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泛素化修饰在 RLR 信号通路中的研究进展

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摘 要：病毒入侵后被细胞的模式识别受体 RIG-I 样受体(RIG-I-like receptor, RLR)识别从而启动抗病毒 RLR 信号通路的激活,先天免疫反应的异常激活将导致慢性炎症和免疫器官损伤,甚至引起自身免疫性疾病。为了防止抗病毒信号过早激活或过度激活,机体建立了完善的调节系统防止信号传导过程发生紊乱。蛋白的翻译后修饰(Post-translational modification, PTM)是调节模式识别受体及其下游信号蛋白稳定性和活性的关键机制,而泛素化(Ubiquitination, UB)作为蛋白质翻译后修饰的重要部分在抗病毒信号通路中被广泛研究。其中 K48 和 K63 连接的泛素化最为常见,通过 K48 连接的泛素链能够引起靶蛋白通过蛋白酶体途径降解,而 K63 连接的泛素链能够促进蛋白激活和细胞信号转导。RIG-I、MAVS、TBK1 以及 TRAF 家族相关蛋白作为 RLR 通路的信号传递分子,其蛋白的泛素化修饰也成为研究的重点。本文讨论了 K48 和 K63 泛素化在抗病毒免疫信号通路中的研究进展,特别是 RIG-I 样受体引发的信号传导途径中蛋白的泛素化修饰。

关键词：先天免疫；抗病毒反应；RIG-I 样受体；泛素化；K48 泛素化；K63 泛素化

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先天免疫系统是宿主抵御病原入侵的第一道防线,病原入侵会触发宿主细胞的即时反应,也称为先天免疫反应。先天免疫系统包括多种信号级联反应,这些信号级联反应是由细胞内外的模式识别受体(Pattern recognition receptor, PRRs)检测识别病原相关分子模式(Pathogen associated molecular patterns, PAMP)引发的,最终诱导下游 I 型干扰素(Interferon-I, IFN-I)和促炎性细胞因子的产生。其中 Toll 样受体(Toll-like receptor, TLR)、核苷酸结合寡聚化结构域 NOD 样受体(NOD-like receptor, NLR)和 RIG-I 样受体(RIG-I-like receptor, RLR)[1]是被广泛研究的 3 种模式识别受体家族。Toll 样受体大多存在于细胞膜或细胞器膜上,是一类具有跨膜属性的模式识别受体,可识别多种细菌和病毒的入侵[2-3];RIG-I 样受体可以识别病毒感染时产生的核酸成分并对其做出反应[4];NOD 样受体作为调节 IFN-I 和 NF-κB(Nuclear factor kappa B)活化的抗病毒介质,同样能被 Toll 样受体激活并参与抗病毒免疫调节。模式识别受体识别入侵的病原后,关键的衔接蛋白通过级联反应将免疫信号层层传递,最终将信号转导到细胞核中,激活免疫基因的转录和翻译。过度的免疫反应会影响细胞稳定,随着机体对外来病原的清除,蛋白级联反应会巧妙的进行自我限制以减轻过度免疫反应对机体的损害[5]。

蛋白翻译后修饰(Post-translational modification, PTM)通过靶向细胞内蛋白,在先天免疫反应中的病原识别和免疫调节中起到重要作用[6]。PTM 主要包括泛素化修饰、磷酸化修饰以及乙酰化修饰等;泛素化作为蛋白翻译后修饰类型之一,在抗病毒信号通路中被广泛研究。泛素是一种由 76 个氨基酸组成的小蛋白,可以通过两种方式靶向目标蛋白,即共价键结合(锚定泛素)或非共价结合(非锚定泛素),被泛素靶向的蛋白由泛素蛋白自身的泛素化位点决定其在信号通路中的命运[6-7]。泛素化修饰通过 3 种泛素酶的协同作用来启动泛素化过程:第一阶段,

