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RLRs翻译后修饰在抗病毒先天免疫中的研究进展

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摘　要

维甲酸诱导基因I (Retinoic Acid-Inducible Gene I, RIG-I)样受体(Retinoic Acid Gene I-Like Receptors, RLRs)是病毒感染的关键感受器，能够识别病毒的RNA，激活线粒体抗病毒信号蛋白(Mitochondrial Antiviral Signaling Protein, MAVS)启动下游信号传导，诱导I型干扰素(Interferon, IFN)的产生，建立有效的抗病毒免疫响应。蛋白质翻译后修饰(Post-Translational Modifications, PTMs)作为调控模式识别受体及其下游信号分子稳定性和活性的关键机制，对干扰素介导的免疫反应至关重要。通过不同的PTMs，包括经典的磷酸化和泛素化，以及其他PTMs如甲基化、乙酰化、SUMO化以及ISG化等，不仅影响RLRs自身的功能状态，还影响着其下游信号分子的活性与定位。本文综述了近年来关于RLRs的PTMs在抗病毒免疫方面的研究进展，旨在为挖掘抗病毒治疗的新靶点提供创新思路。

关键词

RIG-I样受体，翻译后修饰，抗病毒免疫

Advance in Post-Translational Modification of RLRs in Antiviral Innate Immunity

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Abstract

Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are RNA sensor molecules, which mediated intracellular virus recognition. Activated RLRs induce downstream signaling via their interactions with mitochondrial antiviral signaling proteins (MAVS), thereby lead to the transcriptional induction of type I interferons (IFN-I) and establish an antiviral host response. Post-translational modification (PTM), as a key mechanism to regulate the activity and stability of pattern recognition receptors and their downstream signaling molecules, plays a critical role in regulating interferon-mediated immune responses. A variety of PTM modifications, including classical phosphorylation and ubiquitination, as well as methylation, acetylation, SUMOylation, and ISGylation, not only affect the functional status of RLRs, but also the activity and localization of their downstream signaling molecules. This paper reviews the PTM regulation of RLRs in antiviral immunity in recent years, aiming to provide new insights of innate immunity and antiviral therapy.

Keywords

RIG-I Like Receptor, Post-Translational Modification, Antiviral Immunity

1. 引言

先天免疫系统作为宿主抵御病原微生物的首道防线，识别病原体相关分子模式(Pathogen-Associated Molecular Patterns, PAMP)区分外源入侵体。感染病毒后，PAMP 被模式识别受体(Pattern Recognition Receptor, PRRs)识别，产生免疫应答。RNA 病毒的双链 RNA (Double-Stranded, dsRNA)是一种常见的 PAMP，RLRs 作为 PRR 主要负责在细胞质中识别病毒复制过程产生的 dsRNA，迅速释放级联信号，诱导分泌I型和III型 IFN 应对病毒侵袭[1]。

PTMs 指蛋白质翻译后经历的一系列共价修饰过程，在机体内广泛存在，几乎参与细胞所有的生命活动。PTMs 形式复杂多样，包括肽链骨架的剪接、在特定氨基酸侧链上添加新基团，以及对已有基团进行化学修饰等[2]。作为一类关键的调控方式，PTMs 对 RLRs 及其下游信号蛋白的活性、稳定性和功能起着至关重要的作用。深入研究 RLRs 翻译后修饰在抗病毒先天免疫中的作用机制，对于揭示病毒感染与宿主免疫之间的相互作用、开发新型抗病毒药物和免疫治疗策略具有重要意义。

