# 泛素–蛋白酶体通路介导细胞内c-Myc调控的研究进展

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**摘要** c-Myc是由原癌基因*c-myc*编码的、具有bHLH/LZ结构域的转录调节因子, 它不仅可以直接或通过其他蛋白质间接调控转录激活, 而且能够抑制某些基因的表达。近年来的研究表明, c-Myc通过泛素–蛋白酶体通路维持其在体内的相对稳定, 参与调控了细胞增殖、凋亡、细胞周期和细胞代谢等多种生物学功能, 其功能异常与多种疾病的发生、发展密切相关。该文综述了泛素–蛋白酶体通路介导细胞内c-Myc蛋白质调控的最新研究进展。

**关键词** c-Myc; 泛素化; 去泛素化; 蛋白酶体

# Advance in the Regulation of c-Myc Mediated by the Ubiquitin-Proreasome Pathway

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**Abstract** c-Myc, encoded by *c-myc* protooncogene, is a transcriptional regulatory factor containing bHLH/LZ domain. It can not only directly or indirectly regulate transcriptional activation, but also inhibit the expression of certain genes. Recent studies showed that c-Myc maintains its stability by the ubiquitin-proteasome pathway and participates in regulating many biological functions, such as cell proliferation, apoptosis, cell cycle and metabolism. Dysregulation of c-Myc is involved in the process of disease development. In this review, we focused on recent advances in the regulation of c-Myc mediated by the ubiquitin-proreasome pathway.

**Keywords** c-Myc; ubiquitination; deubiquitination; proteasome

泛素–蛋白酶体系统(ubiquitin-proreasome system, UPS)是细胞内蛋白质降解的主要途径, 参与80%以上的蛋白质的降解, 由泛素(ubiquitin, Ub)、泛素活化酶(ubiquitin-activating enzyme, E1)、泛素结合酶(ubiquitin-conjugating enzyme, E2)、泛素连接酶(ubiquitin protein ligase, E3)、去泛素化酶(deubiquitinating enzyme, DUB)和蛋白酶体(proteasome)等组成[1]。靶蛋白在接受泛素化信号后, 首先在ATP的参与下, 泛素C-端的甘氨酸残基与E1的半胱氨酸残基形成高能硫酯键, 然后E1将活化的泛素分子传递给E2, 接着在E3的作用下, 泛素C-端以异肽键(这里指赖氨酸的Σ-氨基和泛素C-端羧基形成的酰胺键)与底物蛋白质的赖氨酸残基连接, 最后由泛素–蛋白酶体途径(ubiquitin-proreasome pathway, UPP)特异性地识别并降解底物蛋白质[2]。去泛素化是泛素化的逆过程, 通过去泛素化酶水解泛素C-端与底物蛋白质间以及多聚泛素链间的异肽键[3-4], 释放泛素分子, 调节靶蛋白的稳定性、定位和活性[5]。

细胞内蛋白质的稳定对维持正常的细胞生长

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和生理功能起着非常重要的作用。c-Myc作为一种在进化上比较保守的转录调节因子, 参与调控人类基因组中15%的基因表达[6]。但在细胞内, c-Myc是一种极不稳定的蛋白质, 半衰期只有20~30 min[7], 主要通过泛素–蛋白酶体途径降解[8-10]。研究表明, c-Myc蛋白质的稳定对于细胞的生长增殖、细胞凋亡、细胞周期和细胞代谢等多种生物学功能的调控起着非常重要的作用, 它的失调与肿瘤等疾病的发生、发展密切相关。