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E1 泛素激活酶在其活性位点半胱氨酸(Cys)与泛素蛋白 C 末端甘氨酸(Gly)之间形成硫酯键;第二阶段,泛素通过硫基化反应转移到 E2 泛素结合酶的 Cys 位点;最后阶段,泛素通过 E2 泛素结合酶与 E3 泛素连接酶的相互作用转移到靶向的蛋白上[8-10]。泛素可以通过在其自身的 7 个赖氨酸位点(K6 / K11 / K27 / K29 / K33 / K48 / K63)上进行泛素蛋白连接形成线性多聚泛素链[11]。在蛋白连接不同赖氨酸位点的泛素化中,K48 连接的多聚泛素链通常使靶蛋白通过蛋白酶体途径被降解。而 K63 连接的线性多聚泛素链参与控制蛋白激酶的激活以及众多细胞信号通路的有序转导[12]。本文重点关注 RLR 信号通路中 RIG-I、MAVS、TBK1、TRAF3 和 TRAF6 等重要分子的泛素修饰的相关研究进展(图 1)。

1　RLR 信号的识别及启动

模式识别受体下游信号转导的调节对抗病毒免疫反应至关重要。作为 RLR 信号级联反应中的 3 个蛋白受体,RIG-I(Retinoic Acid-inducible Gene-I)、MDA5 (Melanoma differentiation-associated protein 5)和 LGP2 (Laboratory of genetics and physiology 2)都包含 1 个具有 ATP 水解和 RNA 结合活性的 DExD/H-box 解旋酶结构域[4,13],和一个能够识别 RNA 底物的 C 端结构域(C-terminal domain,CTD)[14-15]。然而,只有 RIG-I 和 MDA5 具有 N-末端 caspase 激活和募集结构域(Caspase activation and recruitment domain,CARD)来激活下游免疫信号转导[16]。RIG-I 和 MDA5 均可以识别双链 RNA(dsRNA),研究发现 dsRNA 的长短对于 RIG-I 样受体的识别十分重要。RIG-I 可以结合相对较短的 dsRNA(< 1 kb),MDA5 可以特异性结合长双链 dsRNA;将 dsRNA 的长度缩短后,由 MDA5 受体转变成 RIG-I受体来识别 dsRNA[17-19]。RIG-I 和 MDA5 在识别病毒 RNA 时构象会发生变化,SUMO E3 泛素连接酶 TRIM38 (Tripartite motif-containing protein 38)可以动态修饰 RIG-I 和 MDA5 的类泛素化修饰(Sumoylation),以确保其处于最佳激活状态[20]。磷酸酶 PP1(Protein phosphatase 1)的亚基 PP1α 和 PP1γ 将 RIG-I 和 MDA5 去磷酸化并使其活化[21],K63 连接的多聚泛素链被转移到 RIG-I 和 MDA5 上[22-24],RIG-I 和 MDA5 在线粒体内膜上招募并激活了线粒体抗病毒信号蛋白 MAVS(Mitochondrial antiviral-signaling)[25-26]。在 K63 多聚泛素链存在的情况下,线粒体上的 MAVS 将转化为功能性聚集体[27]。MAVS 聚集了 E3 泛素连接酶 TRAF(TNF receptor-associated factor)家族中的 TRAF2、TRAF3、TRAF6 等,这些 E3 连接酶参与 MAVS 复合体形成并且促进 MAVS 发生 K63 泛素化,进而促进 TBK1(TANK binding kinase 1)和 IKKα/β(Inhibitor kappa B kinase α/β)复合物的磷酸化[27-30]。磷酸化后的 TBK1 和 IKKα/β 分别激活 IRF(IFN regulatory factor)3/7 和 NF-κB,随后它们从线粒体释放并易位进入细胞核,诱导下游抗病毒基因 I 型干扰素(IFN-I)产生,进而促进干扰素激活基因(IFN-stimulated genes, ISGs)的转录,使免疫细胞和周围细胞处于抗病毒状态。

