

ATM调节体细胞重编程

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摘要 共济失调-毛细血管扩张突变(ataxia telangiectasia mutated, ATM)蛋白属于磷脂酰肌醇-3-激酶相关激酶家族(phosphatidylinositol-3-kinase related kinase family, PIKK)成员, 是DNA损伤的感应器并将DNA损伤信号传递到下游修复蛋白, 从而启动DNA修复、细胞周期阻滞和细胞凋亡等一系列事件, 进而维持细胞基因组完整性。近期的研究揭示, ATM参与了体细胞重编程过程, 当ATM完全缺失后显著影响诱导多能干细胞(induced pluripotent stem cells, iPS cells)获得以及染色质的稳定; ATM还通过参与重编程过程中的染色质重塑进而调控体细胞重编程。ATM下游的效应因子p53和H2AX(histone 2A member X)等在重编程引起的细胞周期阻滞和凋亡中发挥重要作用。该文重点探讨了ATM及其下游细胞因子在参与调控体细胞重编程过程中的作用机制。

关键词 ATM; p53; H2AX; 体细胞重编程

The Mechanism of ATM Regulating Somatic Cell Reprogramming

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Abstract Ataxia telangiectasia mutated (ATM), as a member of the phosphatidylinositol-3-kinase related kinase family (PIKK), is a DNA-damaging sensor. It transmits DNA damage signals to DNA repair proteins, activates several signal pathways, such as DNA repair, cell cycle blockage, apoptosis and so on, in order to repair DNA damages and keep genomic integrality. Recently, ATM was known to be involved in somatic reprogramming by transcriptional factors. During the process, ATM knock-out significantly affected final generation of induced pluripotent stem cells (iPS cells), and increased the chances of abnormal chromosomes in these iPS cells. In addition, ATM also took part in chromatin remodeling during somatic reprogramming. Furthermore, downstream effectors of ATM, such as p53 and H2AX (histone 2A member X), regulated the reprogramming-activated cell cycle blockage and apoptosis. For the theoretical supports of improving iPS cells research in future, the aim of this review is to provide a systematic overview on the mechanism of ATM and its downstream effectors in regulating somatic reprogramming.

Keywords ATM; p53; H2AX; somatic cell reprogramming

自2006年首次使用体细胞通过转录因子介导的方法获得诱导多能干细胞(induced pluripotent

stem cells, iPS cells)以来^[1], 体细胞诱导多能性机理以及iPS细胞在再生医学中的应用已成为干细胞研

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究领域的热点。然而, 至今为止, 重编程过程涉及的分子调控机制在很大程度上仍然未完全阐明^[2]。此外, 体细胞诱导重编程的效率极低, 对于解释低重编程效率的原因已有相关报道^[3]。其中, 重编程过程中产生的DNA损伤可能是导致iPS细胞诱导效率低的原因之一。重编程经历的过程包括病毒的整合、大范围的染色质重塑以及连续的细胞分裂增殖, 使得细胞极易造成DNA损伤, DNA损伤风险的增加可能激活细胞的衰老凋亡途径, 从而影响重编程效率^[4]。共济失调-毛细血管扩张突变(ataxia telangiectasia mutated, ATM)蛋白作为DNA损伤应答信号通路中关键的应答元件, 其失活显著地影响重编程效率和iPS细胞的质量。同时, ATM相关调控网络中几个重要靶基因, 如肿瘤抑制因子*p53*和组蛋白变体*H2AX*(histone 2A member X)的缺失也对重编程效率和iPS细胞的质量产生影响^[5-6]。除此之外, ATM也在其他体细胞诱导转分化过程中发挥重要作用^[7]。本文主要讨论了核心应答元件ATM以及它的两个主要靶基因, 通过应对重编程过程中发生的DNA损伤和染色质重塑, 进而对于重编程的影响。

