**DOI**:10.3724/cbls.2026006 **CSTR**:32203.14.cbls.2026006
**文章编号**:1004-0374(2026)01-0150-13

# 未折叠蛋白反应和泛素化修饰在免疫调节中的协同作用

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**摘 要**:内质网(endoplasmic reticulum,ER)在蛋白质合成、折叠和组装中发挥重要作用,其内部蛋白质产生受一组驻留机制紧密调节。在多种生理或病理条件下,未折叠蛋白或错误折叠蛋白在内质网腔蓄积引起内质网应激(endoplasmic reticulum stress,ERS),触发未折叠蛋白反应(unfolded protein response,UPR)以维持ER稳态。泛素化修饰是一种可逆的翻译后修饰,可调节蛋白质稳态。UPR和泛素化修饰均为细胞内重要的蛋白质质量控制机制,二者协同确保蛋白质生物合成的高准确度和高保真度,任一功能异常将导致蛋白质累积,进而加剧ERS,损伤细胞功能,引发疾病。本文首先概括了UPR和泛素化修饰的基本原理和功能,聚焦二者调控免疫细胞命运和维持免疫稳态等方面的协同作用,以期为寻找疾病诊疗相关的潜在靶点提供新视角。

**关键词**:未折叠蛋白反应;泛素化修饰;免疫调节
**中图分类号**:Q507;R392.1 **文献标识码**:A

# Synergistic roles of unfolded protein responses and ubiquitination modifications in immunomodulation

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**Abstract:** This review aims to explore the intricate and synergistic interplay between the unfolded protein response (UPR) and ubiquitination modifications in regulating the immune system. Maintaining cellular protein homeostasis is fundamental for immune cell function, which often involves high rates of protein synthesis, folding, and degradation. Endoplasmic reticulum stress (ERS), caused by the accumulation of unfolded or misfolded proteins, triggers UPR to restore ER homeostasis. Simultaneously, ubiquitination, a reversible post-translational modification, precisely controls protein stability and degradation. Both mechanisms act as critical intracellular protein quality control systems, working in concert to ensure protein biosynthesis fidelity and proper immune function. Dysfunction in either pathway can lead to protein accumulation, exacerbating ERS and contributing to immune-related pathologies. The review systematically delineates the core principles of UPR signaling (via PERK, ATF6, and IRE1) and ubiquitination (via E1/E2/E3 enzymes), then examines their collaborative mechanisms across immune cell subsets. In innate immunity, dendritic cells (DCs) employ the HRD1-UBE2J1 ERAD (ER associateddegradation) complex to ubiquitinate misfolded MHC-I heavy chains, ensuring antigen presentation fidelity. Macrophages exhibit IFN-γ-induced STAT1/PIAS1-mediated ubiquitination of LXR-α, triggering PERK-CHOP-driven apoptosis and inflammation. NK cells utilize IL-15-PI3K/AKT signaling to suppress XBP1s ubiquitination, stabilizing this UPR transcription factor to enhance survival and granzyme B expression. In allergic responses, Cbl ligases ubiquitinate FcεRI and protein tyrosine kinases to attenuate UPR activation in basophils and mast cells. Conversely, in mast cell leukemia, valosin-containing protein (VCP) inhibitors disrupt ERAD, stabilizing oncogenic MTDH and perpetuating IRE1α-driven

**收稿日期**:2025-06-30; **修回日期**:2025-08-14
**基金项目**:国家自然科学基金项目(81701590,32000495,82202862);山东省高校青年创新科技支持计划项目(2021KJ106,2023KJ254);山东省自然科学基金项目(ZR2020MH202,ZR2024MH338);潍坊市科技发展计划项目(2023GX033)
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tumor survival. Intestinal innate lymphoid cells rely on IRE1α-XBP1s for cytokine production, a process restrained by Itch-mediated RORγt ubiquitination. In adaptive immunity, B cell development requires SEL1L-HRD1 ERAD-mediated degradation of pre-B cell receptors, while plasma cell differentiation depends on IRE1/XBP1-driven ER expansion for antibody secretion. Regulatory T cells employ HRD1 to ubiquitinate both misfolded FoxP3 and IRE1α, preventing excessive UPR and preserving suppressive function. $CD4^+$ and $CD8^+$ T cell activation is modulated by PERK-eIF2α inhibition of MHC-I synthesis and MARCH1-mediated MHC-II ubiquitination, collectively impairing antigen presentation in metabolic and immunodeficiency disorders. This analysis reveals that UPR-ubiquitination synergy orchestrates proteostasis, antigen presentation, survival, differentiation, and inflammation across innate and adaptive immunity. Therapeutically, targeting UPR kinases (IRE1α, PERK) or specific E3 ligases offers promise for cancer, autoimmunity, and allergy, with VCP inhibitors already showing efficacy in mast cell leukemia. Combination strategies simultaneously modulating both pathways may prevent compensatory activation and achieve superior clinical outcomes. This review provides a framework for precision immunotherapy by revealing how proteostasis networks shape immune function and disease.

**Key words:** unfolded protein response; ubiquitination modifications; immunoregulation

内质网(ER)是蛋白质合成、折叠和修饰的主要场所[1]。在应激、缺氧及DNA损伤等压力条件下,ER内蛋白质稳态失衡导致未折叠/错误折叠蛋白蓄积,引发内质网应激(ERS)。为避免持续ERS造成严重后果,细胞将激活未折叠蛋白反应(UPR)内源性保护机制,其目的在于增强ER对蛋白质正确折叠的力度,同时削减ER的蛋白质装载负荷,并且激活ER相关降解(ER associated degradation,ERAD),减弱mRNA的整体翻译,增加错误折叠蛋白的清除,减轻ER中的折叠负荷[2,3]。泛素化修饰是一种重要的蛋白质翻译后修饰方式,在多种疾病的病理性过程中发挥重要调控作用[4,5]。持续有效的泛素化修饰确保正确折叠的蛋白质被稳定储存或运输,避免错误折叠蛋白在细胞内累积而引发细胞功能受损,维持细胞生存和正常功能[6-9]。基于免疫细胞在多种疾病的病理过程中发挥关键作用,本文将重点关注UPR与泛素化修饰对免疫细胞的协同调节作用。

