转录因子CREB对细胞周期调控机制的研究进展

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摘要 细胞周期是一个复杂而精细的调节过程, 有许多蛋白参与。其中cyclin、CDK、CKI是细胞周期调控的内源性分子, 三者在细胞周期中相互协调并与细胞信号转导通路之间形成复杂的调控网络。cAMP应答元件结合蛋白(cAMP response element binding protein, CREB)作为细胞核内调控因子, 通过自身磷酸化实现调节功能, 改变cyclin、CDK和CKI的转录, 从而调控细胞周期。该文就近年来CREB对细胞周期调控的研究进展作一综述。

关键词 CREB; cyclin; CDK; CKI

细胞周期是细胞生命活动的基本过程, 指细胞从前一次分裂结束开始到下一次分裂结束为止所经历的连续而有序的过程。细胞周期有间期和分裂期两个阶段, 其中间期又分为三期, 即DNA合成前期(G_1期)、合成期(S期)和合成后期(G_2期)。在生命体进化过程中, 细胞发展并建立了一系列的调控机制, 进而确保细胞周期严格有序地交替和各时相依次有序地变更。相关文献表明, cyclin/CDK/CKI复合体在这种高度有序的运转过程中起关键性作用[1]。CREB是1987年首次从PC_{12}细胞系核中分离出的核内转录因子, 根据剪接位点不同, 有CREBα、CREBβ、CREBδ等多种形式[2]。CREB蛋白C端附近含有较多的碱性氨基酸, 是CREB分子与DNA结合的区域[3], N端的KID区是一个高度保守的结构域, 其Ser133位点为蛋白激酶A(PKA)的磷酸化位点[4]。CREB主要对cAMP等信号发生应答反应, 通过自身磷酸化实现其调节转录功能[5]。新近研究表明, 细胞核内转录因子CREB通过调控cyclin、CDK和CKI的转录水平, 从而控制细胞周期进展。

CREB对细胞周期的调控首先依赖于CREB蛋白的磷酸化, 这对于其靶基因的反式激活具有关键作用[6]。其中, CREB Ser133的磷酸化促进CBP(CREB binding protein)的结合及靶基因的转录激活[7-9]。PKA、Ca^{2+}以及PKC均与CREB的磷酸化有关, 而Ser/Thr磷酸化酶PP1和PP2A能使CREB去磷酸化, 降低其活性[10~12]。CREB的总体活性取决于其磷酸化水平, 反映了相应激酶和磷酸化酶之间的平衡[13]。外来因素引起CREB蛋白磷酸化水平改变后, 与相应辅激活物结合, 诱导cAMP应答元件(cAMP response element, CRE)下游基因表达的改变, 进而对细胞周期进程展开调控(图1)。

本文就CREB对细胞周期调控的最新研究进展作一综述。

1 CREB对cyclins的调控

Cyclins是一组与细胞周期呈同步周期性浓度升降的蛋白质。现已发现的cyclins主要有cyclin A、B(1、2)、C、D(1、2、3)和E等。Cyclins分子在结构上存在一定差异, 但都有一个高度保守的细胞周期蛋白盒序列和降解盒结构, 前者结合CDK, 后者参与自身降解[14,15]。根据它们在细胞周期中调控阶段不同, 分为G_1期(如cyclin C、D、E)、S期和M期周期素(如cyclin A、B、H)。CRE是广泛存在于真核生物许多基因启动区的一段DNA序列。研究表明, CREB可识别许多靶基因上8个碱基对回文序列的cAMP反应元件(5'-TGA CGT CA-3'), 调控基因转录; 也可与活性较低的基序形式的CRE(5'-CGT CA-3')结合, 进而提高CRE下游基因的转录活性[16]。CREB通过与CRE的结合, 从而调控cyclins的转录水平, 进而影响细胞周期进展。

Cyclin D1是 cyclin D中研究较为深入的一种周期蛋白。在*cyclin D1*启动子中包含的TRE、E2F、Oct、SP1和CRE等多个调节元件中[17], 位于*cyclin D1*