1 ATM调节DNA损伤应答与体细胞重编程

1.1 ATM应答DNA损伤

ATM作为磷脂酰肌醇-3-激酶相关激酶家族(phosphatidylinositol-3-kinase related kinase family, PIKK)成员, 是DNA双链断裂(DNA double-strand breaks, DSBs)的重要感应元件并可将DSBs信号传递给下游底物^[8]。未激活的ATM以二聚体或多聚体等非活性形式存在^[9]。当基因组发生双链断裂后, MRN(Mre11-Rad50-Nbs1)复合物识别DSBs位点, 无活性的ATM聚合物在第1 981丝氨酸(S1981)残基位点发生磷酸化, 同时ATM二聚体解聚并激活^[10-12]。此外, *p53*结合蛋白1(*p53*-binding protein 1, *p53BP1*)^[13]和叉头框蛋白O3(forkhead box O3, *FOXO3*)^[14-15]也参与了ATM的募集和活化过程。ATM的多数底物为细胞周期调节蛋白, 如*p53*和检查点激酶2(checkpoint kinase 2, *Chk2*)等^[16]。活化的ATM可激活*Chk2*, 后者磷酸化细胞分裂周期蛋白25A(cell division cycle 25A, *Cdc25A*), 磷酸化的*Cdc25A*不能进入细胞核而被泛素化降解, 进而导致周期素依赖性蛋白激酶2(cyclin-dependent protein kinase 2, *CDK2*)的活性不能维持, *CDK*-cyclin复合物无法形成, 细胞周期受到阻滞^[17]。

经ATM活化的*Chk2*还可通过*p53*调节*p21^{Cdkn1a}*(*p21*)的表达, *p21*抑制*CDK*活性和*CDK*-cyclin复合物的形成, 从而产生周期阻滞^[18]。ATM的底物还参与损伤修复, 如ATM可磷酸化*p53*-*Mdm2*(mouse double minute 2)复合物中的相应位点, 使二者解离, *p53*随即被激活, 随后转录因子*CBP/p300*(*CREB* binding protein)乙酰化*p53*, 促进*RAD51/RAD52*(recombination protein 51/52)复合物的形成, 后者直接结合到DNA损伤处完成修复作用^[19-20]。乳腺癌基因1(breast cancer gene 1, *BRCA1*)也是ATM的重要底物, 其磷酸化后进一步激活下游的DNA损伤修复蛋白*RAD51*, 后者参与DNA同源重组修复作用^[21]。此外, ATM还可促进H2AX的磷酸化(phosphorylated H2AX, γ H2AX), 后者募集DNA损伤检查点蛋白1(mediator of DNA damage checkpoint protein 1, *MDC1*)到DSBs位点^[22], *MDC1*作为支架有利于其他DNA损伤应答蛋白的募集, 并且级联放大DNA损伤效应^[23]。DNA高度损伤后, 修复失败的细胞一方面通过*p53*介导的损伤调节自噬因子(damage-regulated autophagy modulator, *DRAM*)诱导细胞自噬^[24], 另一方面通过*p53*介导的TP53诱导糖酵解与凋亡调节因子(TP53-induced glycolysis and apoptosis regulator, *TIGAR*)诱导细胞凋亡^[25]。这些DNA损伤修复相关蛋白质作为DNA损伤反应的关键调节剂, 它们之间的相互依赖性及其功能使得其中任何一种因子失活都会引起细胞对DSBs致敏^[26-27]。

1.2 ATM调节重编程

ATM作为调节基因组损伤修复过程中的关键调节因子, 除了传统意义上的作用, 其在体细胞重编程过程中也扮演着重要角色。Kinoshita等^[4]用ATM缺陷型(AT)小鼠的尾尖成纤维细胞(tail-tip fibroblasts, TTFs)进行iPS细胞的诱导, 发现重编程效率极低, 尽管能够获得AT-iPS细胞, 并且AT-iPS细胞在形态、多能性等方面与野生型iPS细胞呈现出相似性, 但是前者携带染色质结构异常的克隆显著多于后者, AT-iPS细胞中染色质异位和缺失等染色质异常现象随着传代而逐渐增多。Nayler等^[28]用AT患者的成纤维细胞进行重编程, 得到类似Kinoshita等^[4]的结果。同时, 建系的AT-iPS细胞还呈现对ATM信号依赖的电离辐射(ionizing radiation, IR)超敏现象、细胞周期检查点的缺失和DNA损伤诱导的细胞凋亡增加, 并且AT-iPS细胞诱导分化成特定类型细胞仍然存在上述

