示意图. 在转录早期, Pol Ⅱ与DSIF和NELF组装形成暂停延伸复合物(INTAC-PEC), 在启动子的TSS下游20~100 bp处短暂暂停, 之后Pol Ⅱ可以继续有效延伸或者发生转录提前终止. INTAC-PEC可介导启动子附近的转录终止, INTAC复合体的磷酸酶模块通过去磷酸化CTD的Ser2/5/7位点, 削弱P-TEFb的招募, 阻断其介导的延伸信号, 内切酶模块识别新生RNA的终止信号, 在距离Pol II约15~50 nt处切割RNA链, 促使Pol II从DNA链上解离

Figure 3 The molecular switch governing Pol II fate regulation: Schematic diagram illustrating the mechanistic role of the INTAC-PEC complex. During early termination, Pol II assembles with DSIF and NELF to form a paused elongation complex (INTAC-PEC), transiently arresting 20–100 bp downstream of the transcription start site (TSS). The paused Pol II may either resume productive elongation or undergo premature termination. The INTAC-PEC mediates promoter-proximal termination through its dual enzymatic activities: the phosphatase module dephosphorylates Ser2/Ser5/Ser7 residues on the Pol II C-terminal domain (CTD), thereby suppressing P-TEFb recruitment and elongation signaling, while the endonuclease module recognizes termination signals on nascent RNA and cleaves the transcript 15–50 nucleotides downstream of Pol II to trigger transcription complex disassembly

DNA断裂、突变和基因组重组概率异常增高[65]. 单链DNA识别复合物SOSS通过其保守的SSB1亚基特异性结合R-loop结构中的ssDNA, 并与INTAC复合体的INTS3亚基互作, 形成SOSS-INTAC复合体. 该复合体以生物分子凝聚体的形式被招募至基因组R-loop富集区域, 通过INTS11亚基的内切酶活性切割新生RNA, 消解R-loop结构, 从而维持基因组稳定性[28]. INTAC复合体特异性结合暂停延伸复合物(PEC), 形成"预终止复合物"[28]. 游离状态下的INTAC内切酶是未激活状态, 当INTAC复合体通过与SPT5的特定结构域KOWx-4直接接触来结合PEC时, 其RNA结合通道被打开, INTS11内切酶活性被激活, 在PEC中, 磷酸酶模块的INTS6亚基直接接触NELF-B[29,31]. INTAC复合体结合PEC的同时, 可以阻碍正向延伸因子SPT6和PAF1的结合[31]. 此外, INTAC复合体的辅助模块可能通过与DSIF竞争结合PEC上游的DNA, 从而破坏DSIF-DNA钳, 从而使提前终止更加高效[29]. INTAC复合体的两种酶活性共同作用于PEC, INTAC复合体的内切酶模块在新生RNA的3′端约23个碱基处剪切RNA转录本, 剪切后可暴露下游RNA片段的5′磷酸末端[31,62], INTS11亚基发挥其5′-3′核酸外切酶活性, 破坏RNA-DNA杂交体以促使新生转录终止[29]. INTAC复合体的磷酸酶模块可去磷酸化SPT5的KOWx-4 RNA结合区和Pol Ⅱ CTD七肽重复序列, 这些区域通过和INTS2、INTS4、INTS7的接触被招募到磷酸酶的活性位点[25,31,62]. PP2A磷酸酶拮抗P-TEFb激酶的作用, 后者可磷酸化SPT5和Pol Ⅱ CTD, 从而促进暂停Pol Ⅱ的释放和延伸[10,30], 而去磷酸化如何进一步破坏PEC尚不明确.

4 INTAC复合体在表观修饰中的功能与机制

基因转录进程的顺利进行与DNA修饰、组蛋白修饰和RNA修饰等表观遗传修饰有着密切关联[2], 然而两者之间如何协同发挥功能尚未得到详尽的解读. 近些年INTAC复合体被发现与组蛋白修饰密切相关, 可共同调控转录过程. 组蛋白修饰(histone modification)是指组蛋白在相关酶催化下发生甲基化、乙酰化、磷酸化、泛素化和ADP核糖基化等动态修饰的过程, 它可通过招募效应蛋白来改变染色质开放或凝聚的状态, 进而调控基因的表达.

