泛素化修饰在抗病毒天然免疫反应中的作用

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摘要 蛋白质翻译后修饰几乎调控细胞所有的生命活动, 有大量研究报道了其中的泛素化在病毒感染过程中的作用。受病毒感染时, 宿主可利用泛素化修饰起始抗病毒天然免疫反应, 从而抵抗病毒入侵。相应地, 病毒也可以利用泛素化修饰逃逸细胞的免疫反应。该文从宿主与病毒两个角度综述了蛋白质的泛素化修饰在抗病毒天然免疫中的作用及其调控机制, 为抗病毒的治疗提供一些新的策略。

关键词 泛素化修饰; 抗病毒天然免疫反应; 免疫逃逸

The Role of Ubiquitination in Antiviral Innate Immune Response

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Abstract The post translational modification of proteins regulates almost all the life activities of cells. A large number of studies have reported the role of ubiquitination in the process of viral infection. When infected with the virus, host cells can initiate an antiviral innate immune response to restrict viral infection, and correspondingly, viruses can escape the cellular immune response, through ubiquitination pathways. This paper reviews the role and regulatory mechanism of protein ubiquitination from both host and virus perspectives, providing some new strategies for future antiviral treatments.

Keywords ubiquitination; antiviral innate immune response; immune escape

泛素(ubiquitin, UB)是一种普遍存在于真核生物体内的含有76个氨基酸残基的小分子质量蛋白。UB是一种分子标记蛋白, 经由泛素激活酶E1、泛素偶联酶E2和泛素连接酶E3的级联反应, UB分子C-端甘氨酸残基的羧基共价连接到底物蛋白质的赖氨酸残基侧链的ε-氨基上, 形成异肽键[1]。这一过程被称为蛋白质的泛素化修饰。通过泛素化修饰, 蛋白质的构象、活性、稳定性等多方面都会发生变化, 进而调控多种生物学过程。受病毒感染后, 宿主会激活抗病毒天然免疫反应以抵御病毒对自身的侵害。而同时, 病毒进化出相应的机制以完成免疫逃逸。本文综述了蛋白质泛素化修饰在抗病毒天然免疫反应和病毒免疫逃逸中的作用, 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 泛素化修饰

根据连接方式不同, 可将泛素化修饰分为单泛素化和多泛素化。单泛素化修饰是指单个泛素分子与靶蛋白的赖氨酸侧链相连, 多泛素化修饰则是靶蛋白的多个赖氨酸残基与泛素分子结合。泛素分子的七个赖氨酸残基(K6、K11、K27、K29、K33、K48和K63)和一个甲硫氨酸残基(M1)均可作为泛素化位点, 已经共价修饰到靶蛋白上的泛素分子还可

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继续发生泛素化修饰, 即形成泛素链。目前发现的细胞中存量最多的2种同型泛素链是K48泛素链和K63泛素链, 其中, K48 泛素链是最主要的泛素修饰类型, 在所有泛素修饰中占到50%以上。其他泛素链则属于非典型泛素链。泛素链拓扑结构的复杂性造成了其功能多样性, 包括参与囊泡运输途径、调节组蛋白修饰和病毒出芽等, 这对于细胞周期调节、DNA修复、细胞生长和免疫功能以及激素介导的信号转导意义重大。

泛素化修饰作为一种可逆的翻译后修饰, 能够被去泛素化酶(deubiquitinase, DUB)去除其与底物之间的共价键以及泛素分子之间的共价键。同时DUB能够介导蛋白的降解, 调节靶蛋白性质及相关信号通路, 进而调控底物的生命进程[2]。

2 蛋白质泛素化在病毒感染中的作用

当病毒感染细胞后, 对于宿主而言, 病毒作为外来物, 会刺激宿主启动自身的免疫系统, 激活相关基因及蛋白质的表达, 以限制或约束病毒的感染, 甚至清除病毒。相应地, 对于病毒而言, 则需要尽快地完成自身基因组的复制、装配及增殖, 以逃避甚至抵御宿主免疫系统的约束。本文将从宿主和病毒两个不同角度分别阐述蛋白质泛素化修饰在病毒感染中发挥的作用。