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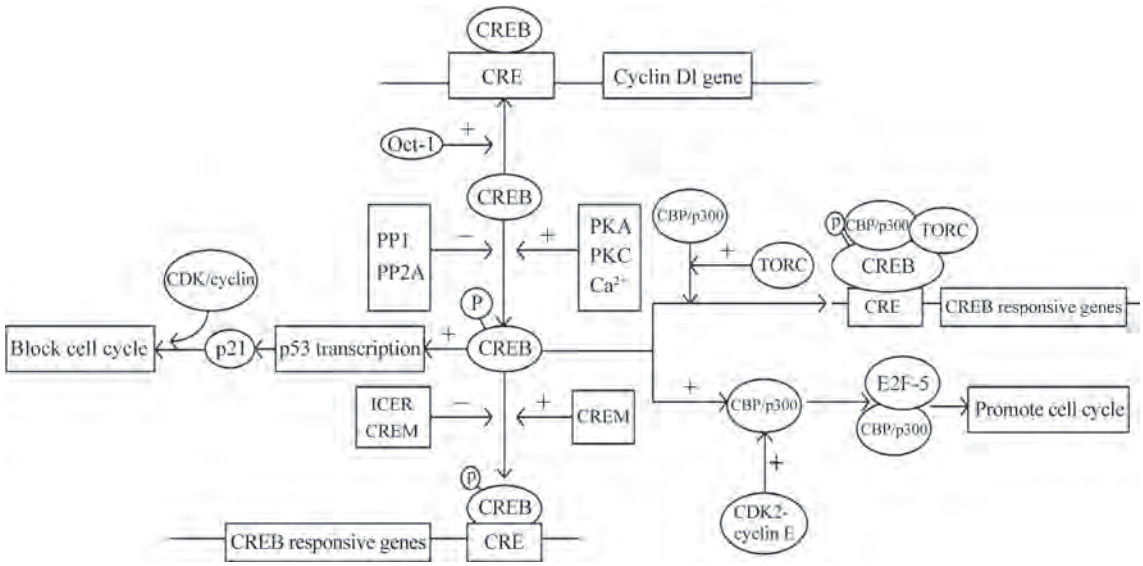

图1　转录因子CREB调控细胞周期的信号通路图

Fig.1　The signaling pathway of transcription factor CREB regulating cell cycle

基因上游的CRE对cyclin D1的诱导起关键作用。在乳腺癌细胞中, 八聚体结合转录因子1(octamer binding protein 1, Oct-1)增强由CREB蛋白介导的*cyclin D1*基因的转录活性, 在此过程中, POU结构域和CREB的Q2区反式激活结构域相互作用, 从而结合于cyclin D1 CRE上; Oct-1和CREB的协调作用不需要CREB Ser133的磷酸化, 并且与CBP无关[18]。另外, 雌激素可通过CRE的第-96~-29序列诱导*cyclin D1*启动子。实验表明, *cyclin D1*的转录需要c-Jun/ATF-2异二聚体的参与[17]。肝细胞中的过氧化物酶体增殖物激活受体γ2(peroxisome proliferator activated receptor-γ2, PPARγ2)激活, 可抑制细胞的生长, 减弱增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)、cyclin D1和β-catenin的表达; 同时他们的研究结果还表明, PPARγ2介导转录的cyclin D1抑制效果可被CREB的过度表达所逆转, 但β-catenin无此作用[19]。

Cyclin A属S期和M期的周期蛋白, 分cyclin A1和A2; 其中cyclin A2在G_1晚期出现, 分别与CDK和CDK1结合; 在S期cyclin A2促进DNA合成, 使细胞越过G_2/M期转折点, 进入M期。研究表明, cyclin A与CDK2结合后使E2F(E2 factor)结合的DRTF1-肽-1(DRTF1-polypeptide-1, DP-1)磷酸化, 引起E2F与DNA的结合活性降低。因此cyclin A负反馈调节E2F[20]。Cyclin A的高表达与其他cyclins一样, 与细胞增殖失控和肿瘤发生有关。在非小细胞肺癌中, cyclin A表达增多与S期细胞数量呈正相关, 与生存期呈负相关, 因此cyclin A可能作为临床肿瘤细胞增殖程度及预后指标[21]。