组蛋白H3第四位赖氨酸的甲基化修饰(H3K4)在进化上高度保守, 其常被认为是基因表达的一个重要正向标记, 其在转录起始位点(TSS)的富集程度与基因表达呈现正相关性. 近期有研究发现, H3K4me2/3似乎对常认为的转录起始没有明显的调控作用, 反而对转录的另一个重要阶段——暂停有直接调控作用. Pol II受表观遗传修饰H3K4me3影响, 能够在启动子近端区域的短暂暂停保持稳定从而促进基因转录表达[66,67], 且INTAC复合体在此功能中可能发挥了重要作用, 但具体机制有待进一步剖析. 此外, 有研究发现INTAC复合体对COMPASS复合物(一种含有SET1的甲基转移酶复合物)有招募功能[40,41]. 这似乎让表观遗传和转录表达之间的相互监督调控存在了可能, 而INTAC复合体和H3K4me3成为维系两者平衡的重要角色.

最新研究发现, INTAC辅助模块与多个染色质结合复合物之间存在相互作用, 其能够与RACK7-KDM5C复合物直接结合, 将其招募至染色质的启动子区域, 参与调控组蛋白H3K4甲基化修饰, 进而影响基因的转录[41].

5 INTAC复合体在生理和疾病中的重要性

INTAC复合体的广泛存在表明它对细胞功能和生物体的发育具有不可或缺的重要作用. INTAC复合体的缺失会扰乱一系列细胞过程和分化途径[68~73]. INTAC复合体在发育和神经细胞的分化过程中发挥重要作用, 研究表明, 除INTS6亚基外, 大多数INTAC复合体亚基的同型合子缺失会导致多种模式生物的早期死亡, 可能是整个复合体不稳定所致[35,69,74~76]. 在小鼠体内, INTAC复合体可与同源染色质蛋白NIPBL和ZFP609相互作用, 并调节发育过程中与神经迁移相关基因的表达[77]. 在果蝇中, 核心骨架或者肩部模块的缺失会导致Ⅱ型神经母细胞的增多[78]. 此外, INTS1或者INTS8亚基的突变会导致严重的神经发育缺陷性疾病, 包括智力障碍、癫痫和脑部结构异常等[18,79]. 最近的研究发现, 与多种神经发育障碍有关的BRAT1, 可与INTS9/11异二聚体相互作用, BRAT1招募INTAC复合体对转录过程进行调控, 进一步影响RNA和蛋白的表达, 对神经发育过程产生影响[80].

INTAC复合体的功能性缺失(如基因突变)导致的病理改变与多种肿瘤类型的发生密切相关, 其中突变率最高的分别是INTS1、INTS2和INTS8. 不仅如此, INTS7的突变会引起胰腺腺癌[81], INTS3的突变与弥漫性大B细胞淋巴瘤[81]和白血病[82]的发生有关. INTS8的上调会导致肝细胞癌中的上皮-间质转化和转移潜能

的增加[83]. INTS6是磷酸酶模块的关键组分, 其缺失或下调与多种肿瘤如前列腺癌[84]、肝细胞癌[19,85]和造血系统恶性肿瘤[86]的不良预后相关. 因此, INTAC复合体多个亚基的突变在肿瘤的发生、发展过程中发挥重要影响, 深入解析INTAC复合体在肿瘤中的作用机制对肿瘤的靶向治疗具有重要价值.

6 总结与展望

本文主要总结了INTAC复合体的组成和结构特征, 这种模块化构象的阐明为理解其功能和机制提供了重要的基础. INTAC复合体参与细胞内的多种生物学过程, 包括RNA剪切、RNA稳定性和基因表达的调节, 这些过程对细胞发挥正常功能至关重要.

