



RNA聚合酶II催化亚基POLR2A自身表达调控及其在肿瘤中作用研究进展

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收稿日期: 2021-10-05; 接受日期: 2021-10-25; 网络版发表日期: 2021-12-15

国家自然科学基金(批准号: 31670823, 31701197)资助

摘要 RNA聚合酶II转录真核生物基因组中所有的蛋白质编码基因和许多非编码RNA. POLR2A是RNA聚合酶II的关键催化亚基, 在基因表达中具有不可替代的作用. POLR2A自身的表达调控对细胞中基因转录至关重要, 且近年来研究表明, POLR2A与肿瘤等多种疾病密切相关. 本文从转录、pre-mRNA剪接、mRNA稳定性, 以及蛋白质降解等方面对POLR2A的自身表达调控进行综述, 并总结了POLR2A在肿瘤等多种疾病中的作用和靶向POLR2A的肿瘤治疗进展, 以期为RNA聚合酶II的研究与应用提供参考.

关键词 RNA聚合酶II, POLR2A, 表达调控, 肿瘤生成

基因表达起始于RNA转录, 是高度复杂的动态调控过程, 包含转录, RNA加工与修饰, RNA转运, RNA降解与翻译, 及蛋白质降解等多个步骤, 这些过程都受到精细调控并相互偶联^[1]. 基因表达调控在个体发育以及多种疾病发生发展中发挥决定性作用. RNA聚合酶II(RNA polymerase II, Pol II)是真核生物基因表达中发挥关键作用的聚合酶, 负责mRNA以及包括miRNA, snRNA及lncRNA在内的多种功能性非编码RNA的转录^[2]. Pol II高度保守, 其中人类Pol II是由12个亚基组成的分子量为516.7 kD的超大蛋白复合体^[3], 其中最大且具有催化功能的亚基被命名为POLR2A, 又称为RPB1. 人POLR2A基因位于第17号染色体上(17p13.1), 含有30个外显子, 其编码蛋白包含

1970个氨基酸, 分子量约为220 kD.

Pol II的典型特征是POLR2A蛋白C端结构域(C-terminal domain, CTD)具有独特的高度保守七肽重复序列(Y₁S₂P₃T₄S₅P₆S₇), 存在于所有真核生物中, 但重复数因物种而异, 其中人为52个, 酿酒酵母为26个, 该结构域对Pol II的多聚酶活性至关重要. 大量研究表明, CTD结构域可以动态发生多个翻译后修饰, 例如, 第二、第五丝氨酸位点的磷酸化修饰等, 在包括转录起始、暂停、延伸和终止等转录的各个阶段, 以及在转录偶联事件(如RNA加工、染色质修饰等)中发挥关键调控作用^[4]. 此外, 最新研究表明, CTD也与组蛋白修饰和其他细胞过程(如DNA损伤和修复、液-液相分离等)密切相关^[4,5]. 关于Pol II CTD的功能研究综述较

引用格式: 侯率, 赖楚童, 付文, 等. RNA聚合酶II催化亚基POLR2A自身表达调控及其在肿瘤中作用研究进展. 中国科学: 生命科学, 2021, 51: 1710–1720
Hou S, Lai C T, Fu W, et al. Catalytic subunit POLR2A of RNA polymerase II: self-expression regulation and its role in tumorigenesis (in Chinese). Sci Sin Vitae, 2021, 51: 1–11, doi: 10.1360/SSV-2021-0416

多^[4-8], 本文不再赘述.

迄今为止, 对POLR2A的研究主要集中于其作为关键组分参与基因转录以及对转录偶联事件的调控, 而对其自身表达调控关注较少. 近期的研究表明, POLR2A与多种疾病的发生密切相关, 但尚未见相关综述. 因此, 本文从转录调控, pre-mRNA剪接, mRNA稳定性, 以及蛋白质降解等不同层面对POLR2A自身表达调控研究进展进行综述, 并总结POLR2A在肿瘤等多种疾病中的作用和以POLR2A为靶点的肿瘤治疗研究进展, 以期对Pol II的研究与应用提供参考.

1 POLR2A自身表达调控

1.1 转录水平调控

转录水平往往是调控基因表达的最主要方式, 可以通过转录因子、中介体、暂停因子及延伸因子等反式作用因子与启动子、增强子等顺式作用元件的相互作用进行调控. 大量研究主要关注POLR2A参与对其他基因的转录调控, 但对其自身转录调控的关注不多.