## 1 c-Myc的结构和功能

### 1.1 c-Myc的分子结构

人*c-myc*原癌基因位于8号染色体长臂2区4带, 包含3个外显子和2个内含子, 其中外显子1起调节作用, 不参与编码蛋白质, c-Myc蛋白质是由外显子2和外显子3共同编码的含有439个氨基酸残基的蛋白质, 分子量62 kDa, 定位在细胞核内。c-Myc包含3个结构域(图1): 1个N-端的转录激活区(transcriptional activation domain, TAD)、1个非特异性DNA结合区和位于C-端的靶序列结合碱性螺旋–环–螺旋(basic-helix-loop-helix, bHLH)及亮氨酸拉链(leucine zipper, LZ)。其中, TAD是激活靶基因表达所必需的, 包含MBI和MBII这2个保守结构域, 中间区域具有调控c-Myc的周转功能[11], bHLH在c-Myc与特异的DNA序列结合中起着重要作用[12], 而且c-Myc的HLH-LZ结构域能与Max形成异二聚体, 激活相关基因的转录[13-15]。

### 1.2 c-Myc的生物学功能

1.2.1 c-Myc调控细胞周期 真核生物的细胞周期有序驱动依赖于以细胞周期依赖性激酶(cyclin-dependent kinase, CDK)为核心的网络调控系统, 其中细胞周期素(cyclin)为正性调节因子, 细胞周期素依赖性激酶抑制子(cyclin-dependent kinase inhibitors, CKIs)为负性调节因子, 两者共同调节CDKs的激酶活性, 准确协调地调控细胞周期的演进。c-Myc在多个层次上能够调控细胞周期的运行: (1)c-Myc作为转录因子, 直接在转录水平调控细胞周期调控因子CDKs、Cyclins、E2F转录因子等的表达[15-17]; (2)c-Myc通过诱导CDK激活激酶CAK(CDK activating kinase)和Cdc25(cell division cycle 25)磷酸酶高度活化cyclin/CDK复合体, 最终实现细胞从$G_1$期进入S期; (3)c-Myc不仅能阻断周期蛋白依赖激酶抑制因子p21的转录[18], 而且可以诱导Skp2调控p27的泛素化降解。通过以上三种方式, c-Myc过表达的细胞能摆脱细胞周期检验点的限制, 因此导致细胞恶化, 进入失控性增殖的状态[19]。

1.2.2 c-Myc调控细胞凋亡 Askew等[20]在前人研究的基础上, 发现髓性白血病细胞系的生长依赖于细胞因子IL-3, 当IL-3缺失时, 内源的*c-myc*基因不表达, 细胞生长受到抑制; 当在IL-3缺失的细胞中过表达c-Myc时, 能明显诱导细胞凋亡。c-Myc既有促进细胞增殖的作用, 也能促进细胞凋亡, 表明c-Myc通过不同的机制来调控增殖和凋亡。

由于c-Myc具有组织的特异性, 也决定其调控细胞凋亡机制的多样性, 主要可以分为两大类。一是通过Fas-FasL死亡受体途径, 在凋亡信号的刺激下, Fas与死亡受体Fas受体发生作用, 使Fas相关死亡结构域蛋白(Fas-associating protein with a novel death domain, FADD)与Fas受体相结合, 然后FADD招募胱冬肽酶-8(caspase-8)前体, 后者发生自剪接活化并启动凋亡。c-Myc通过在转录水平调控FasL并能阻止FasL的下调以及调控Fas的表达, 此外, c-Myc能诱导胱冬肽酶-8催化失活蛋白c-FLIP的下调并作用于肿瘤坏死因子(tumor necrosis factor, TNF), 从而促进死亡受体通路参与的细胞凋亡[21]。二是通过线粒体途径, c-Myc能诱导细胞色素c从线粒体内释放到胞质中, 随后细胞色素c与凋亡酶激活因子-1(apoptotic protease activating factor-1, Apaf-1)和胱冬肽酶-9形成凋亡复合体, 被激活胱冬肽酶-9能激活其他的胱冬肽酶(如胱冬肽酶-3), 最终诱导细胞凋亡[22]。

