蛋白质乙酰化修饰在病毒感染过程中的作用

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摘要 蛋白质乙酰化是一种蛋白质翻译后修饰(post-translational modification, PTM), 参与调控多种生物学过程。当病毒感染宿主时, 病毒可利用乙酰化修饰便于其自身的复制和增殖; 同时, 宿主也会启动自身的抗病毒天然免疫反应以应对外来物质, 达到保护自身以及限制病毒的增殖, 甚至清除病原体的目的。该文主要从病毒与宿主两个角度综述蛋白质乙酰化修饰在病毒感染过程的作用。

关键词 蛋白质翻译后修饰; 乙酰化修饰; 病毒感染; 抗病毒天然免疫反应

The Role of Protein Acetylation during Viral Infection

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Abstract Protein acetylation is a kind of PTM (post-translational modification) of the protein, which can participate in regulating various biological processes. When the virus infects the host, the virus will employ acetylation machinery to influence its replication and proliferation. At the same time, the host will also initiate its own antiviral innate immune response to deal with foreign matter for protecting itself, limiting the proliferation of the virus, and even eliminating pathogens. In this paper, the roles of protein acetylation modification during viral infection are reviewed from the perspectives of the virus and host.

Keywords PTM; acetylation; viral infection; antiviral innate immune response

随着蛋白质组学的发展, 作为其重要部分的蛋白质翻译后修饰逐渐成为近年来的研究热点。蛋白质乙酰化是蛋白质翻译后修饰的一种, 大部分蛋白质都可发生乙酰化修饰。乙酰化修饰可使蛋白质在构象、活性、稳定性及与其他蛋白的互作等方面发生一定变化, 进而调控多种生物学过程。在病毒感染宿主的过程中, 宿主会采取一系列策略抵御病毒对自身的侵害。同时, 病毒也能进化出相应的机制以逃避宿主的防御网络。本文主要论述病毒感染过程中蛋白质乙酰化修饰对宿主和病毒产生的影响, 进而解析在病毒感染过程中两者的蛋白质网络产生复杂变化的分子机制。

1 蛋白质乙酰化修饰

蛋白质乙酰化修饰是指在乙酰转移酶作用下将乙酰基供体分子上的乙酰基团转移至蛋白质N-端的α氨基或赖氨酸的ε氨基上的过程[1], 最初是在真核生物组蛋白的赖氨酸上被发现的[2]。在细胞中主要的乙酰基供体是乙酰辅酶A(acetyl coenzyme A, acetyl-CoA), 因此多数蛋白质的乙酰化水平均受到体内acetyl-CoA水平的影响。乙酰化修饰的发生机制多样, 除了常见的因酶促反应而发生的蛋白质乙酰化修饰外, 近期研究还发现存在非酶促机制诱发的乙酰化修饰[3]。此外, 乙酰化修饰可在细胞内广泛发生, 其所作用的底物蛋白种类也极其丰富, 这就导

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致了乙酰化修饰类型的多样性。

1.1 蛋白质乙酰化修饰类型

根据蛋白质发生乙酰化的氨基的不同，蛋白质乙酰化修饰可分为Nα-和Nε-乙酰化。Nα-乙酰化是指将乙酰基团转移至蛋白质N-端的α氨基上，可发生在蛋白质N-端的丝氨酸、丙氨酸、苏氨酸、半胱氨酸、甲硫氨酸及缬氨酸上，由*N*-乙酰转移酶(*N*-acetyltransferase, NAT)催化。这一乙酰化是不可逆的，主要发生在真核生物中，而在原核生物中其仅在核糖体蛋白(如大肠杆菌的核糖体蛋白S5、S18和L12，以及分枝杆菌的核糖体蛋白L12[4-5])中发生[1]。与Nα-乙酰化不同，Nε-乙酰化则是指将乙酰基团转移至蛋白质氨基酸的ε-氨基侧链上，它是一个动态的、可逆的过程，主要在组蛋白、高迁移率基团(high mobility group, HMG)蛋白、转录因子、核受体和α-tublin上发生[6-9]。其中，最常被研究的是Nε-赖氨酸乙酰化，因此其乙酰转移酶和去乙酰化酶也分别被称赖氨酸乙酰转移酶(lysine acetyltransferase, KAT)和赖氨酸去乙酰化酶(lysine deacetylase, KDAC)。随着乙酰化修饰研究的逐渐深入，科研人员发现Nε-乙酰化还可以与其他的翻译后修饰共同发生，彼此牵制，进而调控多种生物学过程[10]，例如家蚕Bm30K-3蛋白的乙酰化与泛素化存在相互竞争关系，进而影响蛋白质的稳定性[11]，同样地，人的p62蛋白中也有这一现象的发生[12]。