1.1　RIG-I 的泛素化修饰

TRIM25 (Tripartite motif-containing protein 25)是 RIG-I 先天免疫信号转导的关键分子[23, 31]。研究表明 TRIM25 参与了 RIG-I 的泛素化和激活[32-33]。RIG-I 激活依赖于 TRIM25 的调节,TRIM25 的 SPRY 结构域与 RIG-I 互作,促进了 RIG-I CARD 结构域中 Lys172 位点上 K63 连接的多聚泛素化[22]。在研究 TRIM25 的功能中发现了几种影响 TRIM25 的 E3 酶活性的调节剂。NDR2(Nuclear Dbf2-related kinase 2)作为 RIG-I 和 TRIM25 的衔接蛋白促进了 RIG-I/TRIM25 复合物的形成,增强了 TRIM25 介导 RIG-I 连接的 K63 多聚泛素化[34]。RNA pull-down 发现长链非编码 RNA Lnczc3h7a 与 TRIM25 结合,促进 RIG-I 连接 K63 的多聚泛素化[35]。NLRP12 (NLR family pyrin domain containing 12)与 TRIM25 相互作用,阻止 TRIM25 介导 RIG-I 连接的 K63 泛素化和激活[36]。LGP2 作为 3 个 RLR 模式识别受体之一,其作用机制尚未明确。研究发现 LGP2 与 E3 泛素连接酶 TRIM25 相互作用,抑制了 TRIM25 介导 RIG-I 的 K63 泛素化[37]。近来发现另一种名为 Riplet,也称 Ring finger protein 135 (RNF135)的 E3 泛素连接酶,该酶与 TRIM 家族具有高度同源性。Riplet 的 C 末端区域结合 RIG-I 并激活其 K63 连接的泛素化,促进 RIG-I 介导 IFN-β 启动子激活[38]。Riplet 基因敲除的小鼠对水疱性口炎病毒更加敏感,证实了 Riplet 在抗病

毒反应中的重要性[39]。RIG-I 的 Lys788 位点对 Riplet 介导的 K63 泛素化至关重要,研究并未否定 TRIM25 对于 RIG-I 的重要性并认为 Riplet 可能是 TRIM25 激活 RIG-I 信号的先决条件[40]。最新的研究发现敲除 TRIM25 后并未影响机体在甲型流感病毒、乙型流感病毒、仙台病毒等感染中的 IFN-I 信号激活,而敲除 Riplet 削弱了 RIG-I 激活的 IFN-I 信号[41]。E2 泛素结合酶 Ube2D3(Ubiquitin-conjugating enzyme E2D3)和 Ube2N 协同 E3 泛素连接酶 Riplet 激活 RIG-I,Ube2D3-Riplet 促进 RIG-I 连接的 K63 泛素化,而 Ube2N-Riplet 促进未锚定多泛素链的生成,激活 RIG-I 信号[42]。另外两种 E3 泛素连接酶 MEX3C(Mex-3 RNA-Binding Family Member C)和 TRIM4 被确定参与 RIG-I 连接 K63 多聚泛素链的形成,并促进下游信号传导[24, 43]。USP14(Ubiquitin-specific proteases 14)也被认为是抗病毒反应的负调节剂之一,它能与 RIG-I 互作并消除其 K63 连接的多聚泛素化[44]。