2.1 泛素化对宿主的影响

受病毒感染后, 宿主细胞会在第一时间启动自身的天然免疫系统。通过模式识别受体(pattern recognition receptors, PRRs)识别入侵病毒病原相关分子模式(pathogen-associated molecular patterns, PAMPs), 起始系列抗病毒级联反应, 激活下游相关分子如核因子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, 诱导I型干扰素(interferon, IFN-I)和相关细胞因子的表达, 从而招募先天免疫细胞或激活程序性细胞死亡(programmed cell death, PCD), 最终建立起细胞抗病毒状态。

宿主细胞的模式识别受体主要有五类: Toll样受体(Toll-like receptors, TLRs)、维甲酸诱导基因I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)以及胞质DNA受体[3](图1)。

2.1.1 泛素化修饰调控TLRs信号通路 TLRs属于I型跨膜糖蛋白, 具有较高的保守性, 由胞外区富含亮氨酸重复序列、跨膜区含单个α螺旋、胞内区含Toll-白细胞介素-1受体[Toll/interleukin-1(IL-1) receptor, TIR]信号结构域组成[4]。到目前为止, 已发现13种TLR家族成员, 人类细胞中共发现10种(TLR1~TLR10) TLRs。其中, TLR3可识别dsRNA, TLR7和TLR8可识别ssRNA, TLR9则可识别病毒未甲基化的DNA, TLR2和TLR4可识别病毒包膜糖蛋白[3]。

根据接头蛋白的不同, TLRs信号通路可分为含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信号通路和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。其中, TLR3依赖TRIF接头蛋白作用调控IFN-I表达, 其他TLRs依赖MyD88衔头蛋白调控NF-κB通路的表达。TLR4则依赖两种途径[5]。

一方面, MyD88招募下游的白细胞介素-1受体相关激酶(IL-1R-associated serine/threonine kinases, IRAKs), 后者传递信号到泛素连接酶6(TNF receptor-associated factor 6, TRAF6), 随后募集并活化转化生长因子-β激活激酶1(TGFβ-activated kinase 1, TAK1)和IKKα/β/γ(也被称作NEMO), 以促进NF-κB介导的炎症因子的表达。该通路受多种泛素连接酶调控, 如UBL4A和TRIM26可分别催化TRAF6和TAB1发生泛素化以增强先天免疫[6-7]。有趣的是, 宿主细胞可以通过自身合成的泛素连接酶或DUB负调控TLRs信号通路, 从而防止发生过度的免疫反应。如Smurfp1/2、Nrdp1和CYLD可催化MyD88发生泛素化修饰或去除泛素链进行负调控[6-8]; A20、IRAK-M、ST2和SIGIRR等同样可以调节TLRs信号的持续时间和/或强度[9-12]。

另一方面, TRIF通过招募TRAF3, 激活TANK结合激酶1(TANK-binding kinase 1, TBK1)和核因子κB激酶抑制剂ε(inhibitor-κb kinase ε, IKKε), 促进IRF3诱导的IFN-I产生。该通路受多种酶调控, 包括cIAP1/2、Peli1、Triad3A、Mint3、Nedd4l、USP1都能够正向调节TRIF介导的抗病毒免疫应答[13-21]。类似地, Triad3A、USP19、WWP2和TRIM32可降解TRIF防止过度免疫的发生[22-25]; RNF99则可促进TAB2发生K48泛素化修饰进入蛋白酶体被降解, 抑制TAK-TABs复合体形成[26]。不仅如此, 有的泛素连