DNA损伤应答缺陷^[28]。Fukawatase等^[29]研究人AT细胞的重编程过程时,发现AT-iPS细胞呈现出IR应答缺陷,但至少80代以内的AT-iPS细胞没有出现染色质异常,推测重编程过程中端粒的延长可能维持了AT-iPS细胞基因组的稳定。同时,Bhatt等^[30]也证实,由AT患者体细胞建立iPS细胞过程中存在端粒结构延长现象,通过定量AT患者体细胞和正常个体体细胞端粒长度,随后将两种细胞重编程为iPS细胞,发现正常个体获得的iPS细胞端粒维持在相对稳定的长度,而AT患者获得的iPS细胞端粒明显延长。此外,与鼠源AT-iPS细胞不同,人AT-iPS细胞在传代过程中伴随着自发的ATM基因回复突变现象^[31]。这种回复突变,也使人AT-iPS细胞基因组完整增加,但这种回复突变现象的调控机制还不清楚。由上述研究结果可见,ATM在调控体细胞重编程以及在维持重编程后iPS细胞染色质完整性等方面具有重要调控作用。

1.3 ATM参与体细胞重编程中的细胞染色质重塑

在体细胞可以通过转录因子介导重编程为多能性干细胞后,转录因子介导的细胞命运转变的研究成为后iPS时代的重要技术。研究人员相继利用不同转录因子将分化的体细胞直接重编程为不同谱系的其他类型细胞,例如神经元细胞、肝细胞、心肌细胞等^[32-35]。与iPS技术类似,细胞命运的转变也是一个多种细胞生物学事件参与的复杂生物学过程,并且这种重编程效率也比较低。Ji等^[36]使用肝特异性转录因子FOXA3(forkhead box A3)、Hnf1 α (HNF1 homeobox A)和Gata4(GATA binding protein 4)组成的三转录因子(three transcription factor, 3TF)将TTFs转变为诱导型肝样细胞(induced hepatocyte-like cells, iHep cells)过程中,发现TTFs呈现出明显的增殖阻滞和凋亡,极大地阻止了iHep细胞的产生。研究发现,p53及其靶基因*p21*、*p19*、*Puma*(p53-upregulated mediator of apoptosis)和*Mdm2*等在肝转换过程中表达量上调,而且敲低*p53*和*p21*后,3TF诱导的增殖阻滞和凋亡被逆转。进一步分析显示,与p53激活的相关生物学事件,如*c-Myc*(cellular myelocytomatosis oncogene)和*Ras*(resistance to audiogenic seizures)基因的表达、*Ras* GTP酶活性、p38 α 的磷酸化以及活性氧类(reactive oxygen species, ROS)水平等均未发生显著改变。同时,未检测到DSBs和其他DNA损伤信号,参与损伤修复的主要蛋白p53BP1和参与DSB

修复的核苷酸切除修复均未发生变化。但是检测到大量的ATM磷酸化,并且通过基因敲低和小分子化合物抑制ATM的激活,显著下调了p53的磷酸化,并提高了iHep细胞的产生。进而,下调非DNA损伤ATM激活蛋白(ATM-interacting protein, ATMIN)显著抑制了ATM和p53激活,同时增加iHep细胞的形成。这些结果显示,iHep细胞诱导过程中,ATM的激活不依赖于DNA损伤。进一步分析显示,白蛋白和*Hnf4 α* 基因作为肝细胞系建立的主要基因,在3TF转导12 h后,其上游调控区位点被打开,且24 h后ATM和p53被募集到白蛋白和*Hnf4 α* 的开放染色质区域发生磷酸化。染色质重塑复合物是可以开放染色质环境和允许DNA及组蛋白与其他因子相结合的重要调控因子,通过基因敲低SWI/SNF(switch/sucrose nonfermenting)、CHD(chromodomain-helicase-DNA-binding protein)、INO80(inositol auxotroph 80)、ISWI(imitation switch)染色质重塑复合物中的相关组分,发现其中的一个主要成员Baf60b(Brg/Brm-associated factors 60b)的下调表达,减少ATM募集到肝特异性基因调控区。Baf60b介导SWI/SNF复合体中ATP酶亚单位Brg1(brahma related gene 1)与ATM的相互作用,激活ATM-p53途径阻碍肝转换,而不依赖于经典的DSBs信号激活ATM-p53途径。