根据蛋白质的不同，可将蛋白质乙酰化修饰分为组蛋白乙酰化修饰和非组蛋白乙酰化修饰，目前研究最多的是组蛋白乙酰化修饰[13]。组蛋白(histone, H)包括H1、H2A、H2B、H3和H4这5种，参与组成染色质核小体。组蛋白乙酰化主要发生在H3和H4组蛋白的N-端，是一种保守的赖氨酸残基修饰，受组蛋白乙酰转移酶(histone acetyltransferase, HAT)和组蛋白去乙酰化酶(histone deacetylase, HDAC)调节[14]。组蛋白发生乙酰化后，可改变核小体的空间结构，促进基因表达，同时，使染色质结构变得更为松散，促进基因转录和复制，而HDAC可通过去除乙酰基，使得染色质结构进一步浓缩，抑制转录过程发生[15]。同样地，组蛋白的乙酰化修饰也能拮抗其他翻译后修饰的发生，彼此相互抑制，进而干扰不同组蛋白标记[16]。近年研究发现，在哺乳动物中被乙酰化的蛋白质多数是非组蛋白，而被乙酰化的非组蛋白可参与多个生物学过程，如基因转录、DNA损伤修复、信号转导、蛋白质折叠和细胞自噬等[17]。

1.2 乙酰基转移酶以及去乙酰化酶类型

在真核生物中，主要存在以下四类乙酰基转移酶：(1) Gcn5相关的*N*-乙酰基转移酶(Gcn5-related *N*-acetyltransferase, GNAT)超家族；(2) MYST家族；(3) CREB结合蛋白(CREB-binding protein, CBP)/p300家族；(4) YopJ效应蛋白家族[18-19](表1)。其中，GNAT超家族在进化上最为保守，MYST家族成员主要与进化有关，而CBP/p300家族成员参与细胞分化与凋亡。

去乙酰化酶可按照作用机制的不同分为两类：(1) 依赖Zn^{2+}的去乙酰化酶；(2) 依赖NAD^{+}的Sirtuins家族[20-22]。也可根据同源蛋白的不同将去乙酰化酶分为以下四类：I类、II类(IIa类和IIb类)、III类和IV类。其中，I类去乙酰化酶与酵母的Rpd3同源，II类和IV类与酵母的Hda1同源，III类则以Sirtuins家族为主(表2)。

2 蛋白质乙酰化在病毒感染中的作用

在病毒感染过程中，宿主可将病毒视为外来异物，启动自身的免疫系统，激活相关基因及蛋白质的表达，保护自身免遭损伤。同样地，对于病毒而言，需要尽快地完成自身基因组的复制、增殖及装配，以抵御甚至逃避宿主免疫系统的捕获。上述所涉及的一系列反应均有蛋白质参与，以下将从病毒和宿主两个角度阐述作为PTM之一的乙酰化修饰在其中发挥的作用。

2.1 乙酰化修饰对宿主的影响

病毒感染宿主后，宿主可在第一时间启动自身的天然免疫系统。宿主通过模式识别受体(pattern recognition receptors, PRRs)识别病原相关分子如病毒基因组DNA或RNA，进而启动抗病毒级联反应，激活核因子κ增强子结合蛋白(nuclear factor kappa enhancer binding protein, NF-κB)和干扰素调节因子(interferon regulatory factor, IRF)的转录，产生干扰素(interferon, IFN)和相关细胞因子，从而招募先天免疫细胞或激活程序性细胞死亡。现有越来越多的实验证据显示，蛋白质乙酰化参与宿主抗病毒天然免疫反应过程。

在抗病毒天然免疫反应中，PRRs主要有Toll样受体(Toll-like receptors, TLRs)、视黄酸诱导基因I(retinoic acid-inducible gene-I, RIG-I)样受体(RIG-I-like receptors, RLRs)、NOD样受体(NOD-like receptors, NLRs)、黑色素瘤缺乏因子2样受体(AIM2-like receptors, ALRs)以及细胞质中其他的DNA和RNA受