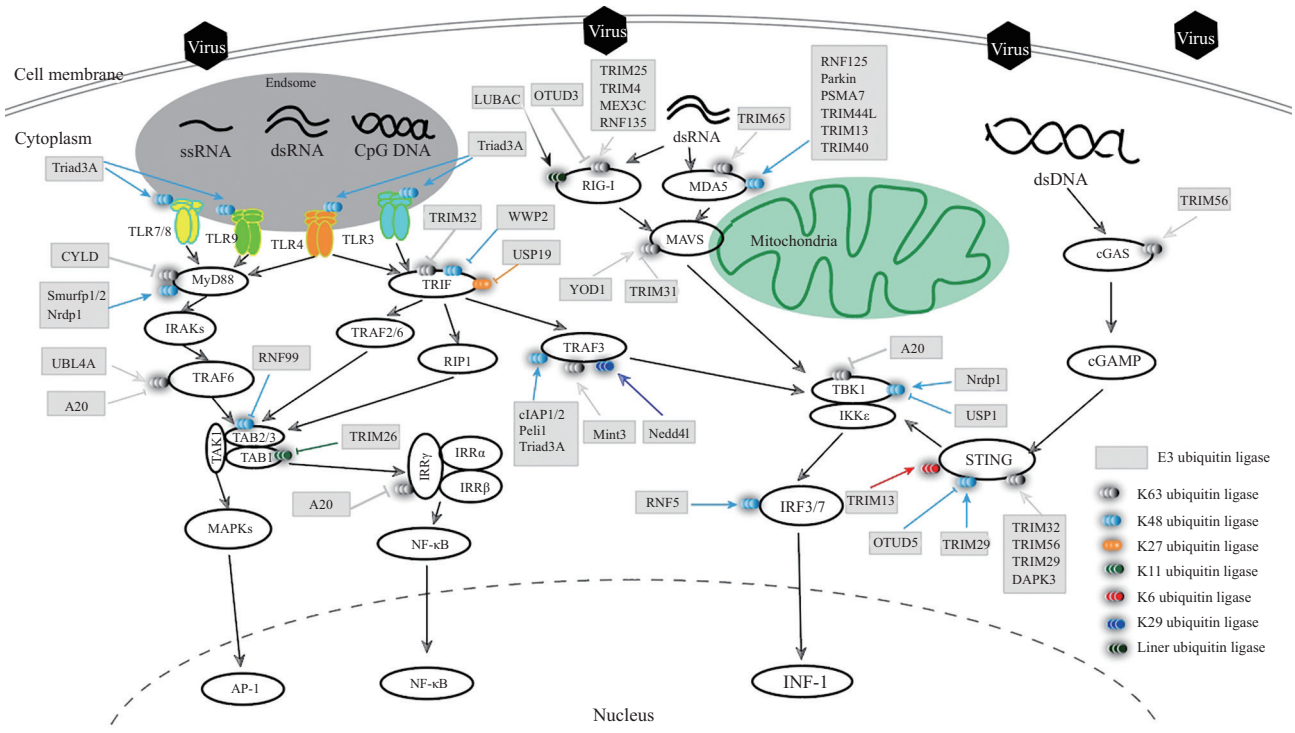

图1　泛素化修饰调控宿主抗病毒天然免疫反应信号通路

Fig.1　Ubiquitination regulates the host's natural immune response signaling pathways

接酶还可针对IFN-I产生通路外的蛋白进行调控，例如RNF182通过K48泛素化促进胞质p65的降解，进而抑制炎症反应[27]。由此可见，宿主细胞自身对天然抗病毒免疫翻译的正调控和负调控对于维持机体稳态至关重要。

2.1.2　泛素化修饰调控RLRs信号通路　RLRs家族成员包括视黄酸(维甲酸)诱导基因蛋白-I(retinoic acid-inducible gene-I, RIG-I, 也被称为DDX58)、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), 主要通过识别胞质中的病毒RNA启动抗病毒天然免疫反应[28]。RIG-I和MDA5具有相似的序列，均由两个N-端的半胱天冬酶招募结构域(caspase-recruitment domains, CARDs)、一个具有RNA结合活性的DExD/H-box解旋酶结构域和一个具有RNA识别功能的C-端结构域(C-terminal domain, CTD, 也被称为调节或抑制结构域)组成。相比之下, LGP2缺乏N-端CARDs。