RIG-I 连接的 K48 泛素化减弱了 RLR 信号传导。RNF125 通过 K48 连接的多聚泛素链降解 RIG-I 和 MDA5 蛋白并抑制 IFN-I 激活[45]。非典型激酶 Riok3(RIO Kinase 3)招募 E3 泛素连接酶 TRIM40,促进 K27 和 K48 连接的多聚泛素化降解 RIG-I 和 MDA5[46]。病毒也能通过对靶蛋白的降解进行免疫逃避,如猪急性腹泻综合征冠状病毒的 N 蛋白与 RIG-I 相互作用并促进其 K48 连接的泛素化,诱导 RIG-I 的蛋白酶体途径降解[47]。USP4 的过表达显著增强了 RIG-I 触发的 IFN-β 信号传导,并通过去除 RIG-I 连接的 K48 泛素化稳定 RLR 信号转导,抑制了 VSV 病毒的复制[48]。蛋白激酶抑制剂 PRKRIR(Protein-kinase, IFN-inducible double-stranded RNA dependent inhibitor, and repressor of P58 repressor)通过阻断 RIG-I 连接的 K48 泛素化,阻止了 RIG-I 通过蛋白酶体途径降解,增强了 RIG-I 的稳定性[49]。研究发现,未锚定泛素链也积极参与 IFN-I 信号传导。锚定的 K48 多聚泛素链被认为参与蛋白酶体途径降解,与此不同的是,未锚定的 K48 泛素化修饰可能具有正向调节作用。TRIM6 合成未锚定的 K48 连接的多聚泛素链激活 IKKε 后,促进 STAT1(Signal transducer and activator of transcription 1)磷酸化[50]。TRIM6 与 DHX16(DEAH box polypeptide 16)和 RIG-I 内源性互作,其合成的未锚定 K48 连接的泛素链能促进 DHX16 与 RIG-I 的结合并介导 IFN-I 的产生和 ISGs 高表达[51]。

1.2 MAVS 的泛素化修饰

目前研究显示,MAVS 的泛素化修饰多发生在病毒感染期间,在静息状态时一般很少受到泛素化修饰。线粒体上的 MAVS 作为 RLR 信号通路中的一个关键衔接蛋白,被多种病毒作为目标以各种方式进行攻击[52]。MAVS 蛋白连接的 K63 泛素化对于抗病毒信号传导十分关键。例如,TRIM31 通过促进 MAVS 连接的 K63 泛素化增强了 MAVS 多聚体的形成[53]。病毒感染后增强了 USP18 与 MAVS 的互作,并促进了 MAVS 连接的 K63 泛素化,而敲除 USP18 的小鼠更容易受到病毒感染[54]。仙台病毒感染多种免疫细胞后促进去泛素化酶 YOD1(Ubiquitin thioesterase OTU1)mRNA 高表达,YOD1 仅在病毒感染后与内源 MAVS 互作,以消除 MAVS 连接的 K63 泛素化并影响多聚体形成,这是为数不多的有关去泛素化酶靶向 MAVS 负调控 IFN 信号的研究[55]。SARS-CoV 病毒基因组编码的辅助蛋白 ORF-9b 可以通过泛素化修饰调节机制降解 MAVS,从而抵抗抗病毒免疫反应[56]。TRIM25 除了参与激活 RIG-I 并增强其与 MAVS 的结合外,还促进 MAVS 的 Lys7 和 Lys10 位点上的泛素化并诱导其降解。该研究证明 MAVS 多聚体的消失并不代表抑制信号传导,反而能够快速释放 MAVS 聚合体并激发了下游 IRF3 的磷酸化[57]。多个 E3 泛素连接酶参与 MAVS 的蛋白酶体降解,例如,RNF5 促进 MAVS 的 Lys362 和 Lys461 位点发生 K48 泛素化[58];而在 MAVS 的 Lys371 和 Lys420 位点,PCBP2(PolyIC binding protein 2)招募包含 HECT 域的 E3 泛素连接酶 AIP4(Atrophin-1-interacting protein 4)促进 MAVS 连接的 K48 泛素化并使其降解[59];RACK1(Receptor for activated C kinase 1)促进了 MAVS 连接的 K48 泛素化,进而降低了 MAVS 介导的抗病毒信号转导,并且减弱了 MAVS 连接的 K63 泛素化从而降低其活性[60];Ndfip1(Nedd4 family interacting protein 1)与 MAVS 结合,并募集 E3 泛素连接酶 Smurf1(SMAD specific E3 ubiquitin protein ligase 1)和 Smurf2 从而促进 MAVS 发生泛素化降解[61-62]。