2. RLRs 的结构与信号启动

2.1. 结构

细胞质病毒 RNA 传感器 RLRs 家族包括三个成员：维甲酸诱导的基因 I (RIG-I)、黑色素瘤分化相关蛋白 5 (Melanoma-Differentiation-Associated Gene, MDA5)和遗传与生理实验室 2 (Laboratory of Genetics and Physiology, LGP2)。三者都含有一个与病毒 RNA 结合的 C 末端调节结构域(C-Terminal Regulatory Domain, CTD)和负责识别 dsRNA 的 DExD/H 盒 RNA 解旋酶结构域，依赖 ATP 激活下游信号转导[3] [4]。中心的 DExD/H 盒 RNA 解旋酶由两个 RecA 样结构域组成，分别为 Hel-1 和 Hel-2，在 Hel-2 中包含一个 Hel-2i 插入，有助于识别 dsRNA [5]。RIG-I 和 MDA5 还包含一个 LGP2 不具备的 N 端串联的 caspase 招

募结构域(N-Terminal Tandem Caspase Recruitment Domains, CARDs)，负责与 MAVS 的 N 端 CARD 区域结合，传达下游信号指令[6]。LGP2 能正向和负向调控 RIG-I 和 MDA5，其角色的多样性表明对 LGP2 机制的深入研究十分必要[7] [8]。RIG-I 识别含有 5’ppp 的 dsRNA 或 5’pp 的部分特征，MDA5 主要识别长 dsRNA，一些高阶结构的 ssRNA 也对 MDA5 产生刺激活性[9] [10]。正常生理状态下，RIG-I 的第二个 CARD 活性区域被解旋酶插入域 2i (Helicase 2i)封闭，处于自抑制构象，干扰结合配体 RNA (图 1)。