1.2.3 c-Myc调控细胞代谢 c-Myc作为一种与细胞生命活动密切相关的转录调节因子, 不仅调控细胞增殖和凋亡, 而且在细胞代谢的调节中也发挥重要作用。细胞中, c-Myc调控的代谢途径主要包括以下几个方面。第一, c-Myc能加强糖酵解, 调控谷氨酰胺代谢和乳酸的产生和运输。c-Myc不仅上调葡萄糖转运蛋白, 增加对葡萄糖的吸收, 加强糖酵解作用, 而且能调控乳酸脱氢酶A(lactate dehydrogenase, LDHA)和乳酸转运蛋白1(lactate transporter 1, MCT1), 产生大量乳酸, 促进瓦伯格效应[23-24]。第二, c-Myc能调控线粒体的生物合成和功能。过表达c-Myc能增加与线粒体蛋白合成有关的蛋白p32的表达[25]。c-Myc的靶基因AMP激活蛋白激酶相关蛋白激酶5(AMPK-related kinase 5, *ARK5*)具有保持线粒体完整和生物

能的平衡[26]。第三, c-Myc能调控脂代谢。通过调节与脂肪生成有关的酶如乙酰辅酶A羧化酶(acetyl-CoA carboxylase, ACACA)、脂肪酸合成酶(fatty acid synthase, FASN)和硬脂酰辅酶A脱氢酶(stearoyl-CoA desaturase, SCD), 调控脂质的合成[27-28]。c-Myc除了直接调节与脂质代谢相关蛋白质的表达, 它还能通过调节与维持代谢平衡有关蛋白质[如去乙酰化酶1(sirtuin type 1, SIRT1)], 间接影响代谢平衡[29]。

## 2 泛素–蛋白酶体通路介导c-Myc稳定性调控

### 2.1 c-Myc的泛素化修饰

在正常细胞中, c-Myc的表达受到严格的调控。在细胞周期的不同时期, 其含量有着明显的变化。当细胞处于静止期时, c-Myc的表达量很低, 在接受生长信号的刺激后, 其含量明显增加, 并在细胞周期的进程中维持较高水平, 直到细胞再次进入静止期才恢复到原来的水平。c-Myc是一种半衰期很短的转录调节因子, 它主要通过泛素–蛋白酶体通路进行降解。近些年的研究发现, 调控c-Myc稳定性的泛素连接酶根据结构域可以分成三类(图2): 含RING结构域的E3泛素连接酶, 如Skp2(S-phase kinase-associated protein 2)、Fbw7(F-box and WD-40 domain protein 7)、FBXO32和β-Trcp[30-33]; 含HECT结构域的E3泛素连接酶, 如HectH9、TRIM32和TRUSS(tumor necrosis factor receptor-associated ubiquitous scaffolding and signaling protein)[34-36]; 含U-box结构域的E3泛素连接酶, 如热休克蛋白70 C-端相互作用蛋白(carboxyl terminus of Hsc70-interacting protein, CHIP)[37]; 其他的E3泛素连接酶, 如ELL(eleven-nineteen lysine-rich leukaemia)[38]。

2.1.1 RING结构域的E3泛素连接酶 Skp2是属于F-box蛋白质家族的泛素连接酶, 识别c-Myc的MBII和bHLH-LZ结构域并使之泛素化, 进而被泛素–蛋白酶体降解。Skp2对c-Myc的作用是双重的, 既能介导c-Myc的泛素化降解, 又能加强c-Myc对靶基因的转录[30-31]。Skp2自身作为一种癌蛋白(oncoprotein), 不仅能通过降低p27控制细胞增殖[39], 而且能增强c-Myc的转录活性促进更多细胞进入S期, 细胞增殖加快。

Fbw7是包含WD重复序列的F-box蛋白质家族成员之一。与Skp2的识别区域不同, c-Myc蛋白质MBI中的T58位点磷酸化能被Fbw7特异性识别, 进而介导c-Myc泛素化降解, 降低c-Myc的转录活性[40]。Fbw7作为肿瘤抑制因子, 能通过负调控c-Myc、cyclin E等, 抑制肿瘤的发展, 但是在大多数肿瘤细胞中, Fbw7发生突变, 表达量降低, 失去肿瘤抑制功能[41]。