INTAC复合体中不同的功能模块既有各自独特的功能, 又能够互相协调, 共同调控转录进程. 作为转录后调控的重要参与者, INTAC复合体具有复杂的转录调控网络, 可与其他转录因子共同调控, 包括RNA内切酶模块介导Pol II的启动子近端转录终止, 以及磷酸酶模块介导的抑制转录延伸. 后续针对INTAC复合体介导的转录调控机制探究, 以及其在关键生物学过程, 如胚胎发育、肿瘤发展中的作用机制研究将具有重要研究意义.

参考文献

1 Jonkers I, Lis J T. Getting up to speed with transcription elongation by RNA polymerase II. Nat Rev Mol Cell Biol, 2015, 16: 167–177
2 Chen F X, Smith E R, Shilatifard A. Born to run: control of transcription elongation by RNA polymerase II. Nat Rev Mol Cell Biol, 2018, 19: 464–478
3 Cramer P. Organization and regulation of gene transcription. Nature, 2019, 573: 45–54
4 Core L, Adelman K. Promoter-proximal pausing of RNA polymerase II: a nexus of gene regulation. Genes Dev, 2019, 33: 960–982
5 Shang X Y, Xu C, Chen F X. From snapshots to a movie: capturing eukaryotic transcription initiation at single-nucleotide resolution. Sci Bull, 2024, 69: 853–855
6 Nagai S, Davis R E, Mattei P J, et al. Chromatin potentiates transcription. Proc Natl Acad Sci USA, 2017, 114: 1536–1541
7 Sanders T J, Lammers M, Marshall C J, et al. TFS and Spt4/5 accelerate transcription through archaeal histone-based chromatin. Mol Microbiol, 2019, 111: 784–797
8 Zhang J, Zhu B. Short, but matters: short tandem repeats confer variation in transcription factor-DNA binding. Sci Bull, 2024, 69: 9–10
9 Richter W F, Nayak S, Iwasa J, et al. The Mediator complex as a master regulator of transcription by RNA polymerase II. Nat Rev Mol Cell Biol, 2022, 23: 732–749
10 Huang K L, Jee D, Stein C B, et al. Integrator recruits protein phosphatase 2A to prevent pause release and facilitate transcription termination. Mol Cell, 2020, 80: 345–358.e9
11 Zheng H, Qi Y, Hu S, et al. Identification of integrator-PP2A complex (INTAC), an RNA polymerase II phosphatase. Science, 2020, 370: eabb5872
12 Baillat D, Hakimi M A, Näär A M, et al. Integrator, a multiprotein mediator of small nuclear RNA processing, associates with the C-terminal repeat of RNA polymerase II. Cell, 2005, 123: 265–276
13 Hu S, Peng L, Song A, et al. INTAC endonuclease and phosphatase modules differentially regulate transcription by RNA polymerase II. Mol Cell, 2023, 83: 1588–1604.e5
14 Lykke-Andersen S, Žumer K, Molska E Š, et al. Integrator is a genome-wide attenuator of non-productive transcription. Mol Cell, 2021, 81: 514–529.e6
15 Stein C B, Field A R, Mimoso C A, et al. Integrator endonuclease drives promoter-proximal termination at all RNA polymerase II-transcribed loci. Mol Cell, 2022, 82: 4232–4245.e11
16 Fujiwara R, Zhai S N, Liang D, et al. IntS6 and the Integrator phosphatase module tune the efficiency of select premature transcription termination events. Mol Cell, 2023, 83: 4445–4460.e7
17 Rienzo M, Casamassimi A. Integrator complex and transcription regulation: recent findings and pathophysiology. Biochim Biophys Acta (BBA)-Gene Regulatory Mech, 2016, 1859: 1269–1280
18 Oegema R, Baillat D, Schot R, et al. Human mutations in integrator complex subunits link transcriptome integrity to brain development. PLoS Genet, 2017, 13: e1006809
19 Lui K Y, Zhao H, Qiu C, et al. Integrator complex subunit 6 (INTS6) inhibits hepatocellular carcinoma growth by Wnt pathway and serve as a