表1 常见的乙酰基转移酶类型

Table 1 General types of acetyltransferases

乙酰基转移酶 Acetyltransferases		抑制剂 Inhibitors		激活剂 Activators
GNAT superfamily	GCN5 (KAT2A)	Spermidine@[23]	CPTH2[24], MB3[25]	/
	PCAF (KAT2B)		L-45[26], Triazolophthalazines 10-32[27]	/
	SRC-1 (KAT13A)		Bufalin[28], Gossypol[29], Verrucarin A[30]	/
	SRC-3(KAT13B)		Bufalin[28], Gossypol[29], Verrucarin A[30]	/
	SRC-2(KAT13C)		/	/
MYST family	TIP60 (KAT5)		NU9056[31], TH1834[32], MG149[33]	/
	MOZ (KAT6A)		WM-8014[34], WM-1119[34]	/
	MORF (KAT6B)		WM-8014[34], WM-1119[34]	/
	HBO1 (KAT7)		WM-3835[35]	/
	MOF (KAT8)		Derivatives of anacardic acid[36]	/
CBP/p300 family	CBP (KAT3A)		MS7972[37], Ischemin[38], SGC-CBP30[39], C646[40], I-CBP112[41], A-485[42]	CTPB[43]
	p300 (KAT3B)		MS7972[37], Ischemin[38], SGC-CBP30[39], C646[40], I-CBP112[41], A-485[42]	CTPB[43]
YopJ effector family	YopJ/YopP		/	/
	AvrA		/	/
	VopA		/	/

@: 乙酰基转移酶广谱抑制剂。/: 未确定。

@: acetyltransferase broad-spectrum inhibitor. /: not determined.

表2 常见的去乙酰化酶类型

Table 2 General types of deacetylases

去乙酰化酶 Deacetylases			抑制剂 Inhibitors		激活剂 Activators
Zn^{2+} dependent deacetylase	I	HDAC1	SAHA&[44], FK228&[44], PXD101&[44], LBH589&[44], TSA&[44], CBHA&[44], Apicidin&[44], NAM*[44], MC2494*[45]	CBUD-1001[46], CI994[47]	Exifone[48]
		HDAC2		CAY10683[49], Valproic acid[50]	/
		HDAC3		RGFP966[51]	/
		HDAC8		PCI-34051[52]	/
	IIa	HDAC4		TMP195[53], LMK235#[54]	/
		HDAC5		TMP195[53], LMK235#[54]	/
		HDAC7		TMP195[53]	/
		HDAC9		TMP195[53]	/
	IIb	HDAC6		A452[55], ACY-1083[56], WT161[57], JW-1[58]	/
		HDAC10		TH34[59]	/
	IV	HADC11		Garcinol[60]	/
NAD^+-dependent deacetylase	III	SIRT1		EX527[61]	Resveratrol[62], SRT2104[63]
		SIRT2		NPD11033[64], SirReal2[65]	/
		SIRT3		YC8-02[66]	/
		SIRT4		ZINC12421989[67]	/
		SIRT5		MC3482[68], NRD167[69]	/
		SIRT6		OSS_128167[70]	MDL-800[71]
		SIRT7		ID:97491[72]	/

/: 未确定。&: 去乙酰化酶广谱抑制剂。*: 泛SIRT抑制剂。#: HDAC4/5特异性抑制剂。

/: not determined. &: deacetylase broad-spectrum inhibitor. *: SIRTs inhibitor. #: HDAC4/5 specific inhibitors.

体[73]。以下从抗病毒免疫反应的不同方面简述蛋白质乙酰化修饰对宿主的影响。

2.1.1 TLRs信号通路因子的乙酰化修饰 TLRs是PRRs的一种，主要由富含亮氨酸重复序列的胞外区、含单个α螺旋的跨膜区以及Toll-白细胞介素-1受体(Toll-interleukin-1 receptor, TIR)结构域的胞质区组成[74]，该家族包括人类的10个成员(TLR1~TLR10)和小鼠的12个成员(TLR1~TLR9、TLR11~TLR13)[75]。TLRs家族成员可选择性地利用接头蛋白，激活相应的信号通路，进而诱导I型干扰素和趋化因子等介质的转录[76]，而这些以TLRs为PPRs所启始的信号通路又可根据接头蛋白的不同被分为髓样分化初级反应蛋白88(myeloid differentiation protein antigen 88, MyD88)依赖的TLRs信号通路和含TIR结构域的诱导IFN-β的接头(TIR domain-containing adaptor-inducing IFN-β, TRIF)蛋白依赖的TLRs信号通路。其中TLR1、TLR2和TLR5~TLR9通过前者起作用，TLR3则通过后者起作用，而TLR4可触发两者[75]。