## 1　UPR及其在免疫调节中的作用

在真核生物体内,维持ER稳态的UPR主要受三个关键的跨膜感受器调控,即蛋白质激酶R样ER激酶 (PKR-like ER kinase,PERK)、激活转录因子6 (activating transcription factor 6,ATF6)和肌醇需求酶1 (inositol-requiring enzyme 1,IRE1) [10-13]。在正常情况下,这三种跨膜蛋白各自与ER内主要分子伴侣——78 kDa葡萄糖调节蛋白/结合免疫球蛋白(glucose regulated protein 78 kDa/binding-immunoglobulin protein,GRP78/BIP)相结合维持非活性状态;GRP78又被称为70 kDa热休克蛋白家族A成员5(heat shock 70 kDa protein 5,HSPA5)。当内质网腔中蛋白质折叠平衡遭破坏,导致未折叠蛋白堆积时,GRP78会选择性地脱离PERK、ATF6和IRE1,转而与未折叠蛋白相互作用[14]。由此,PERK、ATF6和IRE1得以激活,并触发各自的信号转导路径,三条信号通路各自独立而又相互联系,以恢复内质网稳态并保护细胞免受应激损害(图1)。

研究发现,UPR通路PERK信号激活后eIF2a发生磷酸化,直接导致主要组织相容性复合体I类分子(major histocompatibility complex class I molecules,MHC-I)呈递适度减少[15]。在树突状细胞(dendritic cells,DCs)中,IRE1α通路通过激活X-盒结合蛋白1剪接型(X-box binding protein 1 spliced form,XBP1s)调控内质网抗原加工能力,XBP1s活性损害导致体外和体内细胞相关抗原交叉呈递的减少[16]。而在转移性卵巢癌小鼠模型中,肿瘤部位DC表现出IRE1α-XBP1s通路的过度激活,抑制IRE1α-XBP1s通路可以增强肿瘤部位DC的抗原呈递功能,进而诱导T细胞依赖的抗肿瘤免疫应答[17]。由此可见,UPR通过维持免疫细胞内蛋白质稳态深度参与其分化、抗原呈递以及免疫疾病的发生。

## 2　泛素化修饰及其在免疫调节中的作用

真核生物细胞内蛋白质降解主要通过泛素-蛋白酶体系统(UPS)介导;作为高度选择性的蛋白质降解系统,UPS由泛素、E1泛素激活酶、E2泛素结合酶、E3泛素连接酶、26S蛋白酶体和去泛素化酶组成[18-20]。UPS通过酶级联反应实现底物标记:E1激活泛素分子并转移至E2,E2结合到E3,E3特异性识别目标蛋白并催化泛素转移,最终形成共价连接的泛素链[21-23]。多聚泛素链不同的连接类型发挥不同的作用。一般类型包括赖氨酸残基27位点的多聚泛素化(K27)、K48、K63。其中,K27多聚泛素化参

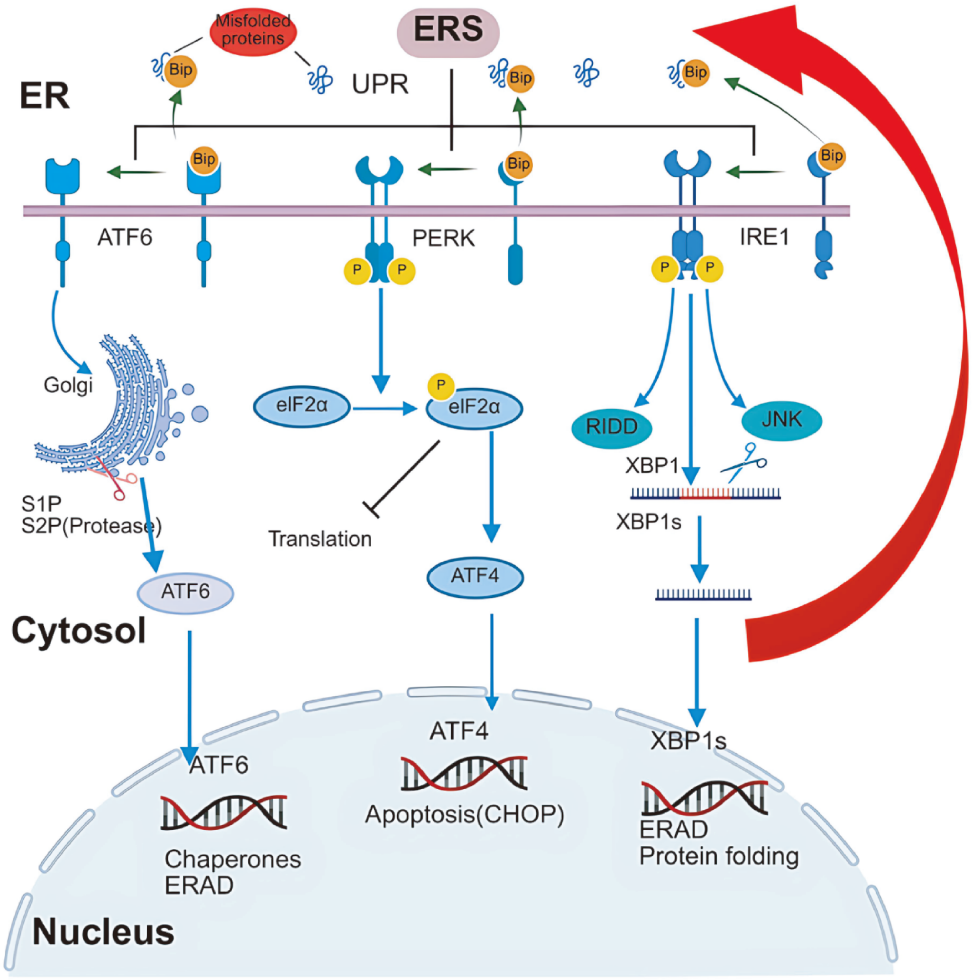


**图1 内质网蛋白质质量控制机制**

内质网中错误折叠的蛋白质激活了三个关键传感器——PERK、IRE1和ATF6，它们检测蛋白质应激并启动信号通路以恢复内质网稳态。这些途径减少蛋白质合成，通过上调伴侣蛋白增强蛋白质折叠，并通过ERAD促进蛋白质降解。然而，持续的内质网应激可以压倒这些机制，最终导致细胞凋亡。任一环节障碍都会导致ERS的持续激活，形成正反馈。ERS，内质网应激；UPR，未折叠蛋白反应；BIP，结合免疫球蛋白；PERK，蛋白质激酶R样ER激酶；ATF6，激活转录因子6；IRE1，肌醇需求酶1；Golgi，高尔基体；S1P/S2P，高尔基体位点1和位点2蛋白酶；eIF2α，真核翻译起始因子2α；RIDD，调控性IRE1依赖性mRNA降解；JNK，c-Jun氨基末端激酶；XBP1s，X-盒结合蛋白1剪接型；ATF4，激活转录因子4；ERAD，ER相关降解；CHOP，C/EBP同源蛋白。

**Figure 1 Endoplasmic reticulum protein quality control mechanisms**

Misfolded proteins within the endoplasmic reticulum activate three key sensors—PERK, IRE1, and ATF6—which detect protein stress and initiate signalling pathways to restore ER homeostasis. These pathways reduce protein synthesis, enhance protein folding by upregulating chaperones, and promote protein degradation via ERAD. However, persistent ER stress can overwhelm these mechanisms, ultimately leading to apoptosis. Impairment at any stage results in sustained activation of ERS, forming a positive feedback loop. ERS, endoplasmic reticulum stress; UPR, unfolded protein response; BIP, binding-immunoglobulin protein; PERK, PKR-like ER kinase; ATF6activating transcription factor 6; IRE1, inositol-requiring enzyme 1; S1P/S2P, Golgi site-1 and site-2 proteases; eIF2α, eukaryotic initiation factor 2α; RIDD, regulated IRE1-dependent decay; JNK, c-Jun N-terminal kinase; XBP1s, X-box binding protein 1 spliced form; ATF4, activating transcription factor 4; ERAD, ER-associated degradation; CHOP, C/EBP homologous protein.