prognostic marker. BMC Cancer, 2017, 17: 644
20 Baillat D, Wagner E J. Integrator: surprisingly diverse functions in gene expression. Trends Biochem Sci, 2015, 40: 257–264
21 Chen J, Ezzeddine N, Waltenspiel B, et al. An RNAi screen identifies additional members of the *Drosophila* Integrator complex and a requirement for cyclin C/Cdk8 in snRNA 3′-end formation. RNA, 2012, 18: 2148–2156
22 Replogle J M, Saunders R A, Pogson A N, et al. Mapping information-rich genotype-phenotype landscapes with genome-scale Perturb-seq. Cell, 2022, 185: 2559–2575.e28
23 Janssens V, Goris J. Protein phosphatase 2A: a highly regulated family of serine/threonine phosphatases implicated in cell growth and signalling. Biochem J, 2001, 353: 417–439
24 Albrecht T R, Shevtsov S P, Wu Y, et al. Integrator subunit 4 is a 'Symplekin-like' scaffold that associates with INTS9/11 to form the Integrator cleavage module. Nucleic Acids Res, 2018, 46: 4241–4255
25 Sabath K, Jonas S. Take a break: transcription regulation and RNA processing by the Integrator complex. Curr Opin Struct Biol, 2022, 77: 102443
26 Sabath K, Stäubli M L, Marti S, et al. INTS10–INTS13–INTS14 form a functional module of Integrator that binds nucleic acids and the cleavage module. Nat Commun, 2020, 11: 3422
27 Razew M, Fraudeau A, Pfleiderer M M, et al. Structural basis of the Integrator complex assembly and association with transcription factors. Mol Cell, 2024, 84: 2542–2552.e5
28 Xu C, Li C, Chen J, et al. R-loop-dependent promoter-proximal termination ensures genome stability. Nature, 2023, 621: 610–619
29 Fianu I, Ochmann M, Walshe J L, et al. Structural basis of Integrator-dependent RNA polymerase II termination. Nature, 2024, 629: 219–227
30 Vervoort S J, Welsh S A, Devlin J R, et al. The PP2A-Integrator-CDK9 axis fine-tunes transcription and can be targeted therapeutically in cancer. Cell, 2021, 184: 3143–3162.e32
31 Fianu I, Chen Y, Dienemann C, et al. Structural basis of Integrator-mediated transcription regulation. Science, 2021, 374: 883–887
32 Pfleiderer M M, Galej W P. Structure of the catalytic core of the Integrator complex. Mol Cell, 2021, 81: 1246–1259.e8
33 Sabath K, Qiu C, Jonas S. Assembly mechanism of Integrator's RNA cleavage module. Mol Cell, 2024, 84: 2882–2899.e10
34 Albrecht T R, Wagner E J. snRNA 3′ end formation requires heterodimeric association of Integrator subunits. Mol Cell Biol, 2012, 32: 1112–1123
35 Ezzeddine N, Chen J, Waltenspiel B, et al. A subset of *Drosophila* integrator proteins is essential for efficient U7 snRNA and spliceosomal snRNA 3′-end formation. Mol Cell Biol, 2011, 31: 328–341
36 Offley S R, Pfleiderer M M, Zucco A, et al. A combinatorial approach to uncover an additional Integrator subunit. Cell Rep, 2023, 42: 112244
37 Mascibroda L G, Shboul M, Elrod N D, et al. INTS13 variants causing a recessive developmental ciliopathy disrupt assembly of the Integrator complex. Nat Commun, 2022, 13: 6054
38 Azuma N, Yokoi T, Tanaka T, et al. Integrator complex subunit 15 controls mRNA splicing and is critical for eye development. Hum Mol Genet, 2023, 32: 2032–2045
39 Barbieri E, Trizzino M, Welsh S A, et al. Targeted enhancer activation by a subunit of the Integrator complex. Mol Cell, 2018, 71: 103–116.e7
40 Sabath K, Nabih A, Arnold C, et al. Basis of gene-specific transcription regulation by the Integrator complex. Mol Cell, 2024, 84: 2525–2541.e12
41 Fan P, Shang X Y, Song A, et al. Catalytic-independent functions of the Integrator–PP2A complex (INTAC) confer sensitivity to BET inhibition. Nat Chem Biol, 2025, doi: 10.1038/s41589-024-01807-x
42 Zhang Y, Hill C M, Leach K A, et al. The enhancer module of Integrator controls cell identity and early neural fate commitment. Nat Cell Biol, 2025, 27: 103–117
43 Skaar J R, Richard D J, Saraf A, et al. INTS3 controls the hSSB1-mediated DNA damage response. J Cell Biol, 2009, 187: 25–32
44 Li Y, Bolderson E, Kumar R, et al. hSSB1 and hSSB2 form similar multiprotein complexes that participate in DNA damage response. J Biol Chem, 2009, 284: 23525–23531
45 Huang J, Gong Z, Ghosal G, et al. SOSS complexes participate in the maintenance of genomic stability. Mol Cell, 2009, 35: 384–393
46 Pang B, van Weerd J H, Hamoen F L, et al. Identification of non-coding silencer elements and their regulation of gene expression. Nat Rev Mol Cell Biol, 2023, 24: 383–395
47 Pombo A, Dillon N. Three-dimensional genome architecture: players and mechanisms. Nat Rev Mol Cell Biol, 2015, 16: 245–257
48 Schaukowitch K, Joo J Y, Liu X, et al. Enhancer RNA facilitates NELF release from immediate early genes. Mol Cell, 2014, 56: 29–42
49 Andersson R, Gebhard C, Miguel-Escalada I, et al. An atlas of active enhancers across human cell types and tissues. Nature, 2014, 507: 455–461
50 Kim T K, Hemberg M, Gray J M, et al. Widespread transcription at neuronal activity-regulated enhancers. Nature, 2010, 465: 182–187
51 Lai F, Gardini A, Zhang A, et al. Integrator mediates the biogenesis of enhancer RNAs. Nature, 2015, 525: 399–403