当感染丙型肝炎病毒(hepatitis C virus, HCV)、卡波氏肉瘤相关疱疹病毒(Kaposi sarcoma-associated herpesvirus, KSHV)后，TLR4的表达水平发生变化，进而影响后续的抗病毒天然免疫反应[77-78]。同样地，TLR3也能促进由病毒感染引起的免疫反应[79]。TANK结合激酶1(TANK-binding kinase 1, TBK1)作为TLRs信号通路中的一个重要的节点蛋白，是激活干扰素调节因子3(interferon regulatory factor 3, IRF3)的关键激酶，可影响I型干扰素的表达[80]。感染病毒后，TBK1可发生乙酰化修饰，而被乙酰化的TBK1能够增强TBK1与IRF3的相互作用，其中，Lys692位点的乙酰化修饰可抑制TBK1二聚体的活化及自身激酶活性，而HDAC3介导Lys241位点的去乙酰化增强了TBK1磷酸化IRF3的能力，此外，TBK1作为激酶还可以磷酸化HDAC3 Ser424位点以增强其去乙酰化酶活性[81]。DNA甲基转移酶3a(DNA methyltransferase 3a, Dnmt3a)也可以通过表观调控维持组蛋白去乙酰化酶9(histone deacetylase 9, HDAC9)的高水平表达，进一步促进TBK1的去乙酰化，从而增强TBK1的激酶活性并介导I型IFN高表达[82]。除了TBK1外，MyD88也可在Lys132位点发生乙酰化，其低乙酰化水平可导致白细胞介素-6水平升高，从而使细胞对HDAC抑制剂敏感，其去乙酰化则由HDAC6介导发生[83]。

2.1.2 cGAS-STING通路因子的乙酰化修饰 环磷酸鸟苷–腺苷酸合酶(cyclic GMP-AMP synthase, cGAS)是细胞质中的DNA受体，可通过识别外源性及自身异常产生的DNA，生成第二信使环二核苷酸(cyclic-GMP-AMP, cGAMP)[84]，激活干扰素基因刺激因子(stimulator of interferon genes, STING)，进而结合并激活TANK-结合激酶1(TANK-binding kinase, TBK1)和IκB激酶(IκB kinase, IKK)，促使干扰素调节因子3(interferon regulatory factor 3, IRF3)和转录因子NF-κB的激活，最终诱导I型IFN的产生[85]。cGAS可在Lys384、Lys394和Lys414位点上发生乙酰化，cGAS的乙酰化可抑制其酶活性，进一步抑制cGAS所介导的免疫应答反应，如干扰素生成等；同时发现，HT-DNA刺激会使得cGAS发生去乙酰化，免疫共沉淀结果显示HDAC3可与cGAS发生相互作用，进一步敲低HDAC3后，cGAMP产量减少[86]。当感染DNA病毒如单纯疱疹病毒1(herpes simplex virus 1, HSV-1)后，乙酰转移酶KAT5能够乙酰化cGAS的N-端非结构域(N-terminal unstructured domain, NUD)，即K47、K56、K62和K83，进而激活并增强其与病毒DNA结合的能力，促进天然抗病毒免疫反应；进一步的qPCR分析结果显示，KAT5活性的降低可使其下游基因如*Ifnb1*、*Cxcl10*和*Il6*的转录被抑制，进而抑制免疫反应发生[87]。

2.1.3 RLRs通路因子的乙酰化修饰 RLRs在所有哺乳动物细胞中均有表达。目前，哺乳动物RLRs主要包括：RIG-I、黑色素瘤分化相关基因5(melanoma differentiation associated factor 5, MDA5)和遗传与生理学实验室蛋白2(laboratory of genetics and physiology 2, LGP2)[88]。其中，RIG-I和MDA5可识别细胞质中的病毒RNA，进一步通过与干扰素β启动子刺激因子1(interferon β promoter stimulator-1, IPS-1)的CARD样结构域相互作用，经TBK1和IKKi依赖性磷酸化激活IRF3和干扰素调节因子7(interferon regulatory factor 7, IRF7)。除此以外，IPS-1还可通过Fas相关死亡域蛋白(Fas-associated death domain protein, FADD)和受体相互作用蛋白1(receptor-interacting protein 1, RIP1)依赖性途径激活NF-κB。以上多种通路可协同激活I型干扰素启动子[89]。