在胞质中，RIG-I和MDA5可通过CTD与病毒RNA结合，改变自身构象以结合线粒体抗病毒信号蛋白(mitochondrial antiviral sig naling protein, MAVS, 也称VISA/Cardif/IPS-1)，后者活化TBK1/IKKi，最终促进I型干扰素的产生，调控天然免疫反应信号通路。当感染水泡性口炎病毒(vesicular stomatitis virus, VSV)时, Riplet(也称RNF135)催化RIG-I的C末端发生K63泛素化，介导IFN-β启动子激活，最终参与人类抗RNA病毒感染的先天免疫[29]。除C末端外，RIG-I氨基端CARD结构域也可发生泛素化修饰，如TRIM25、TRIM4与MEX3C可介导CARD结构域多个位点发生K63多聚泛素化修饰，促进其对MAVS的招募与结合，正向调控干扰素信号通路[30-32]。而负调控方面通过去泛素化酶介导，如OTUD3可去除由Riplet催化的RIG-I的K63泛素链[33]。另外，有研究发现，由血红素氧化IRP2泛素连接酶1L(heme-oxidized IRP2 ubiquitin ligase 1L, HOIL-1L)和HOIL1接头蛋白(HOIL-1-interacting protein, HOIP)构成的复合体LUBAC(linear ubiquitin chain assembly complex)，可以对RIG-I进行线性泛素化修饰并导致其降解; 同时，LUBAC可以与TRIM25竞争性结合RIG-I，进而抑制RLRs所介导的信号通路[34-35]。

当机体感染脑心肌炎病毒(encephalomyocarditis virus, EMCV)时，识别ssRNA的MDA5被TRIM65催化发生K63泛素化，TRIM65缺失会减弱由EMCV诱导的INF-I表达[36]。同样，为防止过度免疫，泛素

连接酶可催化底物发生K48泛素链修饰使其进入蛋白酶体途径被降解, 如RNF125、Parkin、PSMA7、TRIM44 L、TRIM13和TRIM40可通过泛素化修饰MDA5负调控RLRs通路, 抑制病毒介导的天然免疫反应[37-42]。

另外, MAVS复合物的泛素化调控也很有趣, 一方面, TRIM31可以对MAVS多位点进行K63泛素化修饰, 促进MAVS朊蛋白样多聚体的形成, 激活I型干扰素的分泌, 抑制病毒的复制[43]。另一方面, YOD1可通过催化MAVS的K63链去泛素化进而抑制其聚集和激活, 反向调控RLRs通路[44]。也有文章报道支架蛋白FAF1与TRIM31竞争MAVS来拮抗MAVS的多泛素化和聚集。病毒感染后, FAF1的Ser556位点发生磷酸化促进其被溶酶体降解, 从而缓解FAF1对MAVS的抑制[45]。此外, RNF5可通过催化激活的IRF3发生K48泛素化, 减少I型干扰素的产生, 抑制天然免疫反应[46]。

2.1.3 *泛素化修饰调控NLRs信号通路* NLRs具有一个N-端效应结构域、一个中心核苷酸结合和寡聚化结构域(oligomerization domain, NOD)、一个C-端富亮氨酸重复序列(leucine-rich repeat, LRR)。根据N-端效应结构域不同, 动物NLRs可以分为NLRA、NLRB/NAIP、NLRC和NLRP等亚科, 四者分别具有一个酸性反转录激活结构域(acidic transactivation, AD)、三个串联杆状病毒凋亡抑制剂(inhibitor of apoptosis, IAP)重复序列(baculovirus inhibitor of apoptosis repeats, BIRs)、一个半胱天冬酶激活和招募结构域(caspase activation and recruitment domain, CARD)和一个PYRIN结构域(PYD)[47]。NLRs参与炎症小体多蛋白复合物的形成, 该复合物由含有CARD的适配器凋亡相关斑点样蛋白(adaptor apoptosis-associated speck-like protein, ASC)和含有CARD结构域的pro-caspase-1组成, 激活caspase-1, 催化亲白介素(IL)-1β和亲IL-18的蛋白水解裂解, 然后释放IL-1β和IL-18, 导致促炎反应[48]。