病毒诱导 OTUD1(OTU deubiquitinase 1)高表达,OTUD1 通过增强 Smurf1 对 MAVS 的 K48 泛素化,促进 MAVS 的蛋白酶体降解[63];RNF115 能够与 MAVS 互作,并且调节稳态中 MAVS 的 K48 泛素化,RNF115 的缺失增强了 RNA 病毒触发的抗病毒信号传导[64]。SeV 和 VSV 病毒感染免疫细胞 MEF 或 BMDCs 后,增强了 OTUD4 与 MAVS 的互作,消除 MAVS 连接的 K48 泛素化并抑制 MAVS 蛋白降解;在 OTUD4 失活后,这种能力被显著减弱,这也是少数有关去泛素化酶靶向 MAVS 正向调节 IFN 信号的报道[65]。

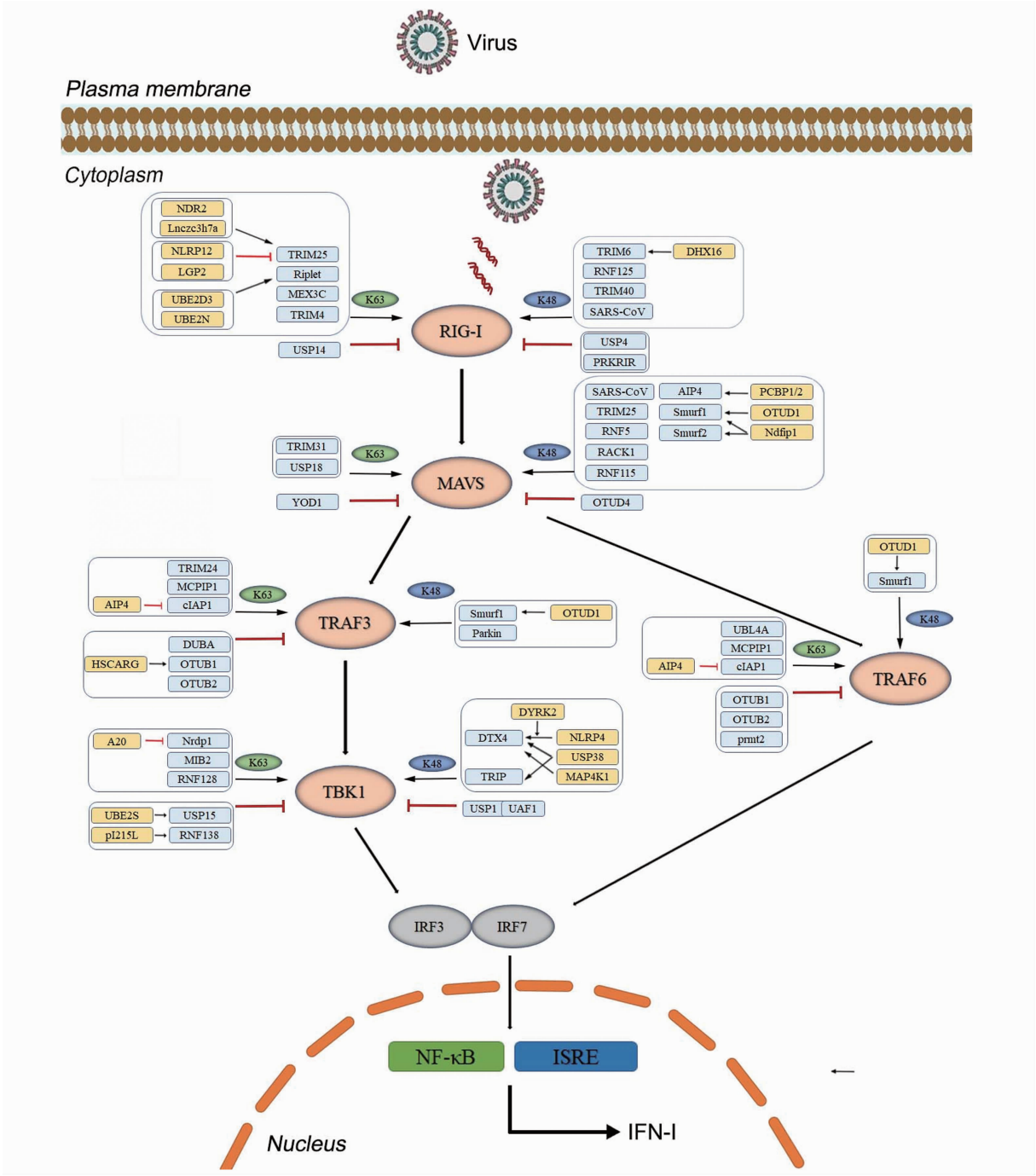
1.3　TBK1 的泛素化修饰

TBK1 是参与先天免疫反应的重要蛋白,包含 1 个 N 末端激酶结构域,1 个泛素样结构域(Ubiquitin-like domain,ULD)和 2 个 C 末端卷曲螺旋结构域(CCD1 和 CCD2)。A20 和 TAX1BP1(Tax1-binding protein 1)通过破坏 TBK1-IKKi 复合体的形成并且抑制 K63 泛素化,抑制病毒感染触发的 IRF3 激活,从而阻断抗病毒信号传导,但并未发现 A20 具体调控 TBK1 泛素化的机制[66]。E3 泛素连接酶 Nrdp1(Neuregulin receptor degradation protein-1)促进 TBK1 的 K63 泛素化,对 IFN 信号传递起到正向作用;A20 通过抑制 Nrdp1 介导的 TBK1 激活,减少了 IFN-β 的产生[67-68]。MIB2(Mindbomb E3 ubiquitin protein ligase 2)被认为可能是参与 MAVS 介导的 TBK1 激活的另一种 E3 泛素连接酶,它与 MAVS 结合后促进了 TBK1 连接的 K63 泛素化,从而激活下游 IRF3/7[69]。E3 泛素连接酶 RNF128 是 TBK1 激活的正调节因子,RNF128 的敲降或缺失会减弱 IRF3 激活和 IFN-β 的产生,RNF128 与 TBK1 结合并通过增强 TBK1 连接的 K63 泛素化促进 IFN-I 信号传导[70]。