八聚体结合转录因子1(octamer transcription factor 1, Oct1)又称POU2F1, 是POU转录因子家族的一员. Tomilin等人^[9]于2000年首次发现, *POLR2A*基因启动子上存在一个Oct1结合序列MORE, 提示Oct1可能在转录水平上调控*POLR2A*的表达. Kang等人^[10]进一步研究发现, *POLR2A*基因启动子上还存在另外一个MORE序列, 通过EMSA体外和ChIP体内结合实验证实, Oct1可以与这两个MORE序列结合, 并且电离辐射或H₂O₂处理造成的细胞损伤明显增强这种结合; 双荧光素酶报告系统检测则显示, 删除这两个MORE序列后显著降低*POLR2A*启动子(-600~+1 bp)的活性. 另外, 对比H₂O₂处理野生型MEF细胞后POLR2A mRNA水平变化不明显, 蛋白水平下降缓慢, 而H₂O₂处理Oct1缺失的MEF细胞后POLR2A mRNA水平明显下调, 蛋白水平也快速下降, 表明Oct1是能在应激条件下抵抗POLR2A下调的转录因子^[10].

1.2 Pre-mRNA剪接水平调控

对于真核细胞多外显子基因的表达, pre-mRNA剪接是一个非常重要的转录后RNA加工过程. Pre-mRNA的剪接由剪接体催化完成, 主要受到大量RNA结合蛋白(如SR蛋白、hnRNP蛋白、Prp19相关蛋白复

合物以及外显子连接复合物EJC等)及剪接调控元件(如5'剪接位点、3'剪接位点、剪接分枝位点、内含子或外显子内的剪接增强子或沉默子等)等的精密调控^[11,12].

有报道表明, 敲低参与pre-mRNA剪接的蛋白导致POLR2A下调. 例如, 在HeLa细胞中敲低剪接因子CWC22导致POLR2A mRNA下调^[13], 而敲低剪接因子SF3a导致POLR2A蛋白表达下降^[14]. 在SRSF1或SRSF2敲低的MEF细胞中, Ser2磷酸化的POLR2A发生显著下调, 而POLR2A总量和Ser5磷酸化的POLR2A表达变化不明显^[15]. 此外, 在HeLa细胞中使用剪接抑制剂SSA或Pla-B处理也观察到类似的结果^[16]. 与这些研究结果相似, Hou等人^[17]报道, 敲低剪接因子XAB2或使用剪接抑制剂madrasin处理细胞后同样导致POLR2A表达显著降低. XAB2是一个参与转录、转录偶联的DNA修复、pre-mRNA剪接、mRNA出核及同源重组等多个生物学过程的重要多功能蛋白, 敲低XAB2后POLR2A的mRNA与蛋白水平皆明显下调. 进一步研究表明, XAB2敲低导致的POLR2A mRNA下调并不依赖于转录, 而主要是由于XAB2缺失导致POLR2A pre-mRNA在剪接过程中发生严重的内含子滞留引起的^[17].

1.3 mRNA稳定性水平调控

转录与RNA加工决定了mRNA的生成数量, 而mRNA的稳定性则决定了进入翻译过程的mRNA数量. 因此, 真核生物mRNA的稳定性同样对基因表达至关重要. 细胞内正常mRNA的降解往往在帽端结构或polyA尾被切除后, 通过核酸内切酶降解途径、5'→3'核酸外切酶降解途径或3'→5'核酸外切酶降解途径由RNA降解复合物exosome所降解. 另外, 加工出现异常的mRNA通常被无义突变介导的RNA降解途径(non-sense-mediated decay, NMD)、non-stop或no-go等RNA质量监控通路识别并降解, 以确保只有加工正常的mRNA才能进入翻译过程^[18,19].

Dom34(哺乳动物中同源蛋白被称为PELO), 可以与HBS1形成exosome-Ski复合体, 进而参与non-stop降解^[20]与no-go降解通路^[21]. Hou等人^[17]对POLR2A mRNA稳定性进行探讨, 发现抑制翻译可以完全恢复因XAB2缺失导致的POLR2A mRNA表达下降. 进一步研究发现, 敲低Dom34可以通过增强POLR2A

mRNA稳定性从而部分恢复因XAB2缺失导致的POLR2A mRNA与蛋白表达水平的降低,表明Dom34是参与POLR2A mRNA稳定性调控的重要因子,且XAB2缺失导致的POLR2A下调不仅依赖于剪接过程中发生的内含子滞留,也依赖于Dom34介导的POLR2A mRNA稳定性调控^[17].