与了自噬、先天免疫调节以及信号转导，K48多聚泛素化一般情况下介导蛋白酶体降解，而K63多聚泛素化则在激酶激活和DNA修复中发挥作用[24]。泛素化修饰的动态平衡由E3泛素连接酶和去泛素化酶共同调控：其中E3标记目标蛋白以引导其功能修饰或促使被标记的错误折叠蛋白被26S蛋白酶体识别并降解[25-27]。因此，泛素化修饰对细胞内错误折叠蛋白进行识别、标记、转运和最后的降解，维持了蛋白质稳态及其功能[28,29]。

免疫细胞成熟、信号转导、细胞分化、抗原呈递

等过程均受到泛素化修饰的严格调控[30]。E3泛素连接酶膜相关环状蛋白1(membrane associated cyclic protein 1,MARCH1)泛素化MHC-II,使其在DCs表面的表达降低,不仅导致抗原呈递受损,还会影响MHC-I的抗原呈递途径[31]。此外,MARCH1还通过诱导MHC-II类分子和共刺激分子CD86的泛素化依赖性降解,进而负调控DCs的成熟[32,33]。E3泛素连接酶库伦-5(Cullin-5,Cul5)通过调节白介素4受体信号决定$CD4^+$ T细胞分化,T细胞中缺乏Cul5的小鼠表现为蛋白质稳态失衡并发生Th 2和Th 9型免疫反应,出现严重的炎症及过敏症状[34]。总之,泛素化修饰通过调节免疫细胞内蛋白质稳态,调控免疫应答,维持免疫稳态。

## 3 UPR与泛素化修饰协同维持细胞稳态与功能

当细胞感受到压力时,UPR被激活,响应ERS以恢复蛋白质稳态[4]。ERS过程中蛋白质翻译后修饰的动态调控尤为重要,一些ERS核心蛋白被泛素化,然后被26S蛋白酶体降解,直接影响ERS的进程;还有一些ERS相关蛋白通过E3泛素连接酶介导的泛素化修饰间接调控ERS进程。比如,E3泛素连接酶羟基甲基戊二酰辅酶A还原酶降解蛋白1 (HMG-CoA reductase degradation protein 1,HRD1)不仅介导靶向底物蛋白泛素化修饰和降解,还可通过lin-12-like抑制/增强子(suppressor/enhancer of lin-12-like,SEL1L)-HRD1复合体与IRE1α信号交互:HRD1催化IRE1α的K48泛素化修饰,促进其进入蛋白酶体降解,负调控UPR强度[35-37]。当泛素化修饰功能障碍时,错误折叠蛋白的持续堆积会过度激活IRE1α,导致XBP1剪接异常和促凋亡信号的释放,最终诱发细胞损伤,甚至癌变[26,38]。除了HRD1,其他泛素酶也可直接靶向UPR通路信号因子使其泛素化[39-43]。而UPR通路转录因子被激活后,以间接的方式调节编码泛素化酶和蛋白酶体组件的基因表达,从而调控细胞清除错误折叠蛋白的能力,如XBP1s[44]。总的来说,ERS触发UPR,利用泛素化修饰处理应激蛋白,直接影响UPR的发生与调控,协同维护细胞内蛋白质稳态和细胞功能的正常运作;若协同失衡,将导致细胞功能障碍、炎症反应加剧、免疫应答异常等一系列病理生理现象,与多种疾病的发生发展密切相关。本文将聚焦UPR和泛素化修饰协同调控免疫细胞的作用机制。

### 3.1 固有免疫细胞

固有免疫细胞的快速应答是机体防御的第一道防线,其功能也受内质网稳态调节[32]。近年研究表明,UPR与泛素化修饰不仅能够自主调控维持各类固有免疫细胞的功能,也通过调节细胞间信号驱动免疫应答。以下将分述不同固有免疫细胞中二者的协同机制。

#### 3.1.1 树突状细胞

DCs是体内最重要的专职抗原提呈细胞,通过MHC-I-抗原肽复合体精确呈递内源性抗原,是激活$CD8^+$ T细胞免疫应答的核心环节,因此MHC-I分子在ER腔的正确折叠是免疫激活功能的必要保证[45]。在ER腔室内,重链与β2微球蛋白(β2-microglobulin,β2m)及8~10个氨基酸的抗原肽通过肽装载复合物完成精确组装[46]。只有完整构象的复合体才能脱离肽装载复合物驻留蛋白的束缚,经高尔基体运输至细胞表面。值得注意的是,缺乏β2m将导致MHC-I重链的拓扑构象紊乱,无法形成稳定的异源三聚体,触发ER质控的识别信号,导致未折叠的重链无法进入分泌通路,造成ERS激活UPR。随后错误折叠重链易位至胞质,HRD1与E2结合酶UBE2J1形成催化模块,将重链泛素化,随后引导其进入蛋白酶体降解[47,48]。UBE2J1是HRD1的专属E2伴侣,其他E2酶无法补偿其功能。通过小干扰RNA(small interfering RNA,siRNA)敲低或HRD1 RING结构域突变实验证实,二者的功能缺失会显著抑制重链的泛素化修饰及其随后的降解,导致未折叠蛋白在ER膜中滞留,加剧ERS-UPR。总之,UPR与泛素化修饰是MHC-I类分子组装和表达调控过程的关键质控环节。二者协同保证内质网中错误折叠的MHC-I重链的有效识别、泛素化及降解,确保DCs抗原提呈的精确性,更为其与适应性T淋巴细胞的功能衔接奠定分子基础,这提示固有免疫连接适应性免疫依赖于ER稳态。

#### 3.1.2 巨噬细胞

不同于DCs主要依赖HRD1调控抗原提呈,巨噬细胞(macrophages,Mø)的ER稳态呈现出更强的炎症信号依赖性。研究发现,干扰素-γ(interferon-gamma,IFN-γ)通过泛素化修饰降解肝脏X受体α(liver X receptor alpha,LXR-α)以激活UPR,进而加剧Mø凋亡。IFN-γ通过激活信号转导及转录激活蛋白1(signal transducer and activator of transcription 1,