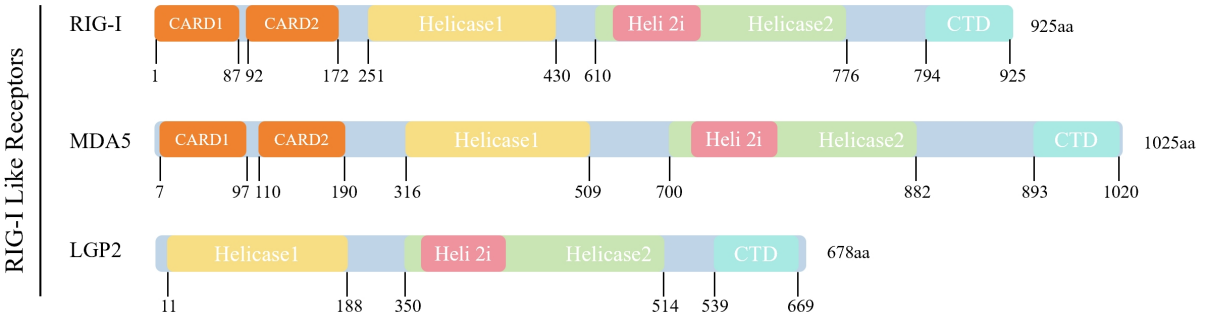

Figure1. The stuctures of RLRs
图 1. RLRs 的结构

2.2. RLRs 的信号激活

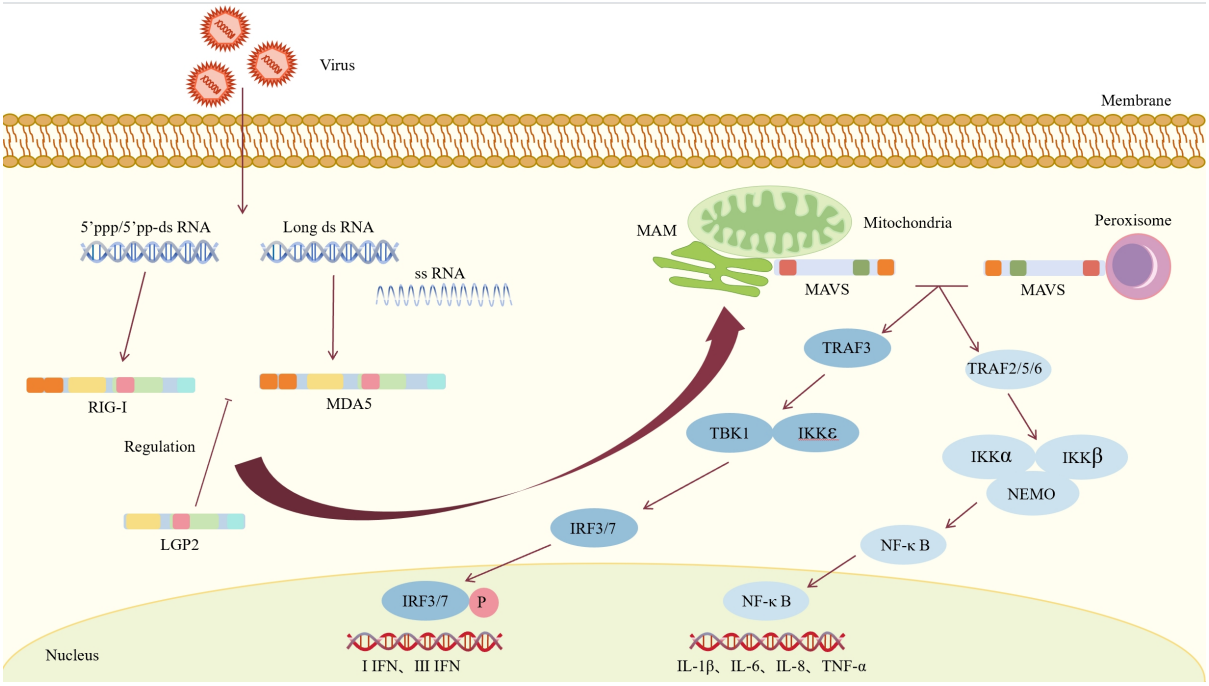

Figure 2. The signaling pathway of RLRs
图 2. RLRs 信号通路

病毒感染后，RIG-I 的 CTD 识别致病 RNA 钝端，发生依赖 ATP 的构象变化，解旋酶结构域包裹在 dsRNA 周围，释放 CARDs 区域，利用 K63 链型多泛素修饰或解旋酶和 CTD 结构域在 dsRNA 末端附近形成短丝状低聚物，形成螺旋对称的四聚体，诱导 MAVS 的细丝形成(MAVS 的活性状态)，触发级联反应[11] [12]。与 RIG-I 相比，MDA5 的 CTD 为相对开放的结构，不能独立识别 RNA，它仅在 dsRNA 识

别过程中形成细丝的情况下寡聚，激活 MAVS。活化的 MAVS 激活肿瘤坏死因子受体相关因子(TNF Receptor Associated Factor, TRAF) 2/3/5/6 [13]，进一步激活 TANK 结合激酶 1 (TANK-Binding Kinase 1, TBK1)和核因子 κB 抑制激酶 ε (Inhibitor Kappa B Kinase ε, IKKε)，然后磷酸化干扰素调节因子 3 (Interferon Regulatory Factor 3, IRF3)和干扰素调节因子 7 (Interferon Regulatory Factor 7, IRF7)，促使转录因子入核，启动I型和III型 IFN 表达，建立抗病毒状态。MAVS 还影响 IKKα/IKKβ/核因子(Nuclear Factor, NF)-κB 基本调节物(NEMO)复合体，激活 NF-κB 途径以诱导包括白介素 1β/6/8 (InterleukinIL-1β/6/8)和肿瘤坏死因子 α (Tumor Necrosis Factor, TNF-α)等促炎因子的分泌[14] (图 2)。