1.4 蛋白质降解水平调控

真核生物主要存在两类蛋白降解系统,即泛素蛋白酶途径和自噬溶酶体途径。细胞中80%~90%的蛋白主要通过泛素蛋白酶途径降解,而蛋白的泛素化修饰是蛋白降解过程中的重要步骤。泛素化修饰分为单泛素化修饰、多泛素化修饰和多聚泛素化修饰,其中Lys48(K48)和Lys63(K63)多聚泛素链修饰的研究最为广泛,K48多聚泛素化修饰主要与蛋白质降解相关,而K63多聚泛素化修饰则与蛋白质降解无关,主要参与信号通路的调控^[22,23]。

转录延伸是一个动态非连续的过程,如UV和化学试剂4-nitroquinoline 1-oxide(4-NQO)等诱导的DNA损伤与6-azauracil(6-AU)诱导的转录压力等许多因素会造成Pol II在转录的基因上停滞,停滞的Pol II不能正常延伸时,POLR2A会发生多聚泛素化修饰,随后被蛋白酶体降解^[24,25]。近年来对POLR2A降解的研究主要聚焦于DNA损伤或转录停滞状态下POLR2A是如何被泛素化降解的,研究表明这是一个多步骤过程:首先由特定泛素连接酶E3介导POLR2A单泛素化,再由其他泛素连接酶E3对单泛素化POLR2A进行多聚泛素链修饰,最终由蛋白酶体进行降解(图1),该过程需要泛素活化酶E1、泛素结合酶E2和泛素连接酶E3等多种因子参与(表1)。

(1) POLR2A蛋白的泛素化修饰。1997年,Huibregtse等人^[26]在酿酒酵母中首次发现参与POLR2A蛋白降解相关的泛素连接酶E3 Rsp5,其属于HECT泛素连接酶家族,Rsp5通过其N端的WW结构域与CTD相互作用促进其泛素化,抑制Rsp5的活性后,POLR2A蛋白水平明显上调。在酿酒酵母中,缺失Rsp5后能明显抑制4-NQO诱导的POLR2A泛素化和蛋白水平的下调^[27]。Reid和Svejstrup^[28]在体外泛素化实验中证明POLR2A的泛素化修饰需要Rsp5参与。Harreman等人^[29]进一步证明,Rsp5参与了POLR2A的单泛素化和K63多聚泛素化修饰。在6-AU造成的DNA损伤非依赖

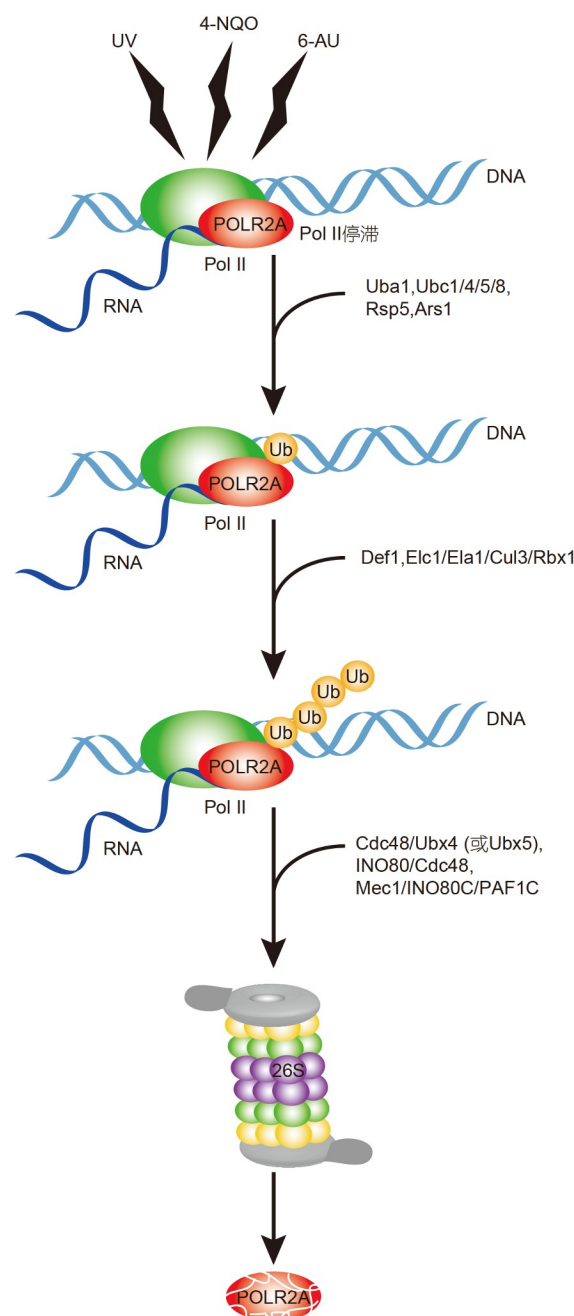


图1 酵母中POLR2A蛋白泛素化降解模式图。E3连接酶Rsp5等介导POLR2A的单泛素化修饰,Def1和Elc1/Ela1/Cul3/Rbx1进一步对单泛素化修饰POLR2A进行K48多聚泛素链修饰,INO80/Cdc48等促进K48多聚泛素化修饰POLR2A从染色质上解离,最终被26S蛋白酶体降解

