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Endoplasmic reticulum-associated degradation and beyond: the multitasking roles for HRD1 in immune regulation and autoimmunity

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Abstract

Endoplasmic reticulum (ER)-associated degradation (ERAD) is a mechanism against ER stress, wherein unfolded/misfolded proteins accumulated in the ER are transported to the cytosol for degradation by the ubiquitin-proteasome system. The ER resident E3 ubiquitin ligase HRD1 has been identified as a key ERAD factor that directly catalyzes ubiquitin conjugation onto the unfolded or misfolded proteins for proteasomal degradation. The abnormally increased HRD1 expression was discovered in rheumatoid synovial cells, providing the first evidence for HRD1 dysregulation involved in human inflammatory pathogenesis. Further studies shown that inflammatory cytokines involved in rheumatoid pathogenesis including IL-1β TNF-α, IL-17 and IL-26 induce HRD1 expression. Recent studies using mice with tissue-specific targeted deletion of HRD1 gene have revealed important functions of HRD1 in immune regulation and inflammatory diseases. HRD1 has been shown critical for dendritic cell expression of antigens to both CD4 and CD8 T cells. Both TCR and costimulatory receptor CD28 signaling induces HRD1 expression, which promotes T cell clonal expansion and IL-2 production. Together with the fact that HRD1 is required for maintaining the stability of regulatory T cell (Treg) stability, HRD1 appears to fine tone T cell immunity. In addition, HRD1 is involved in humoral immune response by regulating early B cell development and maintaining B cell survival upon recognition of specific antigen. HRD1 appears to target its substrates for ubiquitination through, either ERAD-dependent or -independent, at least two distinct molecular mechanisms in a cell or tissue specific manner to achieve its physiological functions. Dysregulation of HRD1 expression and/or it functions are involved in autoimmune inflammatory diseases in particular rheumatoid arthritis and lupus. Here, we review current findings on the mechanism of HRD1 protein in immune regulation and the involvement of HRD1 in the pathogenesis of autoimmune inflammatory diseases.

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Keywords

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Folding and maturation of proteins in eukaryotic cells occur in the **e**ndoplasmic **r**eticulum (ER). Proteins that fail to acquire their proper structure are retained within the ER and eventually degraded to prevent toxicity by the accumulation of misfolded proteins in the secretory pathway. This turnover is mediated by a mechanism known as ER-associated degradation (ERAD). ERAD is one of the quality control systems in the cell to maintain ER homeostasis and adjust ER capacity in response to environmental cues (1). ERAD requires three steps, substrate transportation from the ER to the cytoplasm (dislocation), ubiquitination by specific ubiquitin ligases and proteolysis by proteasome in cytoplasm (2). The ER chaperone, BiP, plays a critical role to recognize the misfolded proteins (3). The ER-resident nucleotide exchange factor Grp170 triggers nucleotide exchange of BiP (**b**inding **i**mmunoglobulin **p**rotein) to generate ATP-BiP. ATP-BiP disengages from the misfolded substrate, enabling it to retrotranslocate to the cytosol for their degradation through ubiquitin-dependent pathways (3–5). Impaired ERAD functions lead to accumulation of aberrant proteins within the ER and triggers the unfolded protein response (UPR) or ER stress. The UPR pathways are mediated by three major ER transmembrane protei factors, including **p**rotein kinase R-like **e**ndoplasmic **r**eticulum **k**inase (PERK), **i**nositol-**r**equiring **e**nzyme-1α (IRE1α), and **a**ctivating **t**ranscription **f**actor 6 (ATF6) (6–8). IRE1α functions as a protein kinase and endoribonuclease. IRE1α executes an unconventional splicing of the mRNA encoding XBP-1 by removing a 26-base intron (9, 10). Spliced *XBP-1* mRNA encodes a potent transcription factor **X**–**b**ox **p**rotein 1 (Xbp-1s) that activates the expression of several genes involved in protein folding, secretion and degradation(11).

HRD1 is an ERAD ubiquitin ligase.

Several ER-resident E3 ubiquitin ligases have been identified so far (2), with hydroxymethylglutaryl reductase degradation protein 1 (HRD1) as the best characterized in regulating ERAD. HRD1 has a six-transmembrane domain and a RING-H2 motif (Fig. 1), it forms a complex with an ER-resident single-transmembrane protein Hrd3 in yeast or a suppressor/enhancer of Lin-12-like (SEL1L) in mammals, for the degradation of a subset of misfolded proteins in the ER (12, 13) (Fig. 1B). In yeast, Hrd3 is stable protein required for the E3 activity of HRD1 (14). Unlike Hrd3, human SEL1L is an unstable protein, which is restored by the association with HRD1 to trigger its E3 ligase activity (15). In addition, HRD1 interacts with Derlin family proteins to form an ERAD complex with SEL1L (16). The scaffold protein Herp is required for forming an active retrotranslocation complex containing HRD1, SEL1L, and Derlin 2 for ERAD (17). Similar to most of the E3 ubiquitin ligases, HRD1 can catalyze autoubiquitination, and this autoubiquitination of HRD1 plays an essential role in retrotranslocating the misfolded protein from ER lumen to cytoplasm (18, 19).