RIG-I主要通过C-端结构域(carboxy-terminal domain, CTD)识别RNA病毒，进而激活抗病毒天然免疫

反应。RIG-I CTD的去乙酰化能够影响其对病毒RNA的敏感度。当病毒RNA存在时, HDAC6可使RIG-I在Lys909位点发生去乙酰化, 增强其对病毒RNA的敏感度, 而敲除*HDAC6*仅增强RIG-I对病毒RNA的敏感度, 而不影响其对DNA病毒的抗病毒免疫反应, 且*HDAC6*基因敲除小鼠对RNA病毒感染高度敏感[90]。

RIP1其C-端含有由112个氨基酸组成的死亡结构域(death domain, DD), 它还具有激酶活性, 可使RIP3发生磷酸化[91]。RIP1有激酶活性, 可磷酸化RIP3。同时, 在RIP1的激酶结构域与DD结构域中共发现5个乙酰化位点, 而SIRT抑制剂MC2494处理能在RIP1其他结构域的两个位点发生乙酰化, 增强RIP1的乙酰化水平[45], 但RIP1蛋白乙酰化与抗病毒天然免疫反应间的关联还未见报道。

2.1.4 NLRs信号通路因子的乙酰化修饰 NLRs家族蛋白结构保守, C-端包含一个caspase招募结构域或Pyrin结构域, 中部包含核酸结合结构域, N-端包含富含亮氨酸重复结构域[92-95]。已知的NLRs包括能够启始NF-κB、MAPK炎症信号通路的NOD1和NOD2, 以及可以促进IL-β/IL-18等炎性因子释放的NLRP1/NALP1、NLRP3/NALP3/cryopyrin和NLRC4/Ipaf[96-98]。

NLRP3作为NLRP3炎症小体的重要核心蛋白, 是识别外源感染和内部损伤等信号的重要部件, 感染寨卡病毒(Zika virus, ZIKV)[99]和肠道病毒71型(enterovirus 71, EV71)[100]后, NLRP3炎症小体的产生被促进。同时, 在巨噬细胞中NLRP3可在Pyrin结构域(pyrin domain, PYD)的Lys21、Lys22和Lys24位点发生乙酰化修饰, 且SIRT2可介导NLRP3的去乙酰化, 从而影响NLRP3与含有CARD的凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a CARD, ASC)之间的相互作用, 进一步影响NLRP3炎症小体的产生[101]。

2.1.5 ALRs信号通路因子的乙酰化修饰 ALR基因型在哺乳动物中差别大, 在人类中发现有4种[黑素瘤缺乏因子2(absent in melanoma 2, AIM2)、IFI16、PYHIN1、MNDA], 而在小鼠中有13种[102]。其中, AIM2研究最为广泛, 其C-端为HIN-200结构域, 可直接结合dsDNA, N-端为PYD结构域, 可与ASC蛋白的PYD结构域相互作用, 而ASC蛋白的CARD结构域可与pro caspase-1的CARD结构域相互作用, 形成大分子复合物[103]。抑制HDAC3(histone deacetylases 3, HDAC3)可减少AIM2炎症小体及其下游相关炎症介质的表达量[51]。当感染疱疹病毒后, IFI16蛋白可在细胞核中识别病毒基因组, 并与p300发生相互作用, 促进自身的乙酰化, 进一步影响细胞核中的炎性体组装和细胞质易位、细胞质中STING的激活以及IFN-β的产生[104]。

除了以上提到的信号通路外, 还存在一些特殊的免疫通路, 例如, 与哺乳动物不同, 果蝇可利用Toll通路和免疫缺陷(immune deficiency, IMD)通路完成天然免疫反应。在IMD通路中, YopJ可使转化生长因子-β激活激酶1(transforming growth factor-beta activated kinase 1, TAK1)在Thr171、Ser176位点发生乙酰化, 进而抑制TAK1的磷酸化, 影响MAP3激酶的激活以及随后的天然免疫反应中的NF-κB信号通路[105], 哺乳动物细胞中的hTAK1也有类似修饰发生, 但这一乙酰化修饰是由细菌感染所引起的[106-107], 所以病毒感染是否也可引起这一效应还需要进一步的考证。

2.2 乙酰化修饰对病毒的影响

在宿主感染病毒的过程中, 乙酰化修饰除了启始宿主的抗病毒天然免疫反应外, 还影响病毒相关的生物学过程, 包括病毒复制、出芽以及包装等。但由于病毒基因组缺乏编码乙酰基转移酶和去乙酰化酶的基因, 因此, 病毒的乙酰化过程主要依靠宿主相关酶来完成。目前研究最多的可发生乙酰化修饰的病毒是流感病毒和肝炎病毒。