STAT1)的磷酸化,促进其与活化STAT蛋白抑制因子1(protein inhibitor of activated STAT 1,PIAS1)形成复合物,通过K48连接多聚泛素化靶向LXR-α至蛋白酶体降解;降解过程伴有ERS相关蛋白的表达上调,包括磷酸化的PERK、eIF2α和C/EBP同源蛋白(C/EBP-homologous protein,CHOP);CHOP驱动Mø凋亡并上调TNF-α、IL-6等促炎因子[49]。总之,IFN-γ通过STAT1/PIAS1复合体调控LXR-α泛素化降解,破坏内质网稳态并激活UPR依赖性凋亡,驱动血管新生内膜增生。这一机制扩展了UPR与泛素化修饰在炎症性疾病中的协同作用,并为靶向LXR-α与ERS轴治疗血管再狭窄提供了理论依据[50]。

HSPA5作为ER腔主要伴侣蛋白,其乙酰化促进未折叠蛋白的折叠与清除,有研究揭示病毒感染的Mø中Septin 2蛋白(SEPT2)通过调控HSPA5的乙酰化与泛素化,调控Mø非依赖IFN-γ的自身激活。SEPT2靶向HSPA5的赖氨酸327位点进行乙酰化修饰,通过空间位阻效应阻断E3泛素连接酶上皮钠通道β亚基(sodium channel epithelial beta subunit,SCNN1B)对该位点的识别,抑制K48连接的泛素链形成,阻止了其对HSPA5的标记和降解[44]。故SEPT2缺失会导致HSPA5泛素化增加、稳定性下降,伴随ER未折叠蛋白堆积,过度激活UPR信号通路,促进Mø释放炎症因子TNF-α及M1样超极化[51,52]。因此,ERS诱导SEPT2表达,SEPT2平衡了HSPA5在K327位的乙酰化和泛素化之间的竞争,从而缓解ERS并抑制M1样极化和促炎细胞因子释放。此研究揭示了一个不依赖于IFN-γ的巨噬细胞促炎自激活通路,并表明SEPT2可能在预防或缓解炎症中发挥作用。综上提示,UPR与泛素化修饰可能以IFN-γ依赖或非依赖的方式协同调控Mø驱动的免疫病理过程。

### 3.1.3 自然杀伤细胞

自然杀伤(natural killer,NK)细胞的活性维持依赖于白细胞介素15(interleukin-15,IL-15)。IL-15是NK调节生物学功能的重要细胞因子之一。它可以上调NK细胞中UPR基因XBP1s的表达,保护细胞免受应激性死亡,增强其效应功能,包括杀伤靶细胞的能力、提高细胞自身的存活率,并对维持和增强NK细胞的免疫监视和响应起到决定性作用[53]。其具体机制是IL-15激活磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase,PI3K) /蛋白激酶 B(protein kinase B,AKT)通路,AKT抑制E3泛素连接酶对XBP1s的K48位泛素化修饰。AKT磷酸化后导致XBP1s的去泛素化,稳定XBP1s的蛋白表达,诱导NK细胞IL-15依赖性存活[54]。另外,XBP1s通过直接结合颗粒酶B(granzyme B,GZMB)启动子区域的特定序列,与T-box转录因子(T-box transcription factor,T-BET)协同作用,增加GZMB转录,增强NK细胞的细胞毒性作用[55]。总之,IL-15/AKT信号通路通过降低XBP1s泛素化水平稳定XBP1s的表达,进而强化UPR对效应基因转录的调控,维持NK细胞的存活与效应功能。靶向XBP1s稳定性可优化NK细胞疗法,这为认识NK细胞在免疫调控中的作用提供了新的视角。

### 3.1.4 自然杀伤T细胞

颗粒酶K(granzyme K,GZMK)作为丝氨酸蛋白酶家族的一员,在自然杀伤T细胞(natural killer T cell,NKT)与NK细胞中高表达,通过穿孔素依赖性胞质递送至靶细胞,介导靶细胞死亡。研究揭示,GZMK能够直接作用于ERAD的核心成分——含缬酪肽蛋白(valosin-containing protein,VCP)及其辅助因子泛素融合降解蛋白1(ubiquitin fusion degradation protein 1,UDF1)-核蛋白定位同源物4(nuclear protein localization homolog 4,NPI4)形成的复合体;该复合体识别泛素链后利用ATP水解能驱动底物逆向转运至胞质,进而由蛋白酶体降解[56]。GZMK切割VCP的D2结构域713位点,破坏其ATP酶活性及六聚体稳定性,使VCP复合体解离,导致泛素化底物在ER中堆积,触发UPR;随后IRE1α被激活,剪切XBP1 mRNA生成XBP1s,上调分子伴侣表达以缓解ERS。同时,ATF4-CHOP轴也被激活,活化c-Jun氨基末端激酶(c-Jun N-terminal kinase,JNK)通路增强死亡信号,诱导凋亡[57]。GZMK-VCP轴通过破坏ERAD-UPR稳态平衡,在感染防御与肿瘤免疫中发挥作用,其特异性靶向干预为免疫代谢性疾病治疗提供新视角,未来仍需深入解析泛素修饰与UPR轴对NKT细胞亚群存活及功能发挥的调节作用。

### 3.1.5 嗜碱性粒细胞

嗜碱性粒细胞(basophils,BAS)在功能上与肥大细胞(mast cells,MC)密切相关,均参与引发介导I型超敏反应[58]。两种类型的细胞都表达高亲和力IgE受体FcεRI(Fc epsilon RI),在结合特异性IgE Fc段后,活化脱颗粒,释放组胺、白三烯等炎症介质,引发多种过敏性疾病并伴随严重的ERS,尤其是过

敏性哮喘[59-61]。慢性过敏性炎症环境可诱导BAS内ERS增强,激活UPR,通过PERK/eIF2α及IRE1/XBP1通路增加促炎因子分泌,形成正反馈[62]。E3泛素连接酶Casitas B细胞淋巴瘤(Casitas B-lineage lymphoma,Cbl)能促使FcεRI发生多泛素化,并指引其进入内吞路径,进一步运送至溶酶体进行分解,有效地减少了膜表面的FcεRI数量,控制着FcεRI介导信号的强度和持续时间。尤为重要的是,Cbl选择性对蛋白酪氨酸激酶(protein tyrosine kinases,PTKs),包括Src家族相关新型酪氨酸蛋白激酶和脾酪氨酸激酶进行标记促使其降解,在分子水平上实现对PTK信号的负向调节,缓解ERS-UPR,最终抑制BAS和MC的异常激活和炎症反应[63]。总之,干预UPR相关分子或增强Cbl介导的泛素化降解,可通过调控FcεRI稳定性与激酶活性抑制过敏。BAS与MC的功能异常是过敏性疾病的核心病理环节,其调控依赖于Cbl介导的泛素化修饰及UPR信号的动态平衡。