52 Gurumurthy A, Yu D T, Stees J R, et al. Super-enhancer mediated regulation of adult β-globin gene expression: the role of eRNA and Integrator. Nucleic Acids Res, 2021, 49: 1383–1396

53 Heinz S, Romanoski C E, Benner C, et al. The selection and function of cell type-specific enhancers. Nat Rev Mol Cell Biol, 2015, 16: 144–154

54 Guiro J, Murphy S. Regulation of expression of human RNA polymerase II-transcribed snRNA genes. Open Biol, 2017, 7: 170073

55 Schümperli D, Pillai R S. The special Sm core structure of the U7 snRNP: far-reaching significance of a small nuclear ribonucleoprotein. Cell Mol Life Sci, 2004, 61: 2560–2570

56 Hoffmann I, Birnstiel M L. Cell cycle-dependent regulation of histone precursor mRNA processing by modulation of U7 snRNA accessibility. Nature, 1990, 346: 665–668

57 Hernandez N. Small nuclear RNA genes: a model system to study fundamental mechanisms of transcription. J Biol Chem, 2001, 276: 26733–26736

58 Mandel C R, Kaneko S, Zhang H, et al. Polyadenylation factor CPSF-73 is the pre-mRNA 3′-end-processing endonuclease. Nature, 2006, 444: 953–956

59 Egloff S, O'Reilly D, Murphy S. Expression of human snRNA genes from beginning to end. Biochem Soc Trans, 2008, 36: 590–594

60 Hernandez N. Formation of the 3′ end of U1 snRNA is directed by a conserved sequence located downstream of the coding region. EMBO J, 1985, 4: 1827–1837

61 Elrod N D, Henriques T, Huang K L, et al. The integrator complex attenuates promoter-proximal transcription at protein-coding genes. Mol Cell, 2019, 76: 738–752.e7