目前, 对于NLRs通路的泛素化调控报道较少。NLRs炎症小体包括NLRP1、NLRP3、NLRP6和NAIP/NLRC4, 其中, 对NLRP3研究相对最多。目前仅知ALNEMRI等[49]证明NLRP3的去泛素化是NLRs形成炎症小体的关键步骤, 而去泛素酶BRCC3介导的NLRP3去泛素化对其激活至关重要[50]。此外, NLRs也可协同参与到TLRs通路中, NLRP3可被TLR4识别信号诱导线粒体活性氧的产生而去泛素化激活以介导炎性小体的组装和激活, 去泛素酶USP50可以通过去除ASC的K63泛素化, 介导ASC寡聚和NLRP3炎性小体激活[49,51]。

2.1.4 *泛素化修饰调控cGAS-STING信号通路* 环状鸟苷单磷酸(cyclic guanosine monophosphate-adenosine monophosphate, cGAMP)合酶(cyclic GMP-AMP synthase, cGAS)是一种可以识别多类dsDNA的胞质DNA受体, 可催化合成内源性cGAMP, 后者可被其下游接头蛋白STING识别, 进而使TBK1、IRF3发生磷酸化, 最终促进I型干扰素的产生[52]。也有文献报道, 在SARS-CoV-2感染时, STING与cGAMP结合后会回到高尔基体, 通过招募TBK1和IRF3激活NF-κB通路[53]。

STING通路受多种泛素化修饰调控。STING的多个位点可被TRIM32、TRIM56、TRIM29、DAPK3等催化发生泛素化修饰, 促进其与下游信号分子TBK1结合, 诱导I型干扰素的产生[24,54-56]。MUL1催化STING的Lys224位点泛素化, 阻断Lys224泛素化可以特异性地阻止IRF3表达减少I型干扰素产生[57]。另外, 去泛素酶OTUD5与STING相互作用, 去除其K48泛素链并增强其稳定性, 敲除*OTUD5*后, 小鼠更容易感染I型单纯疱疹病毒(HSV-1)[58]。cGAS上的泛素化修饰也可由TRIM56催化[59]。

此外, cGAS-STING通路也参与抗RNA病毒的天然免疫反应, 麻疹病毒(measles virus, MeV)和尼帕病毒(nipah virus, NiV)感染细胞后, STING发生K63泛素化以调控cGAS-STING信号通路, 最终产生抗病毒效应[52]。而TRIM13则通过催化STING发生K6连接的泛素化导致STING降解, 负向调控cGAS-STING信号通路[60]。另外, cGAS被泛素连接酶MARCH8修饰后无法与DNA结合, 在小鼠DNA病毒感染模型中, *MARCH8*敲除的小鼠对HSV-1敏感性更低[61]。

2.2 病毒利用泛素化进行免疫逃逸

泛素化修饰作为促进蛋白质相互作用的关键一环, 可以促进和协调宿主的抗病毒天然免疫反应。同样, 病毒也会利用宿主泛素化系统负向调控先天免疫途径并促进其增殖(表1)。