#### 3.1.6 肥大细胞

肥大细胞(MC)是一种重要的免疫细胞,主要分布于皮肤、黏膜组织和结缔组织中,参与过敏反应和炎症,在先天免疫应答和肿瘤微环境的调控中发挥作用[64]。与BAS细胞在过敏反应中的角色相似,Cbl介导的泛素化修饰及UPR信号通路协同调控MC表面的FcεRI数量及激酶活性,抑制过敏[62]。MC异常增殖可能造成严重的、极具侵袭性的肥大细胞白血病(mast cell leukemia,MCL),其恶性转化与UPR和癌基因的协同失控密切相关,致癌蛋白MTDH(metadherin)作为RNA结合蛋白通过调控ERS通路感受器IRE1α表达,形成正反馈环路,促进癌症进展[65]。VCP将错误折叠的 MTDH 转运至胞质,介导其泛素化标记及降解,从而调控 MTDH 的稳定性;其抑制剂致使ERAD受阻,进而导致IRE1α蛋白积累并活化,持续激活UPR,促进XBP1s及下游促存活基因表达[28]。而IRE1α的存在增强了MTDH的稳定性,可能加剧致癌信号,形成持续ERS与肿瘤进展的恶性循环[66]。另一项研究表明,蛋白酶体抑制剂硼替佐米(Bortezomib,BZ)通过抑制UPS导致错误折叠蛋白堆积,触发UPR引起明显的MC毒性反应,表现为eIF2α磷酸化、CHOP上调及JNK通路激活[67,68]。综合以上数据,UPR与泛素化修饰协同调控MC中基因表达的稳定性。这些研究系统揭示MCL中IRE1α适应性UPR与JNK促存活的交叉调控,提出以UPR应激增强与关键靶点为核心的联合治疗策略,为克服MCL改善预后提供机制依据。其协同干预思路可能适用于其他依赖UPR的高分泌性恶性肿瘤。目前的研究主要关注MC中UPR与泛素修饰协同诱导的MC异常增殖,但二者对生理状态下MC功能的调控及其在疾病中的调节作用仍有待深入阐明。

#### 3.1.7 嗜酸性粒细胞

嗜酸性粒细胞(eosinophils,EOS)在对抗寄生虫、细菌、病毒感染和调节过敏反应中发挥重要作用。在过敏性哮喘患者中,EOS异常聚集于气道黏膜下层,其释放的毒性物质可降解气道上皮紧密连接蛋白,诱导黏液高分泌并促进Th2型炎症反应。有研究显示,重度哮喘患者EOS中检测到严重的ERS,诸如ER蛋白伴侣BIP、相关蛋白内质网降解增强,α-甘露糖苷酶样蛋白1及ERS诱导的凋亡基因DNA损伤诱导转录因子3的显著升高[69]。白细胞介素-5(IL-5)作为调控EOS成熟与激活的关键因子,它驱动EOS从外周血迁移至肺部,释放有害蛋白,加剧气道上皮损伤和炎症反应,恶化哮喘症状[70]。在此背景下,MARCH蛋白家族的膜相关RING-CH蛋白2(membrane-associated RING-CH2,MARCH2)和MARCH3作为特定的E3泛素连接酶,通过促进IL-5受体α链在赖氨酸K379和K383位点的K27连接泛素化,引导其至溶酶体降解,有效抑制IL-5引发的信号转导和EOS成熟,避免了EOS驱动的气道高反应性[71]。这表明ERS与泛素化修饰的协同作用在嗜酸性粒细胞介导的免疫调节和哮喘发病机制中发挥关键作用,为哮喘的靶向治疗提供了新的思路。

#### 3.1.8 γδT细胞

γδT细胞是一种独特的T淋巴细胞亚群,在免疫系统中扮演着非常特殊的角色,不仅能够释放白细胞介素17A(IL-17A)和IFN-γ直接清除病毒感染细胞和肿瘤细胞,还参与复杂的免疫调节过程和炎症反应[72]。有研究证实,ERS微环境深刻影响γδT细胞功能状态。在小鼠模型中,Mø响应ERS活化的激活转录因子3(activating transcription factor 3,ATF3),显著促进γδT细胞分泌IL-17A,增强其杀伤效能[73]。另一方面,E3泛素连接酶Cbl-b通过泛素修饰对γδT细胞的杀伤活性施加负向调控。综上,ERS微环境中γδT细胞功能状态,实际上是UPR与泛素化修饰协同作用的结果,其协同调控机制为探索创新免疫疗