62 Zheng H, Jin Q, Wang X, et al. Structural basis of INTAC-regulated transcription. Protein Cell, 2023, 14: 698–702

63 Gardini A, Baillat D, Cesaroni M, et al. Integrator regulates transcriptional initiation and pause release following activation. Mol Cell, 2014, 56: 128–139

64 Stadelmayer B, Micas G, Gamot A, et al. Integrator complex regulates NELF-mediated RNA polymerase II pause/release and processivity at coding genes. Nat Commun, 2014, 5: 5531

65 García-Muse T, Aguilera A. R loops: from physiological to pathological roles. Cell, 2019, 179: 604–618

66 Wang H, Fan Z, Shliaha P V, et al. H3K4me3 regulates RNA polymerase II promoter-proximal pause-release. Nature, 2023, 615: 339–348

67 Hu S, Song A, Peng L, et al. H3K4me2/3 modulate the stability of RNA polymerase II pausing. Cell Res, 2023, 33: 403–406

68 Rubtsova M P, Vasilkova D P, Moshareva M A, et al. Integrator is a key component of human telomerase RNA biogenesis. Sci Rep, 2019, 9: 1701

69 Tao S, Cai Y, Sampath K. The Integrator subunits function in hematopoiesis by modulating Smad/BMP signaling. Development, 2009, 136: 2757–2765

70 Takata H, Nishijima H, Maeshima K, et al. The integrator complex is required for integrity of Cajal bodies. J Cell Sci, 2012, 125: 166–175

71 Otani Y, Nakatsu Y, Sakoda H, et al. Integrator complex plays an essential role in adipose differentiation. Biochem Biophys Res Commun, 2013, 434: 197–202

72 Jodoin J N, Shboul M, Albrecht T R, et al. The snRNA-processing complex, Integrator, is required for ciliogenesis and dynein recruitment to the nuclear envelope via distinct mechanisms. Biol Open, 2013, 2: 1390–1396

73 Kapp L D, Abrams E W, Marlow F L, et al. The integrator complex subunit 6 (Ints6) confines the dorsal organizer in vertebrate embryogenesis. PLoS Genet, 2013, 9: e1003822

74 Han S M, Lee T H, Mun J Y, et al. Deleted in cancer 1 (DICE1) is an essential protein controlling the topology of the inner mitochondrial membrane in *C. elegans*. Development, 2006, 133: 3597–3606

75 Hata T, Nakayama M. Targeted disruption of the murine large nuclear KIAA1440/Ints1 protein causes growth arrest in early blastocyst stage embryos and eventual apoptotic cell death. Biochim Biophys Acta, 2007, 1773: 1039–1051

76 Rutkowski R J, Warren W D. Phenotypic analysis of *deflated/Ints7* function in *Drosophila* development. Dev Dyn, 2009, 238: 1131–1139

77 van den Berg D L C, Azzarelli R, Oishi K, et al. Nipbl interacts with Zfp609 and the Integrator complex to regulate cortical neuron migration. Neuron, 2017, 93: 348–361

78 Zhang Y, Koe C T, Tan Y S, et al. The Integrator complex prevents dedifferentiation of intermediate neural progenitors back into neural stem cells. Cell Rep, 2019, 27: 987–996.e3

79 Krall M, Htun S, Schnur R E, et al. Biallelic sequence variants in INTS1 in patients with developmental delays, cataracts, and craniofacial anomalies. Eur J Hum Genet, 2019, 27: 582–593

80 Cihlarova Z, Kubovciak J, Sobol M, et al. BRAT1 links Integrator and defective RNA processing with neurodegeneration. Nat Commun, 2022, 13: 5026

81 Federico A, Rienzo M, Abbondanza C, et al. Pan-cancer mutational and transcriptional analysis of the Integrator complex. Int J Mol Sci, 2017, 18: 936

82 Yoshimi A, Lin K T, Wiseman D H, et al. Coordinated alterations in RNA splicing and epigenetic regulation drive leukaemogenesis. Nature, 2019, 574: 273–277