3. PTMs 对 RLRs 的重要性

翻译后修饰通过酶促反应或其他机制，在蛋白质的氨基酸残基上添加或去除特定的化学基团或蛋白质，扩展蛋白质的功能范围[15]。PTMs 修饰可改变蛋白的空间构象、稳定性、转运和定位及与其他分子的相互作用，调节机体多样化的生命活动[16]。PTMs 对 RLRs 的作用多面，可改变 RLRs 的活性状态、与配体的结合能力，或影响其与下游信号分子互作，从而调节 RLRs 介导的信号传导途径的强度和持续时间。PTMs 还可影响 RLRs 的稳定性、降解速率及亚细胞定位，这些作用共同调节 RLRs 介导的免疫通路。目前已鉴定出超过 400 种翻译后修饰类型，常见的有磷酸化、泛素化、乙酰化、糖基化和 SUMO 化等。磷酸化对 RLRs 的作用主要体现在调节其活性和信号传导上，未感染病毒时，RLRs 特定丝氨酸位点的磷酸化会使 RLRs 失活，利于维持细胞稳态，而去磷酸化促进病毒感染后的 RLRs 激活。泛素化修饰是 RLRs 信号通路分子调控的经典方式之一，泛素与目标蛋白上不同的氨基酸位点结合，控制蛋白命运，如启动蛋白酶体途径降解蛋白或激活转运。乙酰化修饰改变 RLRs 与核酸配体结合亲和力，增强其抗病毒活性。ISG 化则影响蛋白的稳定性，使抗病毒反应保持平衡状态。

多种翻译后修饰之间存在串扰，大多数 PTM 系统主要由两部分组成，即进行修饰的催化机制和被修饰的底物蛋白。不同 PTM 之间的串扰可以只改变催化机制或底物蛋白，也可以同时改变这两部分。通过催化机制发生的 PTM 串扰是指将催化某种 PTM 的酶变成与之串扰的另一种 PTM 的底物，改变酶活性。而通过底物蛋白发生的 PTM 串扰可以在不同时间点修饰底物蛋白质的同一氨基酸残基，也可以修饰同一底物蛋白质的不同氨基酸残基，起协同作用或拮抗作用，即 PTM 之间竞争相同或附近的修饰位点。此时，底物的生物学功能取决于特定时间内蛋白质上不同修饰的比例[17]。SUMO 化能够协同 RIG-I 的泛素化作用，增强抗病毒信号。某些去甲基化酶也能影响 RIG-I 的泛素化，却不依赖其甲基化活性。病毒则会利用 PTMs，如乙酰化或脱酰胺化进行免疫逃逸。

4. RLRs 翻译后修饰

4.1. 磷酸化修饰

磷酸化是蛋白质在磷酸化激酶的催化作用下把三磷酸腺苷(ATP)或三磷酸鸟苷(GTP)的 γ 位磷酸基转移到蛋白质的特定位点氨基酸残基上的过程。细胞静息状态下，PKCα 和 PKCβ 通过磷酸化 RIG-I 的 Thr 170 和 Ser 8 位点，保持 RIG-I 的封闭构象，并在细胞被 RNA 病毒感染时去磷酸化，严格调控 RIG-I 活性，与 TRIM25 介导的 RIG-I 的 Lys 172 泛素化功能上相互拮抗[18]-[20]。CK2 磷酸化 RIG-I 的 Thr 770 和 Ser 854-855，从而使 RIG-I 处于非活性状态，当病毒感染时，磷酸化位点则发生突变使其重新具有活性[21]。一项在人肝癌细胞中进行的全基因组 RNAi 筛选验证研究发现 DAPK1 由 RIG-I 信号激活后，通过抑制 RIG-I 解旋酶区域 Thr 667 和 CARD 区域 Ser 8 处的磷酸化阻碍其识别 5’ppp dsRNA，抑制抗病毒通路[22]。但 293 细胞中的 DAPK1 也能促进 IRF3/7 激活，作为正调控因子上调 IFN-β 的表达，这种矛盾可能是由于细胞类型差异[23]。IKKε 除了与 TBK1 功能相关外，还能在 Ser855 处直接磷酸化 RIG-I，负