Figure 1 Diagram of the ubiquitination degradation pattern of the POLR2A protein in yeast. E3 ligase like Rsp5 mediates the monoubiquitination of POLR2A. Def1 and Elc1/Ela1/Cul3/Rbx1 further modify the monoubiquitinated POLR2A with K48 polyubiquitin chain modification. INO80/Cdc48 etc. promote the dissociation of K48 polyubiquitinated POLR2A from chromatin. Finally, POLR2A is degraded by 26S proteasome

表 1 酵母和哺乳动物中参与POLR2A蛋白泛素化降解的因子

Table 1 Factors involved in the POLR2A protein degradation by ubiquitination in yeast and mammals

参与蛋白泛素化降解的因子	酵母	哺乳动物
E1	Uba1	Uba1
E2	Ubc1, Ubc4, Ubc5, Ubc8	Ubc5a, UbcH5c, UbcH6, UbcH7
E3	Rsp5, Asr1, Elc1/Ela1/Cul3/Rbx1	NEDD4, BRCA1/BARD1, pVHL/ElonginBC/Cul2/Rbx1, WWP2, CSA/CUL4A, ElonginA/ElonginBC/Cul5/Rbx2
其他泛素化因子	Def1	
降解因子	Cdc48/Ubx4 (或Ubx5), INO80/Cdc48, Mec1/INO80C/PAF1C, 26S蛋白酶体	26S蛋白酶体

的Pol II停滞中, Rsp5介导的POLR2A泛素化修饰也主要是K63多聚泛素化修饰^[30]. 而Jiang等人^[31]研究发现, Ccr4-Not能通过增强Rsp5泛素连接酶的活性, 进而促进Rsp5对POLR2A的泛素化修饰. 在人类细胞中, NEDD4与酵母中Rsp5高度同源, 在体外泛素化实验中NEDD4也能促进POLR2A的单泛素化修饰和K63多聚泛素化修饰^[29]. Daulny等人^[32]报道, RING finger泛素连接酶E3 Asr1能对POLR2A多个位点进行单泛素修饰, 进而影响Pol II亚基的聚合, 并且Asr1对POLR2A的泛素化修饰依赖其CTD Ser5的磷酸化.

Woudstra等人^[33]在酵母细胞中鉴定出Pol II降解因子1(Pol II degradation factor 1, Def1)参与了UV诱导的POLR2A泛素化降解, Def1的缺失能明显抑制UV诱导的POLR2A多聚泛素化修饰和蛋白降解. 在Def1缺失的细胞中, POLR2A的单泛素化水平未受影响, 而缺失Def1能明显抑制UV诱导的POLR2A多聚泛素化修饰和蛋白降解^[28,33-35]. 此外, Somesh等人^[34]报道, CTD Ser5的磷酸化会抑制POLR2A的多聚泛素化修饰, 而CTD Ser5特异的磷酸酶Ssu72能恢复POLR2A的多聚泛素化修饰.

另外, Ribar等人^[36]在酿酒酵母中研究发现, Elc1 (Elongin C)参与UV或4-NQO诱导的DNA损伤后POLR2A的泛素化降解, Elc1缺失明显抑制POLR2A的多聚泛素化修饰和蛋白降解. 进一步研究表明, Ela1/Elc1/Cul3复合物共同调控DNA损伤后POLR2A的K48多聚泛素化修饰, Ela1, Elc1或Cul3的缺失均能明显抑制DNA损伤诱导的POLR2A泛素化降解^[37]. Elc1/Cul3复合物能在Rsp5介导的单泛素化修饰的基础上, 对单泛素修饰的POLR2A蛋白进行K48多聚泛素化修饰, 在Elc1突变的菌株中POLR2A单泛素化水平没有明显

变化, 而多泛素链修饰的POLR2A明显受到抑制^[29].

Yasukawa等人^[38]在哺乳动物中发现, ElonginA/ElonginBC/Cul5/Rbx2复合物参与了DNA损伤介导的POLR2A多聚泛素化修饰, 其中Elongin是酵母中Elc1/Ela1的同源蛋白, 在MEF或HeLa细胞中敲低Cul5或ElonginA能明显抑制UV诱导的DNA损伤后POLR2A的泛素化降解. Harreman等人^[29]在体外重组泛素化实验中发现, 人源的NEDD4和Elongin/Rbx1/Cullin5共同调控POLR2A的多聚泛素化修饰.