一些病毒可以通过自身合成的蛋白对宿主先天免疫反应通路中的重要蛋白进行泛素化修饰来实施免疫逃逸, 目前研究较多的是针对RIG-I通路的泛素

表1 蛋白质泛素化修饰对病毒的影响

Table 1 The effects of protein ubiquitination on virus

病毒 Viruses	病毒蛋白 Virus protein	底物 Substrates	影响 Effects
Arterivirus	Arterivirus OTU	RIG-I[75]	Reduce the production of IFN-I
DENV	sfRNA	USP15[71]	Reduce the production of IFN-I
EBOV	VP35	TRIM6[89]	Reduce the production of IFN-I
FMDV	L	RIG-I[87]	Reduce the production of IFN-I
EBV	BPLF1	P62[92]	Promote viral infection
HBV	HBx	RIG-I, TRAF3[77]	Reduce the production of IFN-I
HIV-1	RNF39	DDX3X[80]	Decrease the signal of RLRs
HCV	/	Riplet[29,62]	Reduce the production of IFN-I
HEV	PCP	RIG-I, TBK1[76]	Reduce the production of IFN-I
HSV	VP1-2	STING[83]	Reduce the production of IFN-I
HSV	UL36USP	IkBa[84]	Decrease the signal of NF-kB
IAV	NS1	Riplet, TRIM25[30,65]	Reduce the production of IFN-I
KSHV	ORF64	RIG-I[93-94]	Reduce the production of IFN-I
Nairo	Nairovirus OTU	RIG-I[75]	Decrease the signal of RLRs
NiV	NiV M	TRIM6[88]	Decrease the phosphorylation of IKKε
PDCoV	PDCoV N	pRiple[63]	Decrease the signal of RLRs
		IRF7[64]	Reduce the production of IFN-I
PEDV	PLP2	RIG-I[74]	Reduce the production of IFN-I
RGNNV	/	LjRNF114[95]	Decrease the signal of RLRs
SARS-CoV	N	TRIM25[69]	Reduce the production of IFN-I
	PLP	TBK1, TRAF3, TRAF6[86]	Reduce the production of IFN-I
SVCV	SVCV N	p53[90]	Decrease p53-mediated innate immune response
	SVCV P	p53[90]	Decrease p53-mediated innate immune response
SVV	3Cpro	RIG-I, TBK1, TRAF3[78]	Decrease the expression of IFN-β and ISG56
TOSV	NSs	RNF5[72-73]	Reduce the production of IFN-I
EV71	3Cpro	miR-526[81-82]	Reduce the production of IFN-I
HRSV	NS1	TRIM25[66]	Decrease the signal of RLRs
HPV	HPV E6	USP15[70]	Decrease the signal of RLRs
WNV	NS1	RIG-I[79]	Reduce the production of IFN-I
SFTSV	NSs	TRIM25[68]	Promote viral infection

/: 未确定。

/: not determined.

化调控。本文将病毒针对RIG-I通路的泛素化调控免疫逃逸分为以下两种机制。一种是病毒蛋白通过宿主的E3泛素连接酶TRIM25或Riplet发挥作用: RIG-I在病毒感染细胞中的激活依赖于TRIM25或Riplet, TRIM25的SPRY结构域可与RIG-IN末端的第一个CARD结合, 催化第二个CARD的Lys172发生K63多聚泛素化, 随后RIG-I与MAVS结合激活RLRs信号通路。而Riplet则通过促进RIG-I的CARD结构域和CTD结构域发生K63多聚泛素化激活RIG-I, 且Riplet诱导RIG-I的Lys788泛素化可能是TRIM25发挥修饰功能的前提。因此, TRIM25和Riplet自然而然地成为了病毒攻击的靶点蛋白。丙型肝炎病毒(hepatitis C virus, HCV)感染肝脏细胞后会下调Riplet的表达水平, 影响其所介导的RIG-I的泛素化[29,62]。这种情况也同样发生在猪三角洲冠状病毒(porcine delta coronavirus, PDCoV)感染中, 不仅如此, PDCoV N还与IRF7相互作用, 促进后者通过蛋白酶体被降解, 最终实现免疫逃逸[63-64]。而甲型流感病毒(influenza A virus, IAV)菌株除与Riplet互作外, 还能够利用TRIM25发生免疫逃逸。其机制类似于人呼吸道合胞体病毒(human respiratory syncytial virus, HRSV), IAV的NS1可以通过与TRIM25结合从而抑制RIG-I泛素化[30,65-66]。缺