调控 RIG-I 介导的抗病毒通路[24]。与 RIG-I 类似，MDA5 在未感染的细胞中 CARD 区域 Ser88 处的磷酸化，使其处于非活性状态，当细胞被病毒感染或 dsRNA 刺激时，PP1 去除 RIG-I 和 MDA5 的 CARD 中的磷酸化，触发先天性免疫反应[25]。RIOK3 可以在 CTD 的 Ser 828 处磷酸化 MDA5，干扰多聚体的形成，减弱 MDA5 介导的先天免疫反应[26]。

4.2. 泛素化修饰

泛素化是将泛素蛋白通过 E1 激活酶、E2 结合酶和 E3 连接酶共价或非共价结合到靶蛋白上的过程。RIG-I 识别病原体后，需要 Riplet (又称 RNF135 和 Reul)激活 RIG-I 在 Lys 788 位点上的 K63 链型泛素化，使构象变化释放 CARD，这是 RIG-I 寡聚的先决条件[27]。K63 泛素链与 RIG-I 核心 2CARD 非共价结合促使四聚体形成，并结合四聚体外围，连接相邻亚基稳定其组装，Riplet 在这一过程中促进 RIG-I 的 CARD 结构域 Lys 154, Lys 164 和 Lys 172 位点的 K63 链型泛素化，依赖 RNA 长度放大 RIG-I 介导的抗病毒信号[28]-[30]。Ube2D3 和 Ube2N 可以与 Riplet 结合，Ube2D3-Riplet 促进多泛素链与 RIG-I 的共价连接，而 Ube2N-Riplet 可以催化形成未锚定的多泛素链，二者都有助于由 RIG-I 激活的 MAVS 寡聚[31]。含环指结构的 E3 泛素连接酶 TRIM25 来自三方基序(Tripartite Motif Containing, TRIM)家族，与 Riplet 具有高度同源性，能介导 RIG-I 四聚体形成，诱导 RIG-I 在 Lys 172 位残基的 K63 链型及 MDA5 的泛素化[32] [33]。近年研究揭示了多种在 K63 连接的泛素化过程中特异调节 TRIM25 的活性因子，包括 Caspase-12、ZCCHC3、NDR2 和 NLRP12 [33]-[36]。长非编码 RNA Lnczc3h7a 在抗病毒感染的早期作为分子支架稳定 TRIM25 与它 308、311 和 332 核苷酸周围的 RIG-I 相互作用，增强下游信号传导[37]。由 E3 连接酶 HOIL-1L 和 HOIP 组成的线性泛素组装复合体 LUBAC 能下调 TRIM25 的蛋白水平并与 TRIM25 竞争 RIG-I 结合，抑制 RIG-I 的 K63 泛素化和信号活性[38]。LGP2 可以抑制 TRIM25 介导 RIG-I 的 K63 泛素化[39]。TRIM4 通过靶向 K63 连接的 RIG-I 的多泛素化来调节干扰素诱导的细胞抗病毒先天免疫[40]。MEX3C 优先于病毒 RNA 和 RIG-I 共定位在感染细胞的胞浆颗粒中，并介导 K63 连接的 RIG-I 泛素化[41]。锌指蛋白 ZFP36 在 RIG-I 的 K15、K164 和 K172 位点促进 RIG-I 的 K63 链型泛素化[42]。