肿瘤抑制因子pVHL(von Hippel-Lindau protein)是ElonginC/ElonginB/Cul2/Rbx1泛素连接酶E3复合物的底物识别因子, 其决定了连接酶底物的特异性^[39,40]. 在UV诱导的DNA损伤后, pVHL/ElonginC/ElonginB/Cul2/Rbx1复合物能与POLR2A相互作用催化POLR2A多聚泛素化修饰. pVHL对POLR2A的多聚泛素化修饰依赖其CTD Ser5的磷酸化和PHD1对POLR2A第1465位脯氨酸的羟化. 在PC12细胞中过表达pVHL, Ser5磷酸化的POLR2A在UV诱导8小时后明显下调, 非磷酸化的POLR2A无明显变化, 而蛋白酶体抑制剂CbzLLn处理抑制Ser5磷酸化的POLR2A下调, 表明在UV诱导下, Ser5磷酸化的POLR2A通过蛋白酶体途径进行降解^[39]. 在H₂O₂诱导下, pVHL介导POLR2A非降解性泛素化修饰, 在786-O细胞中过表达pVHL后, H₂O₂能明显诱导POLR2A泛素化修饰, 但对POLR2A蛋白水平没有明显影响^[40].

Li等人^[41]报道, HECT家族泛素连接酶E3 WWP2通过其WW结构域与CTD相互作用促进POLR2A的K48多聚泛素化修饰, 并且POLR2A与WWP2之间相互作用不依赖CTD的磷酸化和DNA损伤. 在F9细胞中敲低WWP2, 多聚泛素化修饰的POLR2A水平明显降低,

POLR2A的蛋白水平则显著上调^[41]。Caron等人^[42]发现在DNA损伤诱导下, POLR2A发生K48多聚泛素化修饰, 在U2OS细胞中敲低WWP2能明显抑制POLR2A的K48多聚泛素化修饰。

研究表明, 在哺乳动物中还有其他泛素连接酶E3参与POLR2A蛋白的泛素化, 如BRCA1/BARD1和CSA-CUL4A^[43~47]。BRCA1与BARD1相互作用形成具有泛素连接酶活性的复合物, 催化磷酸化的POLR2A泛素化修饰, 进而导致其降解, 在HeLa细胞中同时敲低BRCA1和BARD1能明显抑制UV诱导下POLR2A蛋白的降解^[44]。CSA是CSA-CUL4A泛素连接酶E3复合物的组成成分, 在CSA缺失的成纤维细胞中重新表达CSA能恢复UV诱导的POLR2A的泛素化修饰^[45,47]。最近研究表明, POLR2A K1268多聚泛素化参与了UV诱导的POLR2A降解和DNA损伤修复^[46,48]。

(2) POLR2A蛋白的降解。Karakasili等人^[30]报道, 26S蛋白酶体核心复合物与Pol II存在共定位, 且在转录延伸受阻时, 与Pol II共定位增强, 这提示26S蛋白酶体能被招募到停滞的Pol II处^[49]。Scharf等人^[50]在秀丽隐杆线虫研究中发现, 蛋白酶体与Pol II同样存在共定位, 而且在转录抑制的条件下, 对泛素化修饰的POLR2A进行降解。Verma等人^[51]发现, ATP酶Cdc48作用于泛素蛋白酶体系统受体的上游, UV诱导的POLR2A蛋白降解依赖Cdc48和Ubx4或Ubx5。Cdc48与ATP依赖的染色质重塑复合物组分INO80相互作用, 促进多聚泛素化修饰的POLR2A从染色质上解离, 调控POLR2A泛素化降解^[52]。Poli等人^[53]证明, Mec1-INO80C-PAF1C也能调控Pol II从转录基因上移除, 最后被降解, 而INO80缺失抑制UV诱导下POLR2A的降解^[52,53]。Beaudenon等人^[27]报道, 在酿酒酵母中26S蛋白酶体调控亚基SEN3/RPN2突变能抑制DNA损伤诱导下POLR2A蛋白质的降解。此外, Kuehner等人^[54]报道, 酵母中CFIA(3'-end processing cleavage factor IA)和CPF(cleavage and polyadenylation factor)参与了DNA损伤诱导下POLR2A的泛素化降解, 突变CFIA和CPF则抑制POLR2A的泛素化降解。

(3) 病毒介导的POLR2A蛋白降解。近年研究发现病毒也能介导POLR2A蛋白的降解。Vreede等人^[55]发现, 流感病毒感染宿主细胞后引起宿主细胞POLR2A蛋白质的降解, 且POLR2A蛋白质的降解受到病毒RNA聚合酶的调控, 病毒RNA聚合酶能提高Ser5磷酸