*Cyclin A*启动子中包含*CRE*、*AP-1*、*p53*和*SP1*等元件, 其中*SP1*及*CRE*的变异或缺失将导致*cyclin A*启动子失活[22~28]。相关文献表明, cAMP、钙离子和有丝分裂刺激素等通过Ser133的磷酸化, 进而激活CREB转录因子家族[29]。其中CREB/ATF-1(activating transcription factor 1)结合于cyclin A的ATF序列, 作为*cyclin A*启动子的正相调节因子, 而细胞周期依赖元件/细胞周期同源结构域(cell cycle–dependent elements/cell cycle genes homology region, *CDE*/*CHR*)介导*cyclin A*启动子的负相调节。*CRE*和*CDE*/*CHR*元件在转录起始部位有118对碱基相互成簇, CRE和CDE的协同作用能调节*cyclin A*基因的表达[30]。Bottazzi等[31]研究表明, CREB磷酸化及其与CRE的结合能决定*cyclin A*启动子活性的程度; 而袋蛋白(pocket protein)的激活则在时间上对*cyclin A*启动子活性进行调节。其中, CREB磷酸化以及与CRE的结合受有丝分裂原调控, 而袋蛋白的磷酸化则需有丝分裂原和细胞骨架肌动蛋白的双重调控。Kothapalli等[32]研究表明, 在主动脉平滑肌细胞中, 环前素能阻止CREB和p-CREB结合于*cyclin A*启动子*CRE*上, 而百日咳毒素则能逆转由环前素产生的抑制效应, 如对CRE启动子的占据, cyclin E-CDK2的活性和S期的进入。目

前, CREB对其他细胞周期蛋白的调控研究甚少, 如cyclin E-CDK2、cyclin B-CDK1等, 这些复合体可分别调节细胞周期进程从G_1期到S期和G_2期到M期的过渡[33~36], 对肿瘤的防治具有重要意义, 今后将会成为研究热点。

2 CREB对CDK的调控

CDKs是一组在细胞周期调节中起关键作用的蛋白激酶, 其功能的实现依赖于细胞周期蛋白, 活性也随周期的变化而变化。目前已发现的9个成员, 即CDK1~9, 彼此在 DNA序列上的同源性超过40%。在细胞周期的不同时相中, 不同的cyclins集聚后与相应的CDKs结合并激活之[37,38]。CDK激活的底物主要有人视网膜母细胞瘤抑制蛋白(retinoblastoma protein, pRb)、p107和p103等, 具有促进细胞周期时相转变、启动DNA合成、运行细胞分裂和推进细胞周期运行等重要功能。除细胞周期蛋白外, 在细胞循环中也存在其他水平调节控制CDK活性[37,39]。现已清楚, 泛素介导蛋白的溶解作用在细胞周期中的关键时刻对CDKs和其他调节因子的活性起重要的角色[40], 如通过后期促进复合物(anaphase promoting complex/cyclosome, APC/C)泛素连接酶复合物交联途径, 调节有丝分裂期CDK的活性实现对整个M期和M-G_1过渡期的调控[41]。

转录因子CREB主要通过p300/CBP复合体实现对CDK的调控, CREB磷酸化后, 促使p300/CBP聚积从而促进基因的转录[42,43]。p300/CBP是多功能的转录辅激活子, 它参与细胞周期调控、细胞分化和细胞凋亡等多种生理过程。p300/CBP具有乙酰转移酶活性[44], 通过乙酰化组蛋白和非组蛋白的方式参与基因的转录调控。同时, 它们能在转录因子和基本转录复合物之间起到桥梁作用, 而且也能为整合多种转录辅因子提供支架[45]。此外, p300/CBP是肿瘤抑制因子。在结肠癌和胃癌中, 发现p300/CBP基因的突变或易位与肿瘤发生发展密切相关[46]。研究表明, 转录因子*FoxM1B* (forkhead box M1B)通过细胞周期基因的表达刺激CDK1和CDK2的活性, 从而调节肝细胞的增殖。在此过程中, *FoxM1B*的转录活性需要S期或M期CDK-cyclin复合体的结合从而介导FoxM1B Thr596残基的磷酸化, 这为p300/CBP辅激活物的效应发挥所必需[47]。

新近研究发现, CREB的活性受CREB活性调节转导子(transducer of regulated CREB, TORC)的调节[48], 与TORC、CBP/p300共同形成转录复合体, 其N端上S133磷酸化的KID区与CBP/p300结合, C端的bZIP区与TORC结合[49], 三者协同作用, 控制目的基因的转录与表达。