K48 链型泛素化通常利用蛋白酶体途径降解靶蛋白。RNF122 和 RNF125 都能介导 RIG-I 的 K48 链型多泛素化，RNF125 以相同方式降解 MDA5 [43] [44]。负调控因子包括以 Npl4-Ufd1 为辅助因子的复合物 p97、Trithorax 蛋白家族成员 MLL5 和特异性上调凝集素家族成员 Siglec-g 都可以利用 K48 连接的泛素化或影响 E3 连接酶诱导 RIG-I 的降解，减弱其介导的 I 型干扰素产生[45]-[47]。STAT4 在 RNA 病毒感染时，不经历核转位，而是在胞浆与 E3 连接酶羧基末端相互作用蛋白(Carboxyl Terminus of HSC70-Interacting Protein, CHIP)互作，破坏 CHIP 介导的 RIG-I 的 K48 链型泛素化，阻止 RIG-I 降解[48]。TRIM40 作为 E3 泛素连接酶诱导 RIG-I 和 MDA5 通过 K48 和 K27 连接的泛素化降解，而 RIOK3 不仅能磷酸化 MDA5，还招募并与 E3 泛素连接酶 TRIM40 相互作用，抑制抗病毒信号[49] [50]。MDA5 的解旋酶结构域被 TRIM65 合成的 K63 链型的泛素链修饰，促进其寡聚激活传感器分子[51]。TRIM13 负调控 MDA5 介导的 I 型干扰素产生，对 RIG-I 途径却有正向调节作用[52]。

泛素链可在去泛素化酶(Deubiquitinating Enzymes, DUBs)的作用下被水解，动态调控机体泛素化修饰过程[53]。USP (Ubiquitin Specific Proteinase)家族是数量最多的一类去泛素化酶亚家族。敲除 USP17 可以增加 RIG-I 和 MDA5 的泛素化水平，USP4 和 USP15 分别通过蛋白水解性切割 RIG-I 和 TRIM25 分子的 K48 连接泛素链来增强 RIG-I 和 TRIM25 的稳定性[54]-[56]。研究证明 USP3、USP21、USP14 和 USP27X232 都可特异性去除 RIG-I 的 K63 链型多泛素链，抑制 I 型干扰素信号的激活[57]-[60]。此外，OTUB1 通过消除与 RIG-I 结合的 K48 链型泛素链来稳定 RIG-I 蛋白[61]，去泛素化酶 CyLD 可以移除 K63 链型多泛素链调控 RIG-I 信号[62]。

4.3. 类泛素化修饰

小泛素相关修饰物(Small Ubiquitin-Related Modifier, SUMO)与泛素有 18%的序列同源性和机制相似性[63]。SUMO 化也是可逆的多步酶促反应，通过 E1 激活酶(Aos1/UBA2)、E2 结合酶(UBC9)和一系列不同的 E3 连接酶，将一个 12 kDa 的 SUMO 分子与靶蛋白共价连接，最后由 SUMO 特异性蛋白酶(Sentrin/SUMO-Specific Protease, SENP)将其移除底物，完成 SUMO 成熟化进入新循环[64]。功能上，SUMO 化不促进蛋白质的降解，而是改变核质转位、蛋白质配对、蛋白质-DNA 结合和转录因子的反式激活等功能特性[65]。哺乳动物含有 5 种 SUMO 分子，分别为 SUMO-1/2/3/4/5，SUMO-1 能够增强 RIG-I 的 K63 链型泛素化和 RIG-I 与 MAVS 结合的能力，从而增强I型干扰素的产生[66]。UBR5 通过抑制 TRIM28 的 SUMO 化促进其 K63 链型泛素化，从而正向调节 RLR 的转录，增强抗病毒反应[67]。SUMO 异肽酶 ULP-4 能够 SUMO 化 RIG-I 的直系同系物 DRH-1 来促进秀丽隐杆线虫的抗病毒防御[68]。线粒体 E3 泛素连接酶 MUL1，SUMO 化 RIG-I 并抑制其多泛素化[69]。TRIM38 作为 E3 连接酶 SUMO 化 RIG-I 和 MDA5，防止其在未感染或病毒感染早期降解，并促进 RIG-I 和 MDA5 被 PP1 去磷酸化，正向调节干扰素抗病毒通路[70]。SENP2 在病毒感染的晚期去 SUMO 化 RIG-I 和 MDA5，避免持续激活和过度的先天免疫反应[71]。PIAS 家族成员通过不同机制调控干扰素通路，PIASy 的抑制功能依赖 SUMO 相互作用基序，SUMO E2 酶 UBC9 的敲除能够降低其抑制活性[72] [73]。E3 连接酶 PIAS2β 在 MDA5 的 C 末端发生 SUMO 化，促进抗病毒基因的诱导，而对 K48 连接的 MDA5 泛素化没有影响[74]。