FBXO32通常被认为是一种肌肉特有的E3泛素连接酶, 包含F-box结构域, 但没有WD重复序列和亮氨酸重复单位。FBXO32能与c-Myc的168到367AA直接相互作用。这种作用需要MBIV和PEST结构域, 并不依赖于T58和S62位点磷酸化。FBXO32能催化c-Myc形成K48泛素链, 进而被泛素–蛋白酶体降

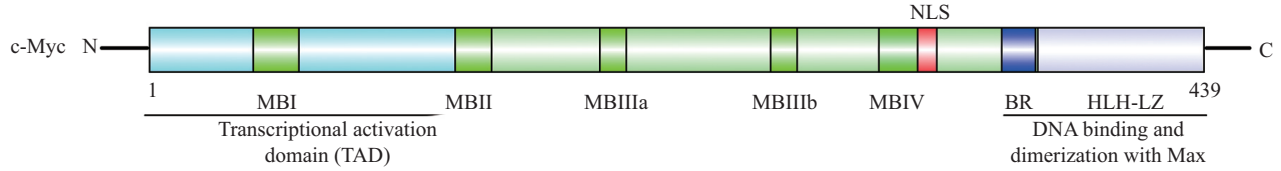


**图1 c-Myc结构**

**Fig.1 The structure of c-Myc**

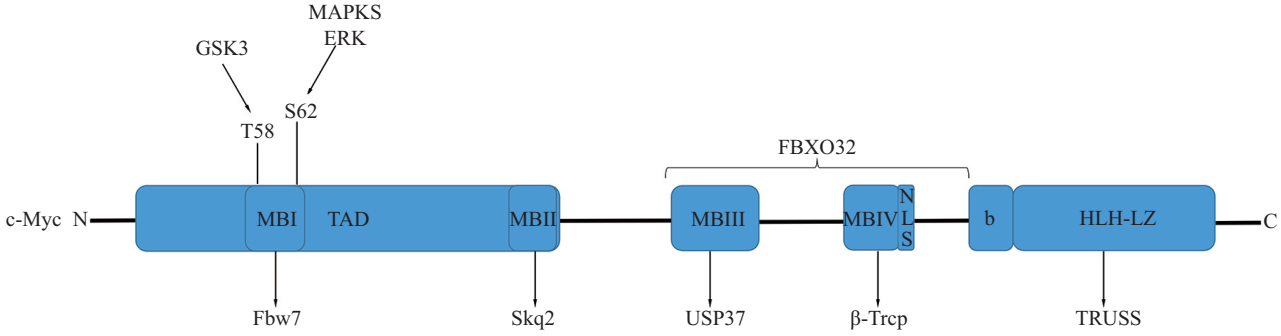


**图2 调控c-Myc的主要E3连接酶和去泛素化酶作用位点示意图**

**Fig.2 Schematic action site of E3 ligases and deubiquitinases of c-Myc**

解, 但c-Myc第326位赖氨酸突变, 能减少c-Myc的泛素化, 阻止c-Myc被FBXO32的泛素化降解。过表达FBXO32能抑制c-Myc的活性, 并抑制细胞的生长。同时, *FBXO32*是c-Myc的直接下游靶基因, 二者形成负反馈调控通路, 共同调节肿瘤的生长[32]。

β-Trcp也是拥有WD重复序列的F-box蛋白家族成员, 能与c-Myc结合并使其泛素化。与Fbw7的作用相反, c-Myc被β-Trcp泛素化后保持稳定。Fbw7对c-Myc的泛素化作用依赖Cdc34泛素结合酶并需要K48泛素链, 而β-Trcp依赖UbcH5泛素结合酶并在c-Myc的N-端形成异型的泛素链即β-Trcp对c-Myc的泛素化需要K33、K48和K63等多种不同连接形式的泛素链[42]。研究发现, 增加Myc的表达, 能加快细胞周期S期的进程[43], 相反, Myc的缺失或表达降低都能延迟细胞周期S期和$G_2$期的进程[44-45]。因此, β-Trcp泛素化依赖的c-Myc稳定对细胞周期的正常运行起重要作用。