失NS1效应区的EALQR基序(AA 191~195)会减弱其对宿主IFN相关细胞因子表达的抑制作用, 从而表现出更低的病毒毒性, 因而EALQR基序或成为未来小分子药物和疫苗的潜在靶点。严重急性呼吸综合征冠状病毒(severe acute respiratory syndrome coronavirus, SARS-CoV)的核衣壳蛋白可以与TRIM25的SPRY结构域结合而破坏TRIM25介导的泛素化, 而重度发热伴血小板减少综合征病毒(severe fever with thrombocytopenia syndrome virus, SFTSV)则可利用自编码的NSs蛋白将TRIM25劫持到病毒包涵体中[67-69]。病毒免疫逃逸的智慧之处不仅如此, 利用TRIM25需要通过USP15去泛素化激活的特性, 某些病毒, 如人乳头瘤病毒(human papilloma virus, HPV)编码的癌蛋白HPV E6、登革病毒(DENV)血清型二株(PR-2B)的黄病毒亚基因组RNA(sfRNA)可通过自身编码的蛋白抑制TRIM25去泛素进而抑制RIG-I的激活[70-71]。

另一种机制是病毒蛋白直接阻碍或去除RIG-I的泛素化修饰。如托斯卡纳病毒(toscana virus, TOSV)、猪流行性腹泻病毒(porcine epidemic diarrhea virus, PEDV)、卡波西肉瘤相关疱疹病毒(Kaposi's sarcoma-associated herpes virus, KSHV), 以及动脉炎病毒(arterivirus)和Nairo等病毒编码的蛋白可直接去除RIG-I的泛素链[72-75]。有些病毒编码的去泛素化蛋白还可以作用于多个受体, 如戊型肝炎病毒(hepatitis E virus, HEV)、乙型肝炎病毒(hepatitis B virus, HBV)、塞内卡谷病毒(seneca valley virus, SVV)及西尼罗河病毒(west nile virus, WNV)等[76-79]。

此外, RLRs信号通路也有一些特殊的免疫逃逸机制, 如RNA解旋酶家族成员DDX3X可识别1型人类免疫缺陷病毒(human immunodeficiency virus 1, HIV-1)的ssRNA, 通过促进MAVS-DDX3X-TRAF3复合体的形成, 增强抗RNA病毒免疫。而HIV-1感染诱导表达的RNF39可以促进DDX3X的55、138和162位点的赖氨酸发生K48偶联的泛素化修饰, 抑制DDX3X表达, 阻断MAVS-DDX3-TRAF3复合体的形成, 从而抑制抗病毒天然免疫反应, 实现病毒的免疫逃逸[80]。肠道病毒71(enterovirus type 71, EV71)编码的3Cpro抑制宿主miR-526的表达, 后者过表达导致CYLD的上调, 由此去除RIG-I的K63泛素链, 阻断RIG-I介导的免疫信号, 促进病毒复制[81-82]。这不难看出, 病毒通过编码蛋白将RLRs通路信号因子去泛素化, 是病毒进行免疫逃逸的重要内容之一。

在长期与宿主免疫系统博弈的过程中, 病毒也进化出针对其他通路信号因子的免疫逃逸机制, 如单纯疱疹病毒(herpes simplex virus, HSV)可调控cGAS-STING和NF-κB信号通路的泛素化以促进其在大脑中的免疫逃逸[83-84]; 新城疫病毒(newcastle disease virus, NDV)、SARS-CoV、FMDV、NiV及埃博拉病毒(Ebola virus, EBOV)等病毒可通过自身编码的蛋白对TLRs信号通路的多种蛋白进行泛素化调控[85-89]。有的病毒如鲤春病毒血症病毒(spring virernia of carp virus, SVCV)可通过p53介导的先天免疫进行逃逸[90-91]; 有的病毒如爱泼斯坦巴尔病毒(epstein barr, EBV)可以编码去泛素化酶BPLF1作用于p62进行免疫逃逸[92]。总体来看, 目前研究中, 针对哺乳动物病毒的免疫逃逸机制研究较为透彻, 但对于昆虫病毒尤其是杆状病毒逃逸机制知之甚少。