在G_1后期, cyclin E-CDK2复合体磷酸化E2F-5转录因子; E2F-5反式激活结构域的磷酸化位点通过p300/CBP转录辅激活物刺激转录和细胞周期进程。然而, 辅激活因子p300/CBP与E2F-5的结合依赖cyclin E-CDK2复合体的磷酸化作用[50]。另外, Perkins等[51]研究发现, 通过NF-κB和p300相互作用, CDKs可调节转录激活。CDK抑制剂p21和呈负显性的CDK2, 均能抑制p300及cyclin E-CDK2的活性, 进而刺激*NF-κB*基因的表达; 而在p21存在的情况下, p300的表达能增强*NF-κB*基因的表达。通过CBP/P300的辅助激活, *NF-κB*和CDKs的相互作用机制为在细胞周期进程中转录激活的协调提供了新的线索。在乳腺癌MCF7细胞中, Park等[52]运用CRE诱骗寡核苷酸阻碍CREB与cyclin D1-CRE(5'-TAA CGT CA-3')的结合; 首先抑制*cyclin D1*基因的表达, 使cyclin D1/CDK4/pRB信号传导通路发生障碍, 进而使G_1期无法平稳过渡到S期; 在表达显性抑制型CRE结合蛋白(dominant negative mutant CREB, dnCREB)的乳腺癌MCF7细胞中, cyclin D1表达同样受到抑制, 通过阻断cyclin D1/CDK4/pRB信号通路使细胞周期进程停滞不前。

同时, CREB的活性还受诱导性cAMP早期阻遏物(the inducible cAMP early repressor, ICER)的影响, 两者都是cAMP介导信号途径中的转录调节因子。在大多数的儿童白血病中, CREB上调, 而内源性阻抑物ICER则下调。在细胞株中外源性表达的ICER能减少CREB的含量, 诱导体外轻度的无性繁殖能力。ICER结合*CRE*启动子[53,54], 控制基因表达, 从而恢复主要细胞信号途径的正常调节。在白血病细胞株HL60中, ICER下调, 从而保持CREB的过度表达, 损害正常的骨髓细胞生成和促进爆发性增殖[53]。以上发现证实ICER可作为白血病的肿瘤抑制物, CREB/ICER的不平衡表达可考虑为白血病生成过程中发病机制的特征性变化。

3 CREB对CKI的调控

CKIs是一组能与CDKs特异结合而抑制其活性的蛋白质, 在细胞周期中起制动器的作用。根据结

构同源性和CDK靶分子的抑制机制, 可分为INK4和CIP/KIP家族。INK4家族包括p15 (INK4b)、p16 (INK4a)、p18 (INK4c)和p19 (INK4d), 这些蛋白在结构上都含有4个锚重复序列, 它们可以识别CDK4和CDK6, 但不识别CDK2, 又称p16家族; CIP/KIP家族包括p21、p27和p57, 这一家族的蛋白都有一个N端的CDK抑制性功能域, 它们与CDK/cyclin复合体相互作用, 抑制CDK2/cyclin A和CDK2/cyclin E激酶活性, 又称p21家族[55]。目前, 研究较清楚的是p53诱导p21介导的细胞周期抑制。p21属于CIP/KIP家族, 即*WAF1/CIP1*基因, p21蛋白为野生型*p53*基因下游激活产物[56], 是人们认识最早的一种细胞周期蛋白依赖激酶的抑制蛋白(CKI)。p21在正常人的细胞中是以四价复合物的形式存在, cyclins、CDKs和PCNA是它发挥生物学功能的结构基础[57]。当DNA损伤和细胞衰老时, p53增多并诱导p21转录, p21与相应的CDK-cyclin复合物结合, 抑制其蛋白激酶的激活, 阻滞细胞周期的运行[58]。

研究表明, 在黑色素细胞中p21结合于小眼畸形相关转录因子(microphthalmia-associated transcription factor, MITF)启动子, 并与CREB协同激活此启动子; 糖识别结构域1(carbohydrate-recognition domains 1, CRD1), 一种抑制结构域, 与p21相互作用, 促进p300/CBP介导的反式激活。黑色素形成刺激物(stimulator of melanogenesis)和cAMP-CREB途径, 协同p21刺激*MITF*及其下游启动子; 在黑色素细胞中, p21增强CREB对启动子的激活效应, 其抗凋亡作用也涉及CREB的正相调节[59]。此外, 人T淋巴细胞白血病病毒-1 *Tax*基因(human T-cell leukemia virus type 1 Tax, *TLV-1 Tax*)能与CREB/ATF家族蛋白相互作用而刺激其活性; Tax突变体M47(L319R-L320S), 其在CREB/ATF途径中转录激活方面缺陷、失活, 激活p21启动子的功效显著下降, 并且在p21启动子序列上没有与CREB/ATF结合的结构域显现。通过ATF, CREB/ATF相关因子对*p21*启动子转录起到重要作用[60]。