化POLR2A的泛素化水平。病毒感染宿主细胞后, 其非结构蛋白能诱导哺乳动物细胞内POLR2A蛋白快速降解, 进而抑制整个细胞的蛋白质合成和抗病毒反应, 而对蚊子细胞内POLR2A蛋白则没有明显影响^[56~60]。Sindbis, Semliki Forest和Chikungunya病毒等 α 病毒的非结构蛋白2(nonstructural protein 2, nsP2)是一种具有多种酶活性的多功能蛋白, 在BHK-21细胞中, 感染nsP2解旋酶结构域点突变的Sindbis病毒则不再诱导POLR2A蛋白降解^[57]。Schoen等人^[61]的最近研究表明, 泛素连接酶E3复合物的亚基Elongin C参与了拉克罗斯病毒感染引起的POLR2A蛋白质降解, 在A549细胞中敲低Elongin C能部分恢复拉克罗斯病毒感染引起的POLR2A蛋白水平下调。

2 POLR2A与肿瘤

POLR2A作为Pol II的最大且具有催化功能的亚基, 在生命活动过程中不可或缺。近年来一系列研究表明, POLR2A与肿瘤等多种疾病密切相关(图2)。

2.1 POLR2A基因SNP与肿瘤的相关性

单核苷酸多态性(single nucleotide polymorphism, SNP)指在基因水平上由单个核苷酸变异引起的DNA序列多态性, 包括单个碱基的插入、缺失以及置换。在某一疾病患者人群中, 出现频率较高的特定等位基因或基因型的SNP, 意味着这种变异可能与该疾病的患病风险相关。

近年来多项研究表明, POLR2A的SNP与多种肿瘤的患病风险以及药物治疗密切相关。Zhou等人^[62]在对311例胃癌患者的病例对照研究中发现, POLR2A基因外显子SNP rs2071504可以降低胃癌的发生风险, 还可以影响中国人胃癌的淋巴结转移和肿瘤的TNM分期。Park团队^[63]在研究紫杉醇-顺铂化疗的非小细胞肺癌晚期患者临床预后和遗传变异的关系中发现, 携带POLR2A SNP rs2071504 C>T的患者化疗效果不佳且生存期缩短。在早期接受手术治疗的非小细胞肺癌患者中, POLR2A SNP rs2071504 C>T变异与低生存率密切相关, 提示可能影响早期患者预后^[63]。在对103个前列腺癌风险相关的SNPs作用区域研究中, 运用ChIP-seq技术在前列腺癌细胞和组织中富集到15个有SNP的基因组区域, 而POLR2A的这一SNP正是位于其