病毒已进化出针对天然免疫反应通路的多种受体蛋白的免疫逃逸能力, 因此研究其蛋白质网络的复杂变化, 进而开发相应的去泛素化酶小分子抑制剂药品则成为重中之重。

3 DUBs抑制剂在抗病毒治疗中的应用

病毒自编码蛋白可以去除TLRs、RLRs和STING通路重要分子的泛素链, 以逃避宿主的抗病毒天然免疫反应, 因此, 针对病毒免疫逃逸开发特定去泛素化酶抑制剂十分重要。而目前对于DUBs抑制剂的开发主要应用于恶性肿瘤、神经退行性疾病的治疗, 如针对USP7的小分子抑制剂P5091、GW7647等都已进入临床应用阶段。

在病毒感染性疾病的治疗中, 研究较多的是针对USP14抑制剂的开发, 本文主要介绍两种USP14小分子抑制剂。第一种USP14的特异性抑制剂IU1, 对于黄病毒尤其是DENV具有良好的抗病毒活性[96]。DENV感染尚无特异治疗方法, 而疫苗接种仅针对具有DENV感染史的人群有效。作为一个强活性的、特异的巯基蛋白酶抑制剂, IU1可以快速并且可逆地结合激活的USP14, 改变USP14的空间结构, 从而降低USP14的活性, 防止其结合蛋白酶体, 感染DENV的宿主细胞内IU1浓度达到100 μmol/L时可抑制病毒的复制, 并且IU1对西尼罗河病毒也具有抗病毒活性[97]。这表明IU1是黄病毒感染患者治疗的一种潜在药物。

另一种USP14抑制剂WP1130是最初被认为是JAK-STAT信号通路的抑制剂, 随后发现其可直接抑制USP9x、USP5、USP14和UCH37的去泛素化活性, 在治疗慢性粒细胞白血病和黑色素瘤中应用较多。WP1130可以显著抑制小鼠巨噬细胞中的诺如病毒(murine norovirus 1, MNV-1)的感染, 进一步的研究表明, WP1130可以通过显著抑制USP14介导的肌醇酶1(inositol-requiring enzyme 1)的失活, 激活未折叠的蛋白反应, 抑制病毒感染, 并且在其他RNA病毒如EMCV、Sindbis病毒和拉克罗斯病毒(La Crosse virus)中也表现出类似的抑制作用[98]。

这些证据表明, DUBs是治疗病毒性传染病的有希望的药物靶点, 针对特定DUBs的抑制剂的开发是一种有效的抗病毒药物筛选策略, 具有良好的前景。

4 总结与展望

天然免疫反应受泛素化调控的机理及病毒的免疫逃逸机制还有很多未被阐明的地方, 如泛素化介导的病毒免疫逃逸受哪些E3泛素连接酶和相应去泛素化酶调控, 除RIG-I外, 还有哪些天然免疫信号通路因子可被病毒去泛素化, 病毒是否会使泛素偶联酶E2丧失活性, 以及面对病毒的逃逸, 宿主可以采取何种方式对抗, 诸如此类问题还需要进一步探索。

本文主要从宿主和病毒方面, 总结了近年来泛素化和去泛素化参与调控宿主的抗病毒天然免疫反应的新发现以及其对病毒免疫逃逸的影响, 为后续研究提供了理论基础。同时, 揭示泛素化和去泛素化在宿主与病毒博弈过程中的作用及其分子调控机制, 有助于寻找病毒性疾病的药物靶点, 发现抗病毒治疗新靶标, 为抗病毒药物和疫苗的研发提供新的思路。

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