2.1.2 HECT结构域的E3泛素连接酶 HectH9能对c-Myc泛素化, 形成K63多聚泛素链, 但并不被泛素–蛋白酶体降解。泛素化的c-Myc能招募辅助活化因子p300, 激活转录多种靶基因并促进细胞增殖, HectH9在多种肿瘤中高表达, 对部分肿瘤的增殖有促进作用[34]。因此, 干扰HectH9的表达为抑制c-Myc在肿瘤细胞中的转录活性提供了新的策略。

TRIM32是包含锌指结构的泛素连接酶, 在分化的神经细胞中高表达, 而在分裂的祖细胞中保持较低的水平。过表达TRIM32能诱导神经元的分化, 而抑制TRIM32的表达能使子代细胞维持祖细胞状态。研究发现, TRIM32与c-Myc相互作用, 通过泛素化降解c-Myc, 诱导神经元的分化[35]。

TRUSS能特异性与c-Myc的C-端结合, 并依赖于bHLH-LZ结构域, 但介导c-Myc的泛素化降解需要C-端和包含高度保守的MBI和MBII结构域的N-端的共同参与[36]。TRUSS在大多数肿瘤细胞中的含量比较低, 导致癌蛋白c-Myc稳定性增加, 促进肿瘤的进一步发展。

2.1.3 U-box结构域的E3泛素连接酶 热休克蛋白70 C-端相互作用蛋白(CHIP)是通过U-box结构域发挥酶功能的E3泛素连接酶。研究发现, c-Myc能与CHIP的TPR(tetratricopeptide repeats)结构域直接相互作用, 然后被泛素化降解[37]。CHIP能够抵消依赖于c-Myc的基因表达和细胞周期进程[37]。

2.1.4 其他的E3泛素连接酶 ELL是不含有典型的RING和HECT结构域的E3连接酶, 最近的研究表明, 它能与c-Myc直接相互作用, 促进c-Myc的泛素化降解, 抑制c-Myc依赖的转录激活和细胞增殖[38]。

### 2.2 c-Myc的去泛素化修饰

泛素化与去泛素化调控细胞内蛋白质的动态平衡。去泛素化酶能水解泛素与底物之间的异肽键, 释放泛素分子, 失去多泛素链标签信号的底物蛋白无法被26S蛋白酶体识别, 从而维持稳定。目前的研究发现, 主要有三种去泛素化酶在不同区域或通过不同方式稳定c-Myc, 包括USP28、USP37和USP36(图2)。

2.2.1 USP28 USP28是第一个被发现的c-Myc的核质去泛素化酶, 但是它们之间并不存在直接相互作用, USP28通过泛素连接酶Fbw7α间接与c-Myc发生作用, 它能减弱Fbw7α的活性间接调控c-Myc的稳定性。Fbw7α的氨基端是USP28、Fbw7α和c-Myc三者形成三元复合物所必需的。此外, 降低细胞内Fbw7的蛋白质水平能提高USP28的稳定性, 预示着USP28可能与WD40重复序列相互作用, 而且可能是Fbw7的底物。其中, c-Myc的S62和T58位点依次被磷酸化能成为Fbw7的识别结合位点, T58和S62位点的突变影响c-Myc与Fbw7α和USP28之间的相互作用, 进而影响c-Myc的稳定性和功能[46-47]。

2.2.2 USP36 USP36是第一个被发现的核仁去泛素化酶, 它在核仁中与c-Myc直接相互作用并使c-Myc去泛素化。在细胞核中, USP36能与核仁中的E3连接酶Fbw7γ相互作用, 与核质中的E3连接酶Fbw7α不存在相互作用, 但是, USP36能够减弱Fbw7γ和Fbw7α调控c-Myc的泛素化降解。USP36通过去泛素化c-Myc使其保持稳定, 反之, c-Myc作为USP36的转录因子, 又能促进USP36的表达, 二者形成正反馈信号通路[48]。