干扰素诱导的 ISG15 直接抑制病毒复制，还能通过酶级联反应共价连接到靶蛋白上，发生一种称为 ISG 化的类泛素化修饰[75]。现已鉴定出 ISG15 酶偶联需要 E1 活化酶 UBE1L、E2 结合酶 UBCM8/H8 与含 HECT 和 RLD 结构域的 E3 泛素蛋白连接酶 5 (HECT and RLD Domain Containing E3 Ubiquitin Protein Ligase 5, HERC5)、ariadne RBR E3 泛素蛋白连接酶 1 (Ariadne RBR E3 Ubiquitin Protein Ligase 1, HHARI)和 TRIM25 参与，ISG 化部分可以被去 ISG 化酶 UBP43 (USP18)移除[76] [77]。ISG15 通过与泛素竞争蛋白质上的结合部位，影响蛋白稳定性和降解[78]。ISG15 与 RIG-I 结合，降低细胞中未结合的 RIG-I 蛋白水平，微调信号强度，而 ADAP 抑制这种结合，启动和维持抗病毒信号[79]。ISG 化对 MDA5 的作用类似于 RIG-I 的 K63 链型泛素化，在 K23 和 K43 处的 ISG 化是其 Ser88 去磷酸化激活所必需的，在 K23/K43 位点基因突变的小鼠中，对抗病毒的能力减弱[80]。MDA5 的 ISG 化限制病毒复制，SARS CoV2 PLPro 能够靶向 MDA5 去 ISG 化，抑制 MDA5 寡聚物的形成[81]。

此外，炎症诱导的泛素样蛋白 FAT10 能与激活的 RIG-I 的 2CARD 结构域非共价结合，调节 RIG-I 蛋白的溶解度，抑制病毒 RNA 诱导的 IRF3 和 NF-kB 激活，TRIM25 能增强 FAT10 的稳定性，加强抑制作用，减弱 RIG-I 诱导的炎症反应[82]。锌指蛋白 ZNF598 既是 E3 泛素连接酶，又能递送 FAT10 到 RIG-I 蛋白，发挥抑制作用，减弱 Riplet 介导的 K63 连接的 RIG-I 的多泛素化，避免通路过度激活[83]。

4.4. 其他翻译后修饰

糖基化作为生物体内分布最广泛的修饰类型，在抗病毒免疫中发挥不可或缺的作用。近年来研究发现 α-(1,6)-岩藻糖基转移酶(Alpha-(1,6)-Fucosyltransferase, FUT8)可以促进 TRIM40 介导的 RIG-I 的 K48 链型泛素化，并通过核心岩藻糖基化抑制 I 型干扰素反应[84]。

蛋白质的甲基化与转录激活有关，RIG-I 在 K18、K48 和 K146 位点发生甲基化，去甲基化酶 JMJD4 能去除 RIG-I 在 K18 和 K146 处的甲基化[85]。去甲基化酶 LSD1 是 RIG-I 信号转导的正调控因子，然而其调控作用不依赖其去甲基化活性，而是通过促进 RIG-I 的 K63 链型泛素化实现的[86]。

蛋白质的乙酰化由组蛋白乙酰基转移酶(Histone Acetyltransferases, HATs)催化，HATs 将乙酰基从乙酰辅酶 A 转移到氨基末端残基的 α-氨基或赖氨酸残基的 ε-氨基，组蛋白脱乙酰酶(Histone Deacetylases,