另外, CREB的活性还受cAMP应答元件调控因子(cAMP response element modulator, CREM)的影响。CREM和CREB高度同源, 尤其在DNA结合区和激酶诱导结构域(KID)。在CREM的异构体中, 除了CREMτ、CREMθ1和CREMθ2, 其它所有异构体都缺乏富含谷氨酰胺的转录激活结构域, 因此在功能上被认为是cAMP调节基因的抑制剂。CREM和CREB相互竞争结合于*CRE*序列上; 或两者异二聚化, 阻止转录激活功能。Thi等[61]研究发现, 在牛白血病病毒(bovine leukemia virus, BLV)感染的细胞中, Tax_{BLV}应答元件(Tax_{BLV}-responsive elements, TxREs)的中部, CREB和CRE样序列相互作用, 在转录激活中起到关键作用。CREB和Tax_{BLV}相互协同, 反式激活*BLV*启动子, 而CREMτ则抑制Tax_{BLV}/CREB的协同作用。通过CREB和CREMτ的拮抗作用, Tax_{BLV}反式激活水平的调节能促进免疫逃逸和肿瘤生长。

Sue等[62]研究表明, 贝前列素(beraprost, BPS)能诱导主动脉平滑肌细胞中p21/p27的表达, 进而抑制细胞增殖。然而, 阻断过氧化物酶体增殖物激活受体δ(peroxisome proliferator-activated receptorδ, PPARδ)后, BPS诱导p21/p27启动子CRE的活性受到抑制。染色质免疫沉淀进一步分析, BPS介导的PPARδ能促进CBP核内易位, 而非CREB; 另外, PPAR应答元件(PPAR-responsive elements, PPREs)位于p21/p27启动子区域CREs附近, 在此PPARδ与CREB相互作用, 调控细胞增殖。这些结果说明，在BPS促进PPARδ活性以及刺激PPARδ和CBP结合于CREB-DNA复合体的模型中, p21/p27诱导增强, 进而导致主动脉平滑肌细胞增殖受到抑制。

在对哺乳动物细胞线粒体的信号传导和转录调节方面, CREB作为转录蛋白对其具有抑制作用。当线粒体损伤严重时, 钙调素依赖蛋白激酶IV(calcium/calmodulin kinase IV, CaMKIV)促发CREB Ser133磷酸化, 而磷酸化的CREB没有促使细胞增殖, 通过增强p53的转录活性而导致$p21^{waf1/cip1}$增多。由于线粒体功能障碍而抑制此信号途径的激活可能对于细胞周期调控具有重要作用[63]。另外, Li等[64]研究发现, 霍乱毒素作用于小鼠C6细胞, 可使G_1期上升, cyclin D1和CDK2活性减弱, 而$p21^{cip1}$和$p27^{kip1}$过度表达; 通过使用PKA抑制剂或利用RNA干扰技术沉默CREB蛋白, 敲除cAMP依赖蛋白激酶A的功能, 从而导致细胞分化受到抑制。

4 小结

细胞周期的调控与个体发育、分化、生长、再生、衰老以及细胞的癌变密切相关, 它的运转由多种机制控制, 参与调节的因子种类繁多, 错综复杂。本文主要就CREB对细胞周期的调控作一综述。CREB与相应的辅激活物结合, 通过磷酸化, 经各种不同信

号途径实现对其靶基因上游启动子的调控, 进而影响*cyclins*、*CDKs*和*CKIs*的转录, 改变细胞周期进程。不同功能的调节因子对正常细胞的生长起正负平衡调节作用, 一旦平衡被打破, 细胞易发生异常增殖。因此, 阐明其中主要的调节因子之间的相互作用, 对肿瘤的预防、治疗和预后都有重要意义。

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Progress in the Regulation of Transcription Factor CREB on Cell Cycle

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Abstract Cell cycle is a complex and precise adjustment process, which involves numerous proteins. Endogenous molecules, cyclin、CDK and CKI, coordinate with each other and form a complexly regulatory network in the process of cell cycle regulation and cell signaling pathways. CREB (cAMP response element binding protein), a transcriptional regulation factor in eucaryotic cell, regulates the cell cycle through changing the transcription of cyclin, CDK and CKI by its phosphorylation. In this review, recent progress in studying the regulatory effects of transcription factor CREB on cell cycle was summarized.

Key words CREB; cyclin; CDK; CKI

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