2 ATM底物参与调节重编程

2.1 p53调节重编程

p53作为ATM主要底物之一调节不同细胞生物学功能,包括抑制细胞增殖、迁移和浸润、阻滞周期、促进凋亡和衰老等^[37-38]。在体细胞重编程过程中,Oct4(organic cation/carnitine transporter 4)、Sox2(SRY-related HMG-box gene 2)、Klf4(Kruppel-like factor 4)和*c-Myc*(cellular myelocytomatosis oncogene)组成的四转录因子(OSKM)可以激活体细胞中p53的表达,引发细胞的凋亡和衰老,从而阻碍细胞的重编程。当在重编程过程中缺失p53的激活,体细胞重编程效率显著提高^[6]。Marion等^[39]利用一种严重端粒缺陷的细胞进行重编程,发现该细胞在重编程过程中DNA损伤显著增加,大量的细胞发生凋亡,不能被重编程为iPS细胞,而当敲除该细胞中的p53后,重编程效率极大地提高,细胞凋亡现象显著被抑制,表明p53显著参加了iPS细胞的诱导过程。随后研究发现,经 γ 射线和紫外线辐射后造成DNA损

伤的细胞,抑制p53的激活,也可以显著提高iPS细胞诱导效率。*p21*作为p53下游的主要靶基因之一,通过抑制CDK活性使细胞停滞在G₁期,进而诱导细胞衰老。*p21*结合B淋巴细胞瘤-w(B-cell lymphoma-w, *Bcl-w*)基因形成p53/p21/Bcl-w复合物,促进Bcl-2相关X蛋白(Bcl-2 associated X protein, Bax)释放,激活的Bax参与促凋亡作用并抑制细胞浸润^[40]。重编程过程中,Yamanaka因子的表达也引起p21的表达量增加,并且在细胞中缺失p53同时过表达p21,可显著抑制iPS细胞的产生,表明p53抑制体细胞重编程是通过p53-p21途径实现的^[41]。重编程过程中,p53还上调PUMA的表达量,PUMA是一种BH-3-only(Bcl-2 homology domain only proteins)促凋亡蛋白。在线粒体中通过诱导ROS产生激活凋亡途径^[42]。在iPS细胞诱导过程中,PUMA缺失可以减轻p53对重编程的限制作用,表明p53抑制体细胞重编程还可通过p53-PUMA途径实现。此外,重编程过程中,相比于p21或p53缺失而引起iPS细胞染色质异常,PUMA的抑制显著降低iPS细胞染色质异常的比率,同时促进重编程过程中细胞的存活率、降低DNA损伤^[43]。

2.2 H2AX调节重编程

H2AX是组蛋白H2A的一个突变体,在哺乳动物基因组中仅占核小体的1%~10%,是DSBs产生后细胞最早的应答元件之一。ATM激酶在DNA损伤反应期间调节H2AX的磷酸化,并募集下游DNA修复蛋白如p53BP1、MDC1、RAD51、BRCA1和MRN复合体到DSBs位点^[44]。在胚胎干细胞(embryonic stem cells, ES cells)中,尾型同源盒2(caudal type homeobox 2, Cdx2)是上调滋养外胚层谱系基因表达并诱导干细胞向滋养外胚层分化的关键因子。H2AX结合于*Gata3*和*Dab2(disabled 2)*基因中的Cdx2蛋白结合区,从而影响Cdx2调控的*Gata3*和*Dab2*基因表达,阻止ES细胞向滋养外胚层的分化。在滋养层干细胞中,H2AX很少结合于上述基因调控位点,在成纤维细胞则不结合,表明H2AX在调控干细胞多能性及分化中起到重要表观遗传修饰作用。H2AX作为参与调控ES细胞多能性的因子之一,在iPS细胞诱导过程中,H2AX缺失显著降低重编程效率,且异常的H2AX累积影响iPS细胞的质量,表明H2AX在重编程过程中也发挥重要作用^[45]。