流感病毒(influenza virus, IV)具有分段单股负链RNA的基因组, 可分为A、B和C 3种类型, 其中A型研究最多。A型流感病毒(influenza A virus, IAV)又称甲型流感病毒, 成熟的甲型流感病毒由来源于宿主的脂质包膜和由8个基因片段编码的病毒蛋白包括PB1、PB2、PA、血凝素(hemagglutinin, HA)、神经氨酸酶(neuraminidase, NA)、核蛋白(nucleoprotein, NP)、基质蛋白1(matrix protein 1, M1)、基质蛋白2(matrix protein 2, M2)、非结构蛋白1(nonstractural protein 1, NS1)和出核蛋白(nuclear export protein, NS2/NEP)所组成, 其中NS1不存在于成熟病毒粒子中[108]。流感病毒的NS1蛋白可在Lys108位点发生乙酰化修饰, 同时, 体内和体外实验结果表明, NS1蛋白的去乙酰化减弱了流感病毒的复制和毒力[109]。流感病毒的NP蛋白可与vRNA及RNA聚合酶结合形成核糖核衣壳(ribonucleoprotein, RNP)复合体而参与病毒基因组的转录和复制, 协助蛋白从细胞质转运至细胞核中[110], NP蛋白

可在Lys77、Lys113和Lys229位点被乙酰化，其中，Lys229位点的去乙酰化能够影响病毒粒子的释放，而Lys77和Lys113位点的超乙酰化可严重降低病毒聚合酶活性[111]。后续研究发现，NP蛋白的乙酰化可由细胞内的GCN5和PCAF催化，这一蛋白的乙酰化状态能够影响病毒聚合酶活性和病毒复制[112]。PB1、PB2、PA蛋白是甲型流感病毒RNA聚合酶的重要组成单位，HDAC6可与IAV的PA蛋白相互作用，使PA蛋白在Lys664位点发生去乙酰化，影响其蛋白稳定性，同时，抑制HDAC6可促进病毒基因的转录与复制[113]。

肝炎病毒可以分为甲型肝炎病毒(hepatitis A virus, HAV)、乙型肝炎病毒(hepatitis B virus, HBV)、丙型肝炎病毒(hepatitis C virus, HCV)、丁型肝炎病毒(hepatitis D virus, HDV)和戊型肝炎病毒(hepatitis E virus, HEV) 5种类型，其中，乙酰化修饰研究最多的是HBV。HBV是具包膜的部分双链DNA病毒，分为10个基因型(A~J)[114]，可编码5种主要蛋白质：聚合酶(基因P)、HBc(基因C上的核心蛋白)、HBeAg(基因C的不同剪接产生的包膜抗原)、HBsAg(基因S上的表面抗原)和HBx(基因X上的复制辅助因子)[115]。贾小芳等[116]的研究发现，当用去乙酰化酶抑制剂TSA和NAM刺激HBV复制细胞模型Hep G2.2.15和Hep AD38后，细胞内蛋白质的乙酰化水平呈时间和浓度依赖性升高，同时，培养上清中的HBsAg蛋白水平降低，而HBV DNA水平升高，且呈时间和浓度依赖关系。此外，在表达HBV的肝癌细胞中SIRT1的表达水平升高，过表达SIRT1可上调HBx蛋白的表达，同时，抑制SIRT1可抑制表达HBx的肝癌细胞的增殖和迁移[117]。前期研究发现，HBx蛋白可直接与CBP/p300结合，在物理上占据CREB结合域，影响后续事件的发生[118]。

HBV共价闭合环状DNA(covalently closed circular DNA, cccDNA)的游离核酸部分是合成病毒RNA的核内转录模板，也可作为原病毒DNA存在并整合在细胞核中[119]。HBV的复制受与cccDNA结合的H3/H4的乙酰化状态调控，用去乙酰化酶抑制剂VPA和TSA处理后，与cccDNA结合且发生乙酰化的H4数量增加，同时HBV复制明显被促进[120]，且细胞内的CBP、p300、PCAF/GCN5、HDAC1和hSirt1都被招募到cccDNA上[121]。