83 Tong H, Liu X, Li T, et al. INTS8 accelerates the epithelial-to-mesenchymal transition in hepatocellular carcinoma by upregulating the TGF-β signaling pathway. Cancer Manag Res, 2019, 11: 1869–1879

84 Filleur S, Hirsch J, Wille A, et al. INTS6/DICE1 inhibits growth of human androgen-independent prostate cancer cells by altering the cell cycle profile and Wnt signaling. Cancer Cell Int, 2009, 9: 28

85 Röpke A, Buhtz P, Böhm M, et al. Promoter CpG hypermethylation and downregulation of DICE1 expression in prostate cancer. Oncogene, 2005, 24: 6667–6675

86 Li J, Zhai X, Wang H, et al. Bioinformatics analysis of gene expression profiles in childhood B-precursor acute lymphoblastic leukemia. Hematology, 2015, 20: 377–383

Summary for “INTAC复合体的功能研究与机制探索新进展”

Recent progress in understanding the functions and mechanisms of the INTAC complex

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The precise spatiotemporal regulation of gene expression is essential for organismal survival and development. Transcription by RNA polymerase II (Pol II) serves as the molecular executor of developmental and differentiation programs. Aberrant transcription dynamics underlie diverse pathologies, including malignancies, metabolic disorders, and neurodegenerative diseases. In metazoans, Pol II transcription progresses through tightly regulated phases: initiation, promoter-proximal pausing, productive elongation, and termination. Promoter-proximal pausing—a rate-limiting checkpoint—determines transcriptional outcomes via kinetic competition between elongation activation and premature termination.

One of the major players in this process is the 1.59 Megadalton Integrator-PP2A-AC complex (INTAC), a metazoan-specific multi-subunit complex, forming a stable complex with the protein phosphatase PP2A core enzyme (PP2A-AC). In short, INTAC complex is composed of a backbone module, a shoulder module, a phosphatase module, an endonuclease module, an auxiliary module and the SOSS module. As an essential regulator for virtually all classes of RNA polymerase II (Pol II)-transcribed genes, the INTAC complex harbors both an RNA cleavage activity from Integrator and a phosphatase activity from the core enzyme of PP2A (PP2A-A and PP2A-C). These two catalytic modules are structurally connected by the scaffolding backbone and shoulder modules, yet have different roles in transcription regulation at gene promoters or enhancers. Specifically, the RNA endonuclease module primarily induces promoter-proximal termination at promoters and attenuates nonproductive transcription at enhancers, while the phosphatase module mainly prevents the release of paused Pol II to limit transcription activation.

By playing a pivotal roles in transcriptional control, INTAC dysfunction is closely linked to abnormalities in physiological processes and disease pathogenesis. Therefore, understanding the structure and function of the INTAC complex is critical to uncovering the mechanisms of gene expression and developing potential therapeutic strategies for related diseases.

In this review, we first provide an overview of the discovery and the modular compositions of the INTAC complex. We then summarize functional advancements of the INTAC complex, with a focus on dissecting its multifaceted roles in transcriptional regulation. The INTAC complex participates in the biogenesis of enhancer RNA and is involved in small nuclear RNA processing. Moreover, the INTAC complex participates in the premature transcription termination of genes. INTAC serves as a transcriptional gatekeeper, licensing productive elongation through kinetic proofreading. We further outline the key functions of INTAC in physiological homeostasis and disease contexts, highlighting its broad significance in eukaryotic biology. These insights not only enhance our understanding of transcriptional regulatory network, but also unveil novel mechanisms underlying critical biological processes of INTAC complex, offering a conceptual roadmap for future investigations into elucidating its crosstalk with chromatin remodelers and transcriptional factors in disease models.

Despite the rapid advancements, the mechanism of how the INTAC complex terminates Pol II remains incompletely understood. Future investigations aimed at elucidating the transcriptional regulatory mechanisms mediated by the INTAC complex, as well as delineating its mechanistic roles in critical biological processes and understanding of epigenetic regulation and disease pathogenesis.

INTAC, integrator, PP2A, Pol II, transcriptional termination

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