此外,Gonzalez等^[46]使用强力霉素诱导慢病毒表达载体进行重编程发现,启动重编程的细胞,即重

编程早期SSEA1(stage-specific embryonic antigens 1)染色呈阳的细胞, γ H2AX的表达量上调,并伴随着凋亡程度的增加;而SSEA1阴性细胞, γ H2AX的表达量则没有上调,且不影响细胞凋亡。这些结果显示,在强力霉素诱导的重编程系统中,重编程因子的异位表达可引起DNA的损伤,从而上调 γ H2AX。同源重组(homologous recombination, HR)、非同源性末端接合(nonhomologous end-joining, NHEJ)和单链退火(single-strand annealing, SSA)是DSBs的三个主要修复途径。然而,NHEJ和SSA的修复作用容易出错且容易产生缺失和其他类型突变。研究表明,强力霉素诱导重编程系统中,引起的DNA双链断裂,通过同源重组的机制进行修复,其中修复基因*Brca1*、*Brca2*和*Rad51*等是有效重编程所必需的,在没有病毒基因整合引起DSBs的条件下,*Brca1*、*Brca2*和*Rad51*缺失后,重编程效率大幅度下降,且重编程细胞的 γ H2AX表达量显著上调,进一步证明编程因子的异位表达上调了 γ H2AX,通过HR途径影响重编程^[46]。

3 结语与展望

DNA的损伤修复及细胞的凋亡对于细胞基因组完整性和阻碍肿瘤形成起关键作用。环境压力所造成的DNA损伤被感应蛋白识别并触发修复机制,修复失败的细胞发生凋亡。体细胞重编程经历大规模的染色质重塑机制,并且该过程极大地提高了基因组损伤的风险,ATM作为应对染色质开放和基因组损伤的感应元件之一,尽管其不是重编程的必要条件,但该功能的缺失显著地降低了重编程效率,显示ATM在重编程过程中发挥重要功能。此外,ATM还参与重编程过程中的染色质重塑的调控,进而与其下游调控基因,例如,*p53*与*H2AX*等相互作用调节体细胞重编程^[5,20]。ATM在细胞的代谢、存活、增殖以及衰老凋亡中发挥着重要作用,参与多个信号通路发挥作用,其在重编程中的作用至今还没有被完全阐明(图1)。进一步了解ATM相关信号通路在诱导重编程过程中的机制,将对深入了解体细胞重编程机制具有重要意义。

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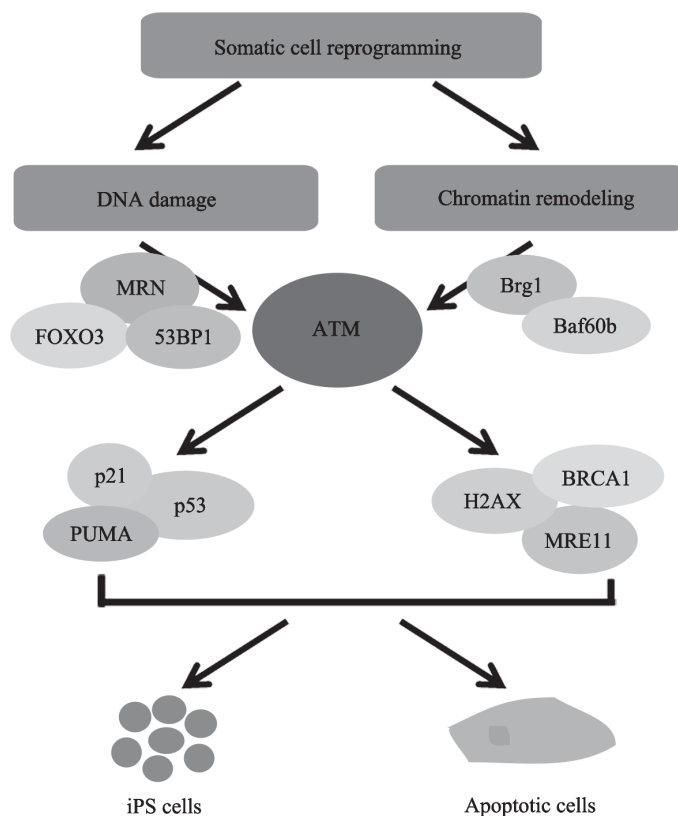


图1 ATM及其几个主要底物调节重编程的机制

Fig.1 The mechanism of ATM and its several major substrates to regulate the reprogramming

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