HRD1 C-terminus is involved in recruitment of signaling molecules.

Accumulated evidences have discovered that the C-terminus cytoplasmic tail of HRD1 is critical for its physiological functions by recruiting a variety of signaling molecules or transcription factors for ubiquitination-mediated degradation. HRD1 has been shown to interact with the tumor suppressor p53 through its linker region between the sixth transmembrane domain and RING finger, and consequently catalyzes p53 ubiquitination (20). Recent studies have demonstrated that HRD1 is a critical regulator in metabolic regulation and energy expenditure. HRD1 destructs the thermogenic coactivator peroxisome proliferator-activated receptor coactivator (PGC)-1β through ubiquitination-mediated degradation. As a consequence, HRD1 deletion resulted in upregulation of PGC-1β target genes and increased mitochondrion number, respiration, and basal energy expenditure in adipose tissue (21). Our laboratory has revealed that mice with HRD1 deletion specifically in the liver display increased energy expenditure and are resistant to high fat diet (HFD)-induced obesity, liver steatosis and insulin resistance due to the elevated activation of pathways for glycolysis and fatty acid oxidation (22). Unexpectedly, liver specific HRD1 gene ablation results in the fragmentation of biological circadian rhythm, which is controlled by hippocampus, indicating that hepatic HRD1 controls the biological clock through a circulating factor. Indeed, HRD1 directly targets CREBH for ubiquitination-mediated degradation to regulate the hepatokine FGF21 production to maintain the circadian rhythm (23). Through analysis of the **p**ro-**o**pio**m**elano**c**ortin (POMC) neuron-specific SEL1 deficient mice, Kim et al discovered that the SEL1/HRD1 complex is required for POMC maturation in preventing mice from age-associated obesity (24). In addition, HRD1 ERAD is required for vasopressin prohormone processing and systemic water homeostasis (25, 26), these studies reveal critical pathophysiological HRD1 functions in tissue and organ-specific manners (Fig. 1). More recently, gene ontology analyses identified a variety of potential HRD1 substrates, many of which function in pathways involved in stress adaptation or immune surveillance (27, 28).

Regulation of HRD1 expression.

As a critical E3 ubiquitin ligase involved in endoplasmic reticulum-associated degradation, it is not surprising that HRD1 is induced by ER stress response. The ER stress downstream transcription factor Xbp-1 spliced form can directly bind to the promoter region of HRD1 and promotes HRD1 mRNA transcription (29, 30). Interestingly, we have discovered that HRD1 controls the protein expression of IRE1α through ubiquitination-mediated degradation to suppress synovial cell apoptosis during rheumatoid arthritis pathogenesis, as well as to maintain intestinal homeostasis (31, 32). Since IRE1α is essential for Xbp-1 mRNA splicing to activate Xbp-1 transcriptional activation, these studies identify a feedback loop in regulating HRD1 expression: on one hand, IRE1α activation induces Xbp-1 mRNA splicing to activate its transcriptional function for the expression of ER stress responsive genes including HRD1; on the other hand, HRD1 destructs IRE1α to suppress Xbp-1 transcriptional activity. In addition to Xbp-1, the MAPK kinase ERK1/2 pathway can be activated upon inflammatory cytokine stimulation, which induces the activation of ETS transcription factor for HRD1 gene transcription (33). At the post-transcription level, it has been shown that the targeted deletion of the adaptor protein SEL1 in the ERAD

complex largely diminishes HRD1 expression possibly due to auto-ubiquitination-mediated degradation (32, 34). In addition, the ER resident ubiquitin specific peptidase USP19 has been identified as a HRD1 deubiquitinase that stabolizes HRD1 protein (35). Therefore, HRD1 expression is tightly controlled at both transcriptional and post-translational levels at different pathophysiological settings.

HRD1 IS A CRITICAL MULTITASKING IMMUNE REGULATOR.

A variety of studies have shown important roles of ER stress response in regulating both innate and adaptive immune response at both physiological and pathological settings (5, 36, 37). The involvement of the altered ERAD protein quality control and/or unfolded protein response contribute to autoimmunity has been elegantly reviewed by Barrera et al (38). This review focuses on one of the ERAD ubiquitin ligases HRD1 in immune regulation and autoimmunity.

HRD1 in antigen presentation.

Early evidence suggests that the ubiquitin pathway is involved in the presentation of viral antigens to MHC class I, because facilitation of