UBE2S 作为 E2 泛素结合酶招募去泛素化酶 USP15 去除 TBK1 连接的 K63 泛素化,抑制 IFN-I 信号[71]。非洲猪瘟病毒 pI215L 蛋白招募 E3 泛素连接酶 RNF138 抑制 TBK1 连接的 K63 泛素化,抑制 TBK1 的活性并进行免疫逃避[72]。

NLRP4(NLR family pyrin domain containing 4)通过靶向 TBK1 作为 I 型干扰素信号的负调节剂,NLRP4 招募 E3 泛素连接酶 DTX4(Deltex E3 ubiquitin ligase 4),促进 TBK1 连接的 K48 泛素化和蛋白降解,防止抗病毒免疫反应的过度激活[73]。DYRK2(Dual-specificity tyrosine-Y-phosphorylation-regulated kinase 2)磷酸化 TBK1 的 Ser527 位点对于招募 NLRP4 和 DTX4 降解 TBK1 至关重要,并以激酶活性依赖性方式促进 TBK1 连接的 K48 泛素化[74]。此外 TRIP(Tumor necrosis factor interacting protein)作为被病毒诱导的 E3 泛素连接酶,通过促进 TBK1 连接的 K48 泛素化和蛋白酶体降解负调控抗病毒免疫反应[75]。USP38 在 TBK1 的 Lys670 位点上特异性地切割了 K33 连接的多泛素链,并促进 DTX4 和 TRIP 介导的 TBK1 连接的 K48 泛素化[76]。蛋白激酶 MAP4K1(Mitogen-activated protein kinase kinase kinase kinase 1)参与先天抗病毒免疫反应调控,MAP4K1 与 TBK1 互作并在 E3 泛素连接酶 DTX4 的帮助下促进 TBK1 连接的 K48 泛素化降解[77]。USP1 与 UAF1(USP1-associated factor 1)形成去泛素化酶蛋白复合体,与 TBK1 结合并去除了 TBK1 连接的 K48 泛素化,稳定了 TBK1 的蛋白表达[78]。