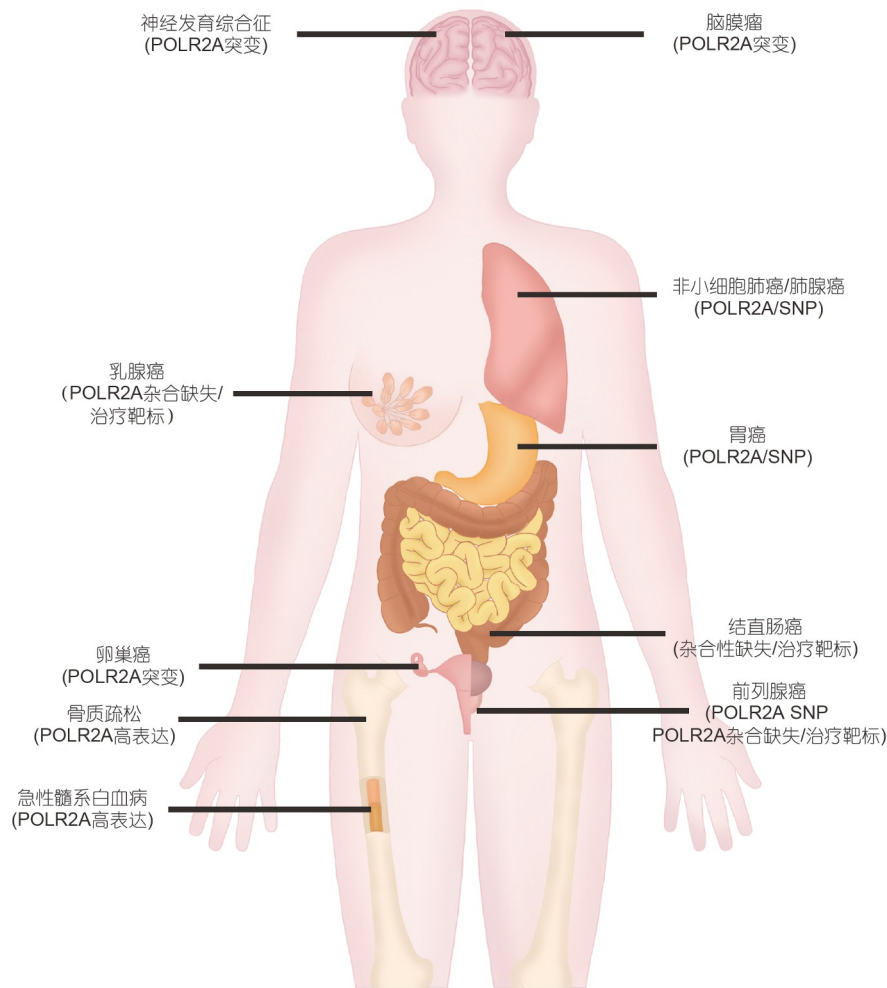


图 2 POLR2A与肿瘤等疾病的相关性. POLR2A特定位点的SNP以及POLR2A的突变或高表达与多种疾病密切相关, 而POLR2A在多种肿瘤中的杂合缺失特性使其有望成为肿瘤治疗新靶点

Figure 2 Correlation between POLR2A and tumors and other diseases. SNP at specific sites of POLR2A and mutation or high expression of POLR2A are closely associated with a variety of diseases, and POLR2A is expected to be a new target for tumor therapy due to its heterozygous deletion in different tumors

中一个明显富集区域^[64].

2.2 POLR2A基因突变和激活与肿瘤的相关性

Clark等人^[65]对775例脑膜瘤患者的基因组学进行分析发现, *POLR2A*中反复发生的p.Gln403Lys或p.Leu438_His439del突变可以驱动脑膜瘤的发生, 携带*POLR2A*突变的肿瘤其关键脑膜识别基因*WNT6*与*ZIC1/ZIC4*发生失调. Yu等人^[66]报道, *POLR2A*在急性髓系白血病(acute myelogenous leukemia, AML)病人的外周血细胞中高表达, 这种高表达与细胞恶性增殖成正相关, 且在AML小鼠模型中抑制*POLR2A*后肿瘤细

胞显著减少. Fransson等人^[67]在对儿童神经母细胞瘤复发性病变患者进行全基因组测序后, 发现在复发性病变中*POLR2A*基因重排和突变普遍存在. Li等人^[68]在研究化疗耐受性相关机制的遗传变化时发现, *POLR2A*基因突变可能在卵巢癌化疗耐药进展中发挥重要作用. 另外, Mao等人^[69]报道, BCAR1可以通过上调*POLR2A*表达促进肺腺癌的细胞增殖, 且*POLR2A*高表达患者预后不良. Francavilla等人^[70]报道, CDK7可以通过磷酸化*POLR2A*促进上皮性卵巢癌细胞的增殖. 综上, *POLR2A*的突变和激活可能与肿瘤增殖、复发以及耐药密切相关.

2.3 POLR2A有望成为癌症治疗新靶点

近年来, 已有多篇文献报道可以使用药物抑制POLR2A以减缓肿瘤进展, 如POLR2A特异性抑制剂 α -鹅膏蕈碱(α -amanitin)^[71,72], α -鹅膏蕈碱通过与POLR2A蛋白残基His1085相互作用, 特异性地抑制Pol II的转录^[73], 此外还有天然产物雷公藤内酯^[74]及Lurbinectedin^[75]等。然而由于POLR2A是所有细胞生存所必需的看家基因, 因此抑制POLR2A不仅会使肿瘤细胞损伤, 也将导致正常细胞的广泛死亡, 所以临床上通过抑制POLR2A的手段治疗肿瘤其效果往往存在局限。然而肿瘤细胞中常见肿瘤生长所必需基因的杂合性缺失, 抑制肿瘤细胞中这些残留的单拷贝基因, 如POLR2A仅导致特定的肿瘤细胞死亡。因此, 针对肿瘤杂合性缺失POLR2A基因设计的特异性反义寡核苷酸^[76,77]、锁核酸^[78]及siRNA^[79], 可以选择性抑制肿瘤细胞POLR2A的表达, 体内体外实验证实可以抑制肿瘤生长。