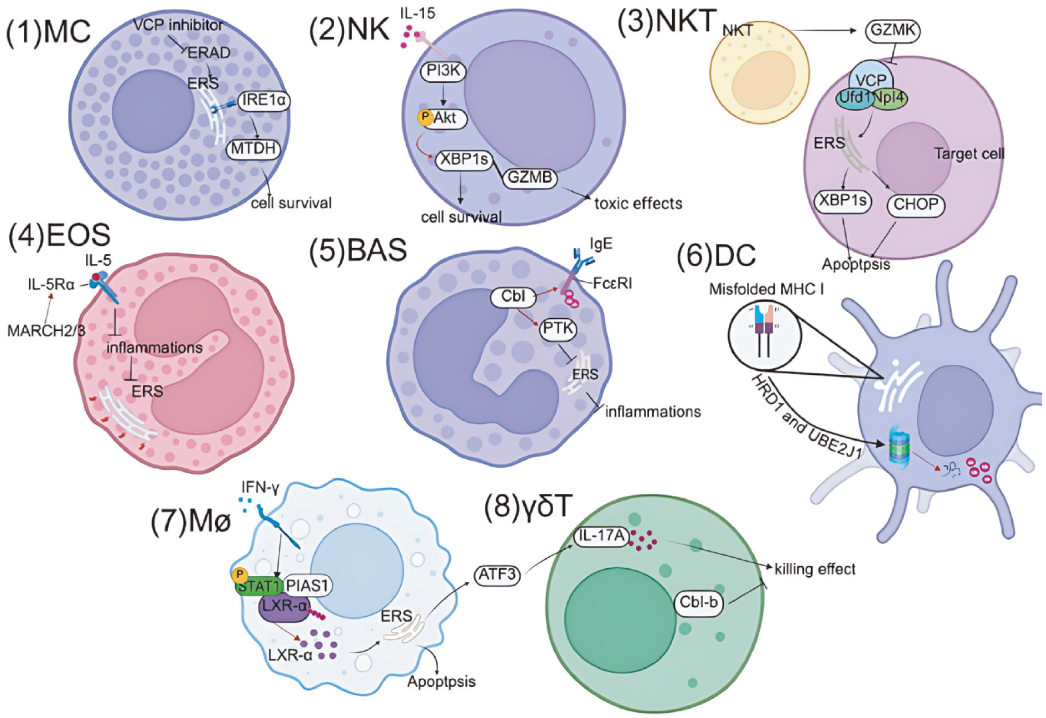


**图2 先天免疫细胞中泛素化修饰与UPR的协同相互作用**

(1)MC:VCP抑制剂使ERAD作用受阻,IRE1α持续激活稳定MTDH,导致癌细胞存活。(2)NK:IL-15激活PI3K-AKT通路,AKT磷酸化使得XBP1s去泛素化,NK存活。另一方面,XBP1s增加GZMB的转录,增强NK的毒性作用。(3)NKT:NKT表面高表达GZMK,它抑制VCP与UDF1-NPI4组成的复合体,ERS被激活,XBP1s和CHOP表达以缓解ERS。(4)EOS:MARCH2/3泛素化IL-5Rα,以抑制炎症和ERS。(5)BAS:Cbl通过泛素化FcεRI和PTK抑制ERS和炎症。(6)DC:HRD1介导的ERAD通路特异性地与UBE2J1合作,介导错误折叠的MHC-I重链的蛋白酶体降解,阻断ERS。(7)Mø:IFN-γ激活STAT1与PIAS1形成复合物,该复合物直接结合LXR-α并将其泛素化,激活ERS和UPR依赖性凋亡。(8)γδT:Mø在响应ERS时激活ATF3,显著促进γδT细胞分泌IL-17A,增强其杀伤作用。而Cbl-b对γδT细胞的杀伤活性具有负向调节作用。VCP,含缬酪肽蛋白;IRE1,肌醇需求酶1;MTDH,致癌蛋白Metadherin;PI3K,磷脂酰肌醇3-激酶;AKT,蛋白激酶B;XBP1s,X-盒结合蛋白1剪接型;GZMB,颗粒酶B;GZMK,颗粒酶K;UDF1,泛素融合降解蛋白1;NPI4,核蛋白定位同源物4;CHOP,C/EBP同源蛋白;IL-5,白细胞介素-5;MARCH2/3,膜相关RING-CH蛋白2/3;Cbl,Casitas B细胞淋巴瘤;PTKs,蛋白酪氨酸激酶;FcεRI,高亲和力IgE受体;MHC-I,主要组织相容性复合体I类分子;HRD1,羟基甲基戊二酰辅酶A还原酶降解蛋白1;IFN-γ,干扰素-γ;STAT1,转录激活蛋白1;PIAS1,活化STAT蛋白抑制因子1;LXR-α,肝脏X受体α;ATF3,激活转录因子3;IL-17A,白细胞介素17A。

**Figure 2 Synergistic interactions between ubiquitination modifications and UPR in innate immune cells**

(1) MC: VCP inhibitors disrupt ERAD, leading to sustained IRE1α activation that stabilises MTDH and promotes cancer cell survival. (2) NK: IL-15 activates the PI3K-AKT pathway; AKT phosphorylation de-ubiquitinates XBP1s, facilitating NK cell survival. Conversely, XBP1s enhances GZMB transcription, amplifying NK cytotoxicity. (3) NKT: NKT cells highly express GZMK on their surface, which inhibits the VCP-UDF1-NPI4 complex, activating ERS. XBP1s and CHOP expression then alleviate ERS. (4) EOS: MARCH2/3 ubiquitinates IL-5Rα to suppress inflammation and ERS. (5) BAS: Cbl inhibits ERS and inflammation by ubiquitinating FcεRI and PTK. (6) DC: The HRD1-mediated ERAD pathway specifically cooperates with UBE2J1 to mediate proteasomal degradation of misfolded MHC-I heavy chains, thereby blocking ERS. (7) Mø: IFN-γ activates STAT1 to form a complex with PIAS1, which directly binds LXR-α and ubiquitinates it, activating ERS and UPR-dependent apoptosis. (8) γδT cells: Macrophages activate ATF3 in response to ERS, significantly enhancing γδT cell secretion of IL-17A and amplifying their cytotoxic activity. Conversely, Cbl-b exerts negative regulation over γδT cell killing capacity. VCP, valosin-containing protein; IRE1, inositol-requiring enzyme 1; MTDH, metadherin; PI3K, phosphatidylinositol 3-kinases; AKT, protein kinase B; XBP1s, X-box binding protein 1 spliced form; GZMB, granzyme B; GZMK, granzyme K; UDF1, ubiquitin fusion degradation protein 1; NPI4, nuclear protein localization homolog 4; CHOP, C/EBP homologous protein; IL-5, interleukin-5; MARCH2/3, membrane-associated RING-CH2/3; Cbl, Casitas B-lineage lymphoma; PTKs, protein tyrosine kinases; FcεRI, Fc epsilon RI; MHC-I, major histocompatibility complex class I molecules; HRD1, HMG-CoA reductase degradation protein 1; IFN-γ, interferon-gamma; STAT1, signal transducer and activator of transcription 1; PIAS1, protein inhibitor of activated STAT 1; LXR-α, liver X receptor; ATF3, activating transcription factor 3; IL-17A, interleukin-17A.

法提供了见解(图2)。通过靶向ERS响应通路来增强γδT细胞的效应功能,或通过调节泛素化修饰来调控γδT细胞的杀伤活性,有望开发出更有效、更精准的细胞治疗或药物干预策略。

#### 3.1.9 固有淋巴细胞

近年研究发现,固有淋巴细胞(innate lymphoid cells,ILCs)作为黏膜免疫稳态调控的关键细胞群,其功能也受到UPR与泛素化修饰影响。ILCs家族包含多种组织定居型淋巴细胞,这些细胞缺乏多样化的抗原受体,但在功能上与效应T细胞显著相似。根据关键转录因子或效应性细胞因子的表达,ILCs被分为NK、1类固有淋巴细胞(group 1 innate lymphoid cells,ILC1s)、ILC2s、ILC3s。在这一家族中,以转录因子视黄酸受体相关孤儿受体γt(retinoic acid receptor-related orphan receptor gamma t,RORγt)为特征性标志的ILC3s在塑造胃肠道的组织生理、免疫、炎症、耐受性和恶性肿瘤方面发挥关键作用。尽管ILC3s在发育期和健康成体肠道中高度富集,但在微生物刺激或疾病状态下,其功能会发生显著失调[74]。值得注意的是,UPR通路对ILC3s具有关键调控作用。小鼠模型研究表明,特异性敲除ILC3中的IRE1α会损害ERS的缓解能力,并导致细胞因子基因表达降低,从而使小鼠对实验性结肠炎高度易感。肠道内XBP1s$^{+}$ ILC3s的数量与炎症性肠病的治疗效果呈正相关,这提示其可作为潜在的生物标志物和治疗靶点[75]。此外,硫链丝菌肽可通过促进E3泛素连接酶Itch蛋白(immunological threshold changing protein)与RORγt的结合,诱导RORγt的泛素化和降解,进而逆转肠道菌群失调,从而缓解结肠炎症。因此,ILC3s可通过IRE1α-XBP1s轴应对ERS,维持正常的细胞因子分泌能力,从而在肠道炎症中发挥保护作用。而泛素化修饰通过降解关键转录因子RORγt来调节ILC3s的功能,进而影响肠道菌群平衡和炎症状态[76]。这不仅深化了我们对ILCs的理解,更揭示了UPR和泛素化修饰在肠道免疫疾病发生发展中的重要病理生理学作用。靶向ILC3s中的UPR和泛素化通路,有望为炎症性肠病等相关疾病的诊断、治疗和药物开发提供新的策略。