1.4　TRAF 的泛素化修饰

肿瘤坏死因子受体相关因子家族共有 6 个已知蛋白(TRAF1-6),参与 RLR,NLR 和 TLR 3 种模式识别受体下游蛋白信号级联反应,调节 NF-κB 激活和 IFN-I 生成。TRAF 蛋白家族具有 RING 指结构域和多个锌指结构位点,这是 E3 泛素连接酶的典型特征之一。TRAF2、TRAF4、TRAF5 和 TRAF6 在自身赖氨酸位点上进行 K63 泛素化连接,激活自身传递信号的功能[79-82]。TRAF3 和 TRAF6 是 RLR 途径中参与 MAVS 激活的蛋白,TRAF3 通过激活 TBK1/IRF3 来促进 IFN-I 表达,TRAF6 则通过激活 MEKK1(MAPK/ERK kinase kinase 1)进而激活 NF-κB,促进 IFN-I 的表达[66, 83]。



黑色箭头代表促进泛素化或激活其他蛋白;红色平头代表抑制泛素化或阻止蛋白发挥功能。
Black arrows represent promotion of ubiquitination or activation of other proteins; red flat heads represent inhibition of ubiquitination or preventing protein function.

图 1 RLR 介导抗病毒免疫反应的泛素化机制示意图

Fig. 1 Schematic diagram of ubiquitination mechanism of RLR-mediated antiviral immune response

病毒感染后增强了内源 UBL4A(Ubiquitin-like protein 4a)与 TRAF6 互作,促进 TRAF6 连接的 K63 泛素化,从而正向调节抗病毒信号中 TRAF6 的活性[84]。TRIM24 直接靶向介导 TRAF3 在 K429/K436 位点上连接的 K63 泛素化,并且促进 MAVS 与 TBK1 的结合以激活下游抗病毒信号[85]。DUBA(Deubiquitinating enzyme A)作为调节 IFN-I 产生的去泛素酶,能特异性将 TRAF3 连接的 K63 泛素化进行切割,抑制 IFN-I 信号激活[86]。病毒入侵后 OTUB1(Otubain-1)和

OTUB2 靶向 TRAF3 和 TRAF6,并同时对 TRAF3 和 TRAF6 进行去泛素化,抑制 IFN-I 信号激活[87]。HSCARG (NmrA-like family domain-containing protein 1,NMRAL1)靶向 TRAF3 并招募 OTUB1 并对其进行去泛素化,从而避免过度的抗病毒先天免疫反应[88]。MCPIP1(MCP-induced protein 1)以 DUB 的方式抑制 RLR 信号通路中 TRAF 家族蛋白的 K63 泛素化,进而抑制了 IFN-β 的产生[89]。AIP4 广泛且多重地抑制 NLR,RLR 和 TLR 介导的免疫信号传导。E3 泛素连接酶 cIAP1(cellular inhibitor of apoptosis proteins 1)在病毒感染期间促进 TRAF3/6 的激活,而 AIP4 促进 cIAP1 发生溶酶体降解,作为 cIAP1 抑制剂来减弱 IFN-I 和 NF-κB 的活化[29,90]。在斑马鱼中,精氨酸甲基转移酶 prmt2(protein arginine methyltransferase 2)通过与 TRAF6 的 C 末端结合,阻止其自身的 K63 泛素化,进而影响抗病毒信号转导[91]。