HBc蛋白是组成病毒衣壳的基本单位，HBV HBc蛋白的Lys96发生突变后，核衣壳仍能形成，但颗粒包膜和病毒粒子形成受阻，甚至达到无法检测的水平[122]，进一步构建Lys96位点的点突变体，结果显示，去乙酰化可抑制HBV核心蛋白HBc的表达，导致病毒组装水平下降，进而影响病毒的致病性[123]。此外，HDAC11可抑制乙肝病毒在小鼠体内的复制[124]，干扰素α(interferon α, IFN-α)可通过降低组蛋白H3、H4乙酰化水平而影响鸭乙型肝炎病毒(duck hepatitis B virus, DHBV)的DNA结构与功能[125]。

除了以上两种研究较多的病毒外，在人类免疫缺陷病毒(human immunodeficiency virus, HIV)[126]、Epstein-Barr病毒(Epstein-Barr virus, EBV)[127]、严重急性呼吸系统综合征冠状病毒(severe acute respiratory syndrome coronavirus, SARS-CoV)[128]等中均有蛋白质乙酰化的存在。随着乙酰化修饰研究的不断深入，研究人员发现昆虫杆状病毒的多种病毒蛋白也可发生乙酰化修饰，修饰后的蛋白能够影响病毒的复制以及病毒蛋白的亚细胞定位。如，在家蚕核型多角体病毒(*Bombyx mori* nucleopolyhedrovirus, BmNPV)中，晚期表达因子(late expression factor, LEF)是一类很重要的蛋白质，在病毒侵染过程中，晚期表达因子6(late expression factor 6, LEF6)的Lys85和Lys94位点发生乙酰化修饰，进而抑制病毒的复制和增殖，降低子代病毒的产量，同时，乙酰化会影响其亚细胞定位，使其无法入核发挥作用[129]。同样地，LEF3[130]、热休克同源蛋白70-4(heat shock cognate protein 70-4, HSC70-4)[131]均能发生乙酰化修饰，进而影响病毒复制和增殖。

3 HDACs抑制剂在抗病毒治疗中的应用

在多数致病性病毒感染宿主的过程中，蛋白质乙酰化修饰起着重要作用，可影响病毒多个生物学过程。HDACs作为调控蛋白质乙酰化的一类重要酶，可以介导乙酰化的蛋白质丢失乙酰基团，而HDACs抑制剂则可使蛋白保持乙酰化状态。因此，在病毒感染性疾病的抗病毒治疗中，HDACs抑制剂类药物的开发也显得愈发重要。

目前，HDACs抑制剂类药物在抗病毒治疗中主要应用于抗HIV。HIV感染可引起宿主获得性免疫缺陷综合征(acquired immune deficiency syndrome, AIDS)的发生，而对于AIDS的治疗，常见策略是利用特定的潜伏逆转剂逆转其潜伏期，结合抗逆转录

病毒疗法(antiretroviral therapy, ART), 使具有潜伏感染能力的病毒库CD4$^+$ T细胞被宿主自身的免疫系统捕获杀死, 以达到治疗的目的。HDACs抑制剂辛二酰苯胺异羟肟酸(suberoylanilide hydroxamic acid, SAHA)是目前已被FDA批准用于治疗淋巴瘤的5种药物之一, SAHA可以在体外扰乱HIV-1的潜伏期[132], 后续研究从病毒血症被抗逆转录病毒疗法完全抑制的患者体内分离出循环静息CD4$^+$ T细胞, 发现SAHA处理不仅增加了细胞体内的乙酰化水平, 同时, 使得HIV RNA表达增多[133], 表明SAHA可能是AIDS患者抗病毒治疗中的一个潜在药物。

多数HDACs抑制剂均能在体外激活处于潜伏期的HIV-1病毒, 但具有一定的细胞毒性和不良副作用, 所以常与其他药物或疗法联用。作为HDACs抑制剂之一的valproic acid可在组织培养中激活潜伏的HIV-1病毒, 但对患者的潜伏病毒库却无明显影响[134]。化合物抗病毒6(antiviral 6, AV6)已被证实可激活原代静息CD4$^+$ T细胞内的潜在HIV病毒, 后续研究将其与valproic acid联用处理细胞系24STNLSG和19STNLSG, 发现这一策略可加快激活潜伏的HIV-1病毒的感染进程[135]。除了与抗病毒药物的联用外, HDACs抑制剂与其他药物(如蛋白激酶激活剂[136]、免疫调节剂[137]等)共处理也可以达到类似的效果。这些事实表明, HDACs抑制剂与其他药物的联用策略可能可以实现抗病毒治疗效果的优化。