2.2.3 USP37 USP37也是c-Myc的核质去泛素化酶, 但与USP28不同的是, 它与c-Myc直接相互作用并使c-Myc去泛素化。USP37能与c-Myc的中间区域结合, 其中间区域的MBIII结构域是它们相互作用所必需的, 删除MBIII, c-Myc失去结合USP37的能力, 从而无法被USP37去泛素化来保持稳定[49]。

## 3 细胞内c-Myc的稳定与肿瘤

在正常生理条件下, c-Myc的表达水平被严格

调控。当细胞处于静止期时, 细胞内c-Myc的含量比较低, 在接受生长因子的刺激时, c-Myc大量表达并影响下游靶基因的转录, 直到细胞再次进入静止期才恢复到原有水平。研究表明, 转录因子c-Myc的泛素化是其对某些基因行使转录活性的必要条件, 当完成转录作用后被降解。当*c-myc*表达异常时, 就会导致多种疾病, 如肿瘤等[69]。研究发现, *c-myc*在肺癌、结肠癌、乳腺癌、淋巴瘤和白血病等多种肿瘤中表达失控(表1)。*c-myc*的突变和表达失控也成为肿瘤治疗的障碍之一[70]。

### 3.1 肺癌

有研究报道, 肺癌患者样本中c-Myc阳性率为66%, 而正常组织均无表达[71]。CHIP、Fbw7作为肿瘤抑制因子, 在肺癌等多种肿瘤中低表达, 导致c-Myc无法正常被降解, 最终引起由c-Myc诱发的肿瘤。USP36和USP37分别在核仁和核质中对c-Myc进行去泛素化, 使其保持稳定, 促进肺癌细胞的增殖[48-49]。

### 3.2 结肠癌

研究发现, 在结肠癌中有较高的c-Myc mRNA和蛋白质水平[72]。HectH9在部分细胞中高表达并与结肠癌发生发展密切相关, 敲除*HectH9*能抑制结肠癌的增殖, 对正常细胞的生长不会产生影响。在结肠癌细胞的增殖过程中, c-Myc的泛素化能限制HectH9的功能, 因此, 抑制HectH9的酶活性可能与干扰*c-myc*的表达具有相同的抑制结肠癌的效果[34]。USP28作为c-Myc的去泛素化酶, 其表达水平在结肠癌中呈正相关, 因此, 抑制USP28的活性可能成为结肠癌治疗的新方法。