TRAF 连接的 K48 泛素化同样是调控抗病毒信号的重要因素,例如,OTUD1 通过去泛素化上调细胞内 Smurf1 的蛋白水平,增强了 Smurf1 与 MAVS、TRAF3 和 TRAF6 的结合,从而促进 MAVS/TRAF3/TRAF6 复合体中蛋白的 K48 泛素化并引发泛素-蛋白酶体降解[63];泛素连接酶 Parkin 通过促进 TRAF3 发生 K48 泛素化,降低蛋白的稳定性来调节 RLR 信号转导[92]。

2　展望

在众多的蛋白翻译后修饰中,泛素化修饰在调节抗病毒先天免疫反应中起到关键性作用,大多数参与信号级联反应的蛋白能够被泛素化修饰,它们的激活过程也受到严格控制,并通过严谨的负反馈调节机制来防止过度免疫,这种动态调整为保护机体起到了积极作用。RIG-I、MAVS、TBK1 和 TRAF3/6 连接的 K63 泛素化积极参与信号传导过程,一些 E3 泛素连接酶和去泛素化酶家族蛋白可以促进 K63 的泛素化从而正向调节抗病毒信号通路。同时也发现病毒能直接通过操控宿主泛素修饰系统抑制先天免疫,或间接利用宿主机制干扰细胞的抗病毒信号传导逃避先天免疫。如部分被病毒诱导后的蛋白促进靶蛋白的 K48 泛素化和泛素-蛋白酶体途径降解。这要求更加精确判断靶点蛋白,确定 E3s 和 DUBs 的作用靶点。此外,未锚定泛素链的研究目前很少,但是其机制更加值得深入研究,如未锚定 K48 泛素链与蛋白酶体降解途径无关,而且具有正向的调控作用,这也将是泛素化的研究重点之一。越来越多的研究正在关注蛋白的泛素修饰机制,更加全面深入的发现具有特异性的 E3 泛素连接酶和去泛素化家族蛋白并探究其生物学机制,将为疾病治疗和免疫防控提供更多的解决方案。在鱼类先天免疫领域,泛素化修饰研究尚处于起步阶段,鱼类的 E3 泛素连接酶家族以及去泛素化蛋白家族相关研究也相对较少。本文通过对哺乳动物先天免疫泛素化修饰机制的深入了解及探讨,以期有助于推动泛素化修饰在鱼类先天免疫反应中的作用及机制研究。

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Research progress of ubiquitination mechanism in RLR signaling pathway

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Abstract: Invading virus is recognized by one of pattern recognition receptors, RIG-I-like receptor (RLR), to activate antiviral RLR signaling pathway. Abnormal activation of PRRs will lead to chronic inflammation, immune organ damage, and even autoimmune diseases. In order to prevent the premature or excessive activation of antiviral signals, the body has established a perfect regulatory system to prevent the disorder of signal transduction process. Post-translational modification (PTM) of proteins is a key mechanism for regulating the stability and activity of pattern recognition receptors and their downstream signaling proteins, while ubiquitination (UB) is an important part of protein post-translational modification in antiviral signaling pathways and has extensively studied. Of these, K48- and K63-linked ubiquitination is the most common: K48-linked ubiquitin chains can cause degradation of target proteins via the proteasomal pathway, while K63-linked ubiquitin chains can promote protein activation and cell signaling. RIG-I, MAVS, TBK1 and TRAF family member proteins are the signaling molecules of RLR signaling, and the ubiquitination mechanism of these proteins has also been studied. This paper discusses the research progress of K48 and K63 ubiquitination in antiviral immune signaling pathways, especially the ubiquitination modification of proteins in signaling pathways triggered by RIG-I-like receptors.

Key words: innate immunity; antiviral response; RIG-I-like receptor; ubiquitination; K48 ubiquitination; K63 ubiquitination