### 3.2 适应性免疫细胞

适应性免疫细胞的调控需要更长期的蛋白质合成与记忆维持能力,这对UPR-泛素修饰协同调控提出了更高要求。UPR与泛素化修饰不仅参与B/T细胞的自主发育调控,其功能异常还可通过抗原提呈和抗体分泌等途径破坏免疫稳态网络。

#### 3.2.1 B细胞

B细胞的发育与分化是一个多步骤的过程,从多能造血干细胞开始,最终发育为成熟B细胞;成熟B细胞在外周淋巴器官中受到抗原刺激后,可以分化为浆细胞或记忆B细胞,参与体液免疫应答,UPR与泛素修饰共同调控这些过程。有研究指出,SEL1L-HRD1 ERAD是泛素化修饰调控B细胞早期发育的关键机制,该复合物通过分子伴侣BIP识别未成熟的前B细胞受体构象异常,介导其K48泛素化并导向蛋白酶体降解,确保前B细胞受体信号终止;SEL1L-HRD1 ERAD任一环节损坏,都会导致前大B细胞向小B细胞转变过程中出现严重的发育缺陷,最终致外周血中B细胞数量显著下降[36,77,78]。在B淋巴细胞向浆细胞转变的过程中,UPR成分IRE1/XBP1分支尤为重要,能够促进抗体有效合成与组装,帮助浆细胞扩展ER;此外,浆细胞分化伴随ER扩容和抗体大量合成,触发UPR[79]。UPR和泛素化修饰并非独立作用,而是协同调控B细胞的整个生命周期。泛素化修饰在早期发育中确保B细胞的正确发育和信号终止。而UPR,特别是IRE1/XBP1分支在后期浆细胞分化中优化抗体生产能力,应对大量蛋白质的合成负荷。总之,UPR和泛素化修饰协同调控B细胞发育、分化以及抗体产生,为免疫系统平衡与疾病干预提供了关键靶点(图3)。

#### 3.2.2 Treg细胞

类似于B细胞在抗体生成中的ER扩容需求,调节性T细胞(regulatory T cells,Tregs)的功能维持同样需要UPR精确调控。Tregs在维持免疫耐受中起着核心作用,其发育主要受转录因子叉头盒蛋白3(transcription factor forkhead box protein 3,FoxP3)的表达调控。在炎症微环境中,促炎细胞因子通过诱导ERS引发UPR,促进相关基因XBP1s和CHOP表达,并显著抑制Tregs中FoxP3的表达,致其功能受损及数量减少,同时活化型T细胞增多,从而限制Tregs在免疫耐受中的作用[80,81]。E3泛素酶HRD1可识别ER中错误折叠的FoxP3蛋白,通过K48泛素化修饰引导其至蛋白酶体降解,阻断持续性UPR形成;HRD1还通过泛素化降解IRE1α,抑制其激酶活性,阻断下游p38丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)信号通路;HRD1缺失可增强p38活化

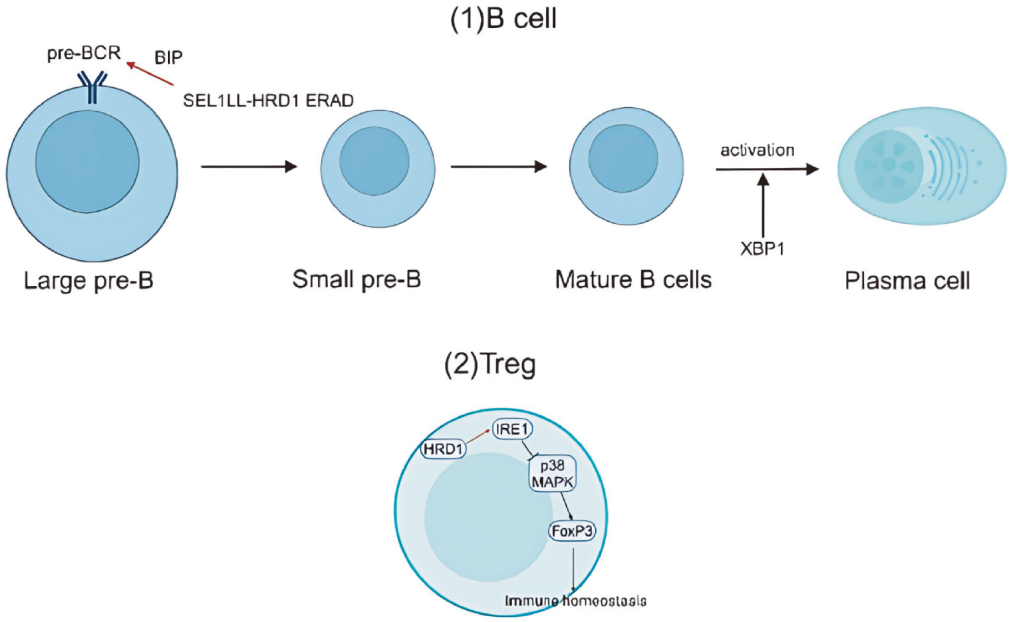


**图3 适应性免疫细胞中泛素化修饰与UPR的协同相互作用**

(1)B细胞:SEL1L-HRD1 ERAD通路通过伴侣蛋白BIP依赖机制识别并选择性地泛素化B细胞前受体,导致其通过蛋白酶体途径降解,这对正常B细胞发育至关重要。IRE1/XBP1分支促进B淋巴细胞向浆细胞转化过程中抗体的有效合成和组装,并帮助浆细胞扩大内质网。(2)Treg:HRD1泛素化IRE1α,抑制p38 MAPK信号通路,促进FoxP3的表达,维持Tregs的稳定。BCR,B细胞受体;BIP,结合免疫球蛋白;ERAD,ER相关降解;XBP1s,X-盒结合蛋白1剪接型;HRD1,羟基甲基戊二酰辅酶A还原酶降解蛋白1;IRE1,肌醇需求酶1;MAPK,丝裂原活化蛋白激酶;FoxP3,转录因子叉头盒蛋白3。