Liu等人^[80]发现在结直肠癌中, 当常见的肿瘤抑制基因TP53缺失导致癌症进展时, 其附近的POLR2A基因也往往发生杂合性缺失。正常细胞中POLR2A和TP53基因均有两个拷贝, 而在53%的结直肠癌, 62%的乳腺癌, 以及75%的卵巢癌中, 这两个基因都只剩余单一拷贝。这类癌细胞由于POLR2A仅有单一拷贝, 对POLR2A的抑制异常敏感。进一步研究发现, 使用低剂量的 α -鹅膏蕈碱抑制POLR2A, 在TP53和POLR2A杂合缺失的情况下, 可以阻断癌细胞生长, 抑制肿瘤的发展, 这提示POLR2A可以成为肿瘤治疗的新靶点^[80]。Li等人^[81]通过CRISPR-Cas9筛选, 发现具有POLR2A杂合性缺失特征的前列腺癌细胞的生存选择性依赖E3泛素连接酶Ring-Box1(RBX1), 而RBX1通过激活POLR2A的K63泛素链修饰, 从而提高POLR2A介导的mRNA合成, 这使得联合抑制RBX1和POLR2A有望成为前列腺癌治疗的新策略。

TP53也是三阴性乳腺癌(triple negative breast cancer, TNBC)中最常见的突变或缺失基因, 而由于TP53的表达难以恢复以及缺乏有效治疗靶点导致TNBC的临床治疗效果欠佳。Xu等人^[82]利用计算机分析发现, TP53邻近区域的POLR2A是TNBC的一个附带易损靶点, 这提示通过siRNA抑制POLR2A表达或许是靶向治疗TNBC的一种可行方法。为了提高siRNA的生物利用度并改善其溶酶体逃逸, 研究人员设计了一种pH响应

的纳米颗粒用于增强POLR2A siRNA的肿瘤细胞靶向递送, 体内体外实验皆显示, 该纳米颗粒可以有效抑制POLR2A缺失的肿瘤生长^[82]。HER2低表达的乳腺癌同样缺乏有效的治疗靶点, 但同时也具有POLR2A和TP53杂合缺失特征, 因此利用POLR2A抑制剂 α -鹅膏蕈碱靶向POLR2A可以成为有效的治疗手段^[83]。综上, POLR2A有望成为癌症治疗的新靶点。

3 POLR2A与其他疾病的关联

除了肿瘤, POLR2A异常也会对其他疾病产生重要影响。有报道表明, POLR2A CTD区域的错义突变导致POLR2A表达下降, 进而使POLR2A转录的基因表达下调并导致神经发育综合征, 其特征是严重的婴儿低张力和发育迟缓^[84]。进一步研究发现, POLR2A的生殖细胞突变导致以转录失调为特征的异质性、多系统发育障碍, 并且在临床患者中得到验证, 表型包括共济失调、关节活动过度、矮小、皮肤异常、先天性心脏异常、免疫系统异常、髋关节发育不良和跟腱缩短^[85]。在对骨质疏松的研究中发现, POLR2A基因在破骨细胞分化过程中表达量显著升高, POLR2A基因通过直接与CREB1启动子区结合, 激活破骨细胞分化相关靶基因c-fos和nfatc1, 进而促进破骨细胞分化^[86]。破骨细胞POLR2A条件性敲除小鼠可以通过抑制骨吸收增加骨量防治绝经性骨质疏松症, 表明POLR2A在骨质疏松中起重要作用^[86]。XAB2缺失导致的POLR2A表达下调或敲低POLR2A可以通过促进p53/p21表达进而导致细胞衰老^[17]。此外, POLR2A在家族性高胆固醇血症^[87]以及I型糖尿病^[88]等疾病中可能也发挥作用。

4 总结与展望

POLR2A作为Pol II最大且具有催化功能的亚基, 在基因表达调控中发挥无可替代的重要作用。然而长期以来, 其自身表达调控主要关注点集中于DNA损伤条件下由泛素化介导的POLR2A蛋白降解。近几年的研究发现, POLR2A与肿瘤等诸多疾病的发生发展密切相关, POLR2A有望成为肿瘤治疗的新靶点, 具有潜在的临床应用价值。系统探讨POLR2A在不同层面以及在生理和病理条件下的自身表达调控机制, 将为Pol II的理论研究和临床应用奠定基础。

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Catalytic subunit POLR2A of RNA polymerase II: self-expression regulation and its role in tumorigenesis

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RNA polymerase II transcribes all protein-coding genes and many noncoding RNAs in eukaryotes. POLR2A is the key catalytic subunit of RNA polymerase II that plays an irreplaceable role in gene expression. The expression regulation of POLR2A itself is vital for gene transcription in cells. Recent studies have also shown that POLR2A is closely related to many diseases, including tumors. This review focuses on the expression regulation of POLR2A itself, covering the transcription levels, pre-mRNA splicing, mRNA stability, and protein degradation, and summarizes the role of POLR2A in tumors and other diseases, as well as the progress of tumor therapy targeting POLR2A.

RNA polymerase II, POLR2A, expression regulation, tumorigenesis

doi: [10.1360/SSV-2021-0416](https://doi.org/10.1360/SSV-2021-0416)