HDACs)能催化赖氨酸的乙酰基去除水解性，抵消 HATs 的作用，而氨基末端的修饰不可逆[87] [88]。一项高分辨率质谱研究鉴定到 RIG-I 的 K858 和 K909 残基上发生赖氨酸乙酰化[89]，可逆乙酰化参与 RIG-I 的激活，静息状态下，RIG-I 的羧基末端抑制结构域(Carboxyl-Terminal Repressor Domain, RD)相邻位点被乙酰化，阻止其寡聚，急性感染期间，HDAC6 瞬间与 RIG-I 结合，在病毒 RNA 存在的情况下移除 K909 位点乙酰化，促进其寡聚化，增强 RIG-I 对病毒 RNA 的敏感活性[90] [91]。组蛋白赖氨酸巴豆酰化缺失能够产生免疫原性 ds RNA，从而激活 MDA5 以增强I型干扰素信号传导[92]。

病毒通过多种策略进行免疫逃逸，疱疹病毒可以通过靶向 RIG-I，部署蛋白质脱酰胺化劫持免疫信号。谷氨酰胺转移酶(Glutamine Transferase, GAT)是一种脱酰胺酶，参与多种代谢物的生物合成，PFAS 是一种 GAT，催化嘌呤生物合成中的第四步。研究发现，小鼠伽马疱疹病毒 68 (Murine Gamma Herpesvirus 68, γHV68)感染后部署非酶活性的病毒伪酶 vGAT 招募 PFAS 脱酰胺化 RIG-I 的 Hel1 结构域残基，导致其结构性激活，此过程不消耗 ATP，这一激活事件被病毒篡夺，阻止真正的 PAMP 激活 RIG-I，促进病毒逃逸[93]。单纯疱疹病毒 1 型(Herpes Simplex Virus-I, HSV-1)及其他 α 疱疹病毒的基因组不含 γ 疱疹病毒 vGAT 的蛋白序列同源物，但 HSV-1 利用其外壳蛋白 UL37 脱酰胺化 RIG-I 的 Hel2i 结构域残基，使 RIG-I 无法感知病毒 dsRNA，ATP 结合和水解受损，导致无法激活，阻断下游信号传导，促进病毒复制，说明 RIG-I 脱酰胺化有着不同机制[94] [95]。经比较和突变分析确定 HSV-1 的 UL37 靶向 RIG-I 的 N495 进行脱酰胺反应，随后是 PPAT 作为脱酰胺酶，针对 RIG-I 解旋酶区域 N549 的脱酰胺反应，抑制其 RNA 传感活性并水解 ATP，促进信号激活[96]。

5. 结语

可逆的蛋白质 PTMs 靶向细胞内蛋白，对蛋白质动态调控，其失调可能导致免疫相关疾病，表明这些修饰对于维持免疫稳态十分重要。随着冷冻电镜与邻近标记技术等先进技术嵌入研究，RLRs 翻译后修饰各环节逐步清晰，非经典修饰类型在免疫中发挥的功能也日益崛起，但是否存在其他具有潜在免疫功能 PTMs 类型在免疫调节中的确切作用仍有待进一步探索。未来研究将利用多组学技术结合 AI 预测模型，突破单一 PTM 的局限性，构建 PTMs 串扰的协同调控网络，有助于解析 RLR 的时空动力学。目前对于 PTMs 的研究仍存在亟待解决的问题。例如，不同的修饰酶如何识别 RLRs 蛋白的特定位点，是否存在能够识别特定氨基酸序列的修饰密码导致了这种选择性修饰。在面临新出现的病毒威胁时，是否可以将 RLRs 的 PTM 调控机制开发为小分子抑制剂，利用宿主的先天免疫系统，设计出广谱抗病毒药物，以及 PTMs 是否可以作为预测疾病进展和治疗效果的免疫检查点。将对机制的理解转化为传染病和免疫相关疾病的治疗策略，是目前免疫学研究需要进一步重视发展的重要方向。

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