**表1 肿瘤中c-Myc相关泛素连接酶和去泛素化酶的变化关系**

**Table 1 Aberrations of the ubiquitin ligases and deubiquitinases of c-Myc in human cancers**

| 蛋白质<br>Protein | 生理功能<br>Physiological function | 生物效应<br>Biological effects | 病理变化<br>Pathological change | 分子机制<br>Molecular mechanism | 参考文献<br>References |
|---|---|---|---|---|---|
| Skp2 | RING finger-containing E3 for c-Myc | Targeting c-Myc for degradation | Overexpression | Downregulation of substrates, CDK inhibitor $p27^{kip1}$ | [30-31,39] |
| Fbw7 | RING finger-containing E3 for c-Myc | Targeting c-Myc for degradation | Loss of function mutation | Upregulation of substrates, cyclinE, c-jun, c-Myc | [40-41,50-51] |
| FBXO32 | RING finger-containing E3 for c-Myc | Targeting c-Myc for degradation | Overexpression in skeletal muscle atrophy | Downregulation of eIF3-f, MyoD | [32,52-53] |
| β-Trcp | RING finger-containing E3 for c-Myc | Ubiquitination and stabilization of c-Myc | Overexpression | Downregulation of IkB, β-catenin, Emi1 | [42,54-55] |
| HectH9 | HECT domain-containing E3 for c-Myc | Catalyzing K-63-mediated ubiquitination of Myc, not targeting proteins to the proteasome | Overexpression | Downregulation of p53, c-Myc | [34,56-57] |
| TRIM32 | HECT domain-containing E3 for c-Myc | Targeting c-Myc for degradation | Overexpression, loss of function mutation | Upregulation of c-Myc, increasing the activity of let-7 miRNA | [35,58] |
| TRUSS | HECT domain-containing E3 for c-Myc | Targeting c-Myc for degradation | Low expression | Dysregulated expression activates JNK and AP-1, upregulation of c-Myc | [36,59] |
| CHIP | U-box domain-containing E3 for c-Myc | Targeting c-Myc for degradation | Low expression | Upregulation of c-Myc, AKT1, BCR-ABL, hTERT | [37,60-61] |
| ELL | E3 for c-Myc lacking typical RING and HECT domain | Targeting c-Myc for degradation | Low expression | Regulating transcriptional elongation, modulating activity of steroid receptors, HIF-1α, E2F1 | [38,62-64] |
| USP28 | Nucleoplasmic deubiquitinase | Deubiquitination and stabilization of c-Myc | Overexpression, loss of function mutation | Upregulation of c-Myc, cyclinE1 | [46,65] |
| USP37 | Nucleoplasmic deubiquitinase | Deubiquitination and stabilization of c-Myc | Overexpression | Upregulation of c-Myc, Cdt1 | [49,66] |
| USP36 | Nucleolar deubiquitinase | Deubiquitination and stabilization of c-Myc | Overexpression | Upregulation of c-Myc, SOD2, RNA polymerase I | [48,67-68] |

### 3.3 乳腺癌

c-Myc在乳腺癌与乳腺良性增生性病变组织中高表达, 而且c-Myc蛋白质水平与乳腺癌组织学分级、组织学转移及淋巴结转移都有明显关系。c-Myc过表达可能与乳腺癌预后不良密切相关[73]。因此, 通过调控泛素–蛋白酶系统来调节细胞内c-Myc的蛋白质含量, 对乳腺癌的治疗和预后不良反应有重要意义。

### 3.4 肝癌

c-Myc的表达与肝癌组织分化程度、转移及肿瘤大小有关, 其在肝癌组织中的表达显著高于肝硬化组织和正常组织, 提示c-Myc与肝癌的发生、发展有密切关系[74]。李华等[75]的研究表明, c-Myc可作为判断肝癌患者预后的主要因素之一。但目前c-Myc与肝癌的发生机制还尚未阐释清楚, 因此, 深入研究c-Myc与肝癌之间的关系对肝癌的治疗有重要临床应用前景。

### 3.5 白血病

c-Myc在急性白血病细胞(acute lymphoid leukemia, ALL)中高表达, 可能是c-Myc的高表达启动了急性白血病细胞的增生和凋亡信号, 导致白血病的形成和发展[76]。最新的研究表明, 在ALL中, c-Myc蛋白质及基因异常同时存在的病例与预后差有关, 提示其可能加剧了ALL的恶化[77]。目前, c-Myc的抑制剂JQ1(是一种BET-bromodomain抑制剂)和SAHA(HDAC抑制剂)能降低c-Myc的表达从而降低白血病细胞繁殖能力[78], 提示 c-Myc可能作为ALL临床治疗上新的分子靶标。

## 4 展望

c-Myc作为一种极不稳定的蛋白质, 其主要通过泛素–蛋白酶体进行降解或通过去泛素化作用保持稳定。c-Myc能调节细胞内多生物学功能, 如细胞增殖、凋亡、细胞周期进程、细胞代谢和胚胎发育等, 在疾病的发生、发展及演进过程中起着非常重要的作用, c-Myc的异常与多种疾病息息相关。因此, 以泛素–蛋白酶体系统为靶标维持细胞内c-Myc的正常水平或以c-Myc作为分子靶标来治疗疾病的策略对肿瘤治疗将有极大的推动作用。

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