**Figure 3 Synergistic interaction of ubiquitination modifications with the UPR in adaptive immune cells**

(1) B cells: The SEL1L-HRD1 ERAD pathway recognises and selectively ubiquitinates the B-cell precursor receptor via a chaperone protein BIP-dependent mechanism, leading to its degradation through the proteasome pathway. This process is crucial for normal B-cell development. The IRE1/XBP1 branch promotes efficient antibody synthesis and assembly during B-lymphocyte differentiation into plasma cells and assists plasma cells in expanding the endoplasmic reticulum. (2) Treg: HRD1 ubiquitinates IRE1α, thereby inhibiting the p38 MAPK signalling pathway, promoting FoxP3 expression, and maintaining Treg stability. BCR, B-cell receptor; BIP, binding-immunoglobulin protein; ERAD, ER associated degradation; XBP1s, X-box binding protein 1 spliced form; HRD1, HMG-CoA reductase degradation protein 1; IRE1, inositol-requiring enzyme 1; MAPK, mitogen-activated protein kinase; FoxP3, transcription factor forkhead box protein 3.

并减少白细胞介素-10(IL-10)的产生,导致FoxP3表达抑制,从而破坏Tregs的稳定性[82-84]。综上所述,ERS与泛素化修饰在调控Tregs功能方面协同作用。ERS能够通过UPR影响FoxP3的表达,而HRD1等泛素化酶则通过降解异常蛋白和调控UPR通路来维持Tregs的稳态和功能。通过精确调节HRD1的活性,可能有助于恢复Tregs的功能,从而重建免疫耐受,或缓解过度炎症反应,可能有助于开发针对自身免疫病和慢性炎症性疾病的免疫疗法。

### 3.2.3 $CD4^+$ T和$CD8^+$ T细胞

$CD4^+$ T和$CD8^+$ T细胞是适应性免疫的核心效应细胞,其功能高度依赖于对MHC分子-抗原肽复合物的特异性识别。$CD4^+$ T细胞通过TCR-CD4复合物共受体识别 MHC-II类分子,分化为辅助性T细胞(helper T cells,Th cells),通过分泌细胞因子协调B细胞抗体产生、巨噬细胞活化及$CD8^+$ T细胞应答。$CD8^+$ T细胞则通过TCR-CD8复合物识别MHC-I类分子,分化为细胞毒性T细胞(cytotoxic T lymphocyte,CTL),直接杀伤病变细胞[85]。UPR与泛素化修饰通过共同调控MHC类分子的表达影响$CD4^+$ T和$CD8^+$ T细胞的功能。E3泛素连接MARCH1泛素化MHC-II使其在B细胞和DCs表面的表达降低,不仅导致抗原呈递受损,同时削弱MHC-I的抗原肽装载能力。UPR信号通路中PERK-eIF2α磷酸化级联激活后,直接抑制MHC-I分子的合成,内源性抗原呈递速率降低[15]。UPR与泛素化修饰损害MHC-II/I的抗原呈递,可能导致$CD4^+$/$CD8^+$ T细胞的激活障碍。在一些疾病中,如糖尿病、特发性血小板减少性紫癜及免疫缺陷病,都会出现

$CD4^+$/$CD8^+$ T细胞数量失衡,这一机制可为这类疾病的诊疗提供思路。因以上涉及的细胞类型较多,故根据UPR与泛素化修饰在各细胞中的机制整理为表格(表1)。

**表1　免疫细胞中泛素化修饰与UPR的协同作用**
**Table 1　Synergistic effect of ubiquitination modification with UPR in immune cells**

| 免疫细胞 | UPR相关机制 | 泛素化修饰相关机制 | 参考文献 |
|---|---|---|---|
| DC | ERS-UPR | HRD1-UBE2J1复合体 | [47] |
| Mø | PERK-CHOP | STAT1/PIAS1复合体 | [49] |
| | ERS-UPR | E3泛素酶SCNN1B | [45] |
| NK | XBP1s | PI3K/AKT通路介导去泛素化修饰 | [54, 55] |
| NKT | IRE1/XBP1s和ATF4/CHOP | ERAD | [56, 57] |
| BAS | ERS-UPR | Cbl | [61-63] |
| MC | IRE1/XBP1s | ERAD | [65, 66] |
| EOS | ERS-UPR | E3泛素酶MARCH2/3 | [71] |
| γδT | ATF3 | E3泛素酶Cbl-b | [73] |
| B cells | IRE1/XBP1 | SEL1L-HRD1 ERAD | [77, 78] |
| Tregs | XBP1s和CHOP | E3泛素酶HRD1 | [80, 81] |

## 4 展望

上述讨论表明,UPR与泛素化修饰的动态平衡不仅存在于单一免疫细胞内,更通过细胞因子及细胞膜分子交互调节多种免疫细胞的功能。ERS与泛素修饰协同调控免疫细胞内蛋白质稳态,在机体免疫应答与疾病病理过程中发挥重要作用。然而,领域内仍存在若干关键科学问题亟待突破。UPR与泛素化修饰的互作模式在不同免疫细胞中展现出显著异质性,例如,HRD1介导DC细胞MHC-I重链降解以确保抗原呈递精确性,却又通过降解IRE1α维持Tregs免疫抑制功能。同一种分子在不同免疫细胞中发挥多重功能的生物学机制亟待解析。UPR与泛素化修饰的协同调控作用确保了细胞内蛋白质的正确折叠、成熟与降解,从而保障了免疫细胞的正常生理功能,并在病理条件下通过协同作用介导疾病的发生发展。针对UPR通路上游激活因子、关键信号分子(如IRE1α、PERK)的抑制剂,或特异性E3泛素连接酶的调节剂,都可能成为新型免疫调节药物。例如,VCP抑制剂已被证明可阻碍ERAD并影响IRE1α的活化,这为肥大细胞白血病的治疗提供了新思路。鉴于UPR与泛素化修饰的协同作用,未来的治疗可能不再是单一靶点的干预,而是通过联合用药,同时调节这两个通路,以达到更优的治疗效果。虽然目前研究大多在理论阶段,但是随着研究不断进步,相关理论成果终将逐步转化为实际应用。总之,本综述不仅加深了我们对免疫细胞内稳态调控的理解,更重要的是,它为免疫相关疾病的精准诊断和靶向治疗提供了丰富的理论依据和潜在的临床转化方向,预示着未来免疫学研究和临床实践的广阔前景。

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