癌症相关病毒人巨细胞病毒(human cytomegalovirus, HCMV)是一种疱疹病毒, 能够参与结肠癌、乳腺癌和前列腺癌的发生发展[138], 而乳腺癌作为女性高发性癌症, 近年来出现的一种较为安全的溶瘤单纯疱疹病毒(oncolytic herpes simplex virus, oHSV)疗法, 因缺乏足够的效力, 使得其临床应用被延滞。而用不同HDACs抑制剂处理乳腺癌MDA-MB-231、oHSV抗性细胞系4T1后, oHSV的复制均有不同程度的增加[139]。这为转移性乳腺癌的治疗提供了一种新策略。

总之, 目前所开发的HDACs抑制剂类药物主要针对的适应症是肿瘤以及相关的炎症, 而其在抗病毒治疗方面的应用还有很多的障碍需要克服。

4 总结与展望

本文主要从宿主和病毒两个角度, 总结了乙酰化参与宿主抗病毒免疫反应的靶蛋白(表3)以及对病毒自身能力的影响(表4), 这为乙酰化修饰激活或抑制宿主的抗病毒天然免疫反应通路以及影响病毒感染能力的具体机制的探索开拓了新方向, 也为后续病毒性疾病相关药物的研发提供了一定的理论基础, 同时, 有利于在细胞中寻找病毒变异的分子靶点。

表3 蛋白质乙酰化修饰对宿主的影响

Table 3 The effects of protein acetylation on host

通路类型 Pathways	乙酰基转移酶 Acetyltransferases	去乙酰化酶 Deacetylases	底物 Substrates	位点 Sites	代表性病毒 Representative viruses
TLRs signaling pathway	/	HDAC3, HDAC9	TBK1	Lys241, Lys692	VSV[81-82], SeV[81-82], HSV[81-82]
	/	HDAC6	MyD88	Lys132	HIV[140]
cGAS-STING signaling pathway	KAT5	HDAC3	cGAS	Lys384, Lys394, Lys414, Lys47, Lys56, Lys62, Lys83	HSV-1[87]
RLRs signaling pathway	/	HDAC6	RIG-I	Lys909	VSV[90], IAV[141]
	/	SIRT1/2	RIP1	Lys115, Lys625, Lys627, Lys642, Lys648, Lys596, Lys599	NDV[142], HSV-1[143]
NLRs signaling pathway	/	SIRT2	NLRP3	Lys21, Lys22, Lys24	ZIKV[99], EV71[100]
ALRs signaling pathway	/	HDAC3	AIM2	/	EBV[144], HBV[145]
	p300	/	IFI16	/	KSHV[104], HSV-1[104], EBV[104]

/: 未确定。

/: not determined.

表4 蛋白质乙酰化修饰对病毒的影响

Table 4 The effects of protein acetylation on virus

病毒 Viruses	乙酰基转移酶 Acetyltransferses	去乙酰化酶 Deacetylases	底物 Substrates	影响 Effects
IAV	/	/	NS1[115]	Deacetylation attenuates replication and virulence of IAV
	GCN5, PCAF	/	NP[117-118]	Deacetylation affects the release of virions, and hyper-acetylation reduces viral polymerase activity
	/	HDAC6	PA[119]	Deacetylation promotes protein degradation, transcription and replication of viral genes
HBV	CBP/p300	SIRT1	HBx[123-124]	Deacetylation enhances the expression of HBx protein
	/	/	HBc[129]	Deacetylation inhibits the expression of HBc, reduces the level of viral assembly, and affects the pathogenicity of the virus
	CBP, p300, PCAF/GCN5	HDAC1, hSirt1	H3/H4[126-127]	Acetylation increases the level of acetylated H4 bound to cccDNA and promotes viral replication
SARS-CoV	PCAF, GCN5	/	NP[134]	/
BmNPV	/	/	LEF3[136], LEF6[135], HSC70-4[137]	Acetylation affects viral replication and proliferation

/: 未确定。

/: not determined.

因此, 对乙酰化修饰效应蛋白作用机制研究的深入不仅有助于理解蛋白质间的相互作用是如何被乙酰化修饰所调控的, 也有助于在分子水平上了解宿主抗病毒过程中蛋白质的网络调控机制。

随着HDACs抑制剂类药物在抗病毒治疗中的不断应用, 其与其他药物或疗法的联用可能是未来抗病毒治疗的发展方向, 可更好地降低药物自身的不良反应, 且进一步探索联合治疗的优化条件必然会成为这类药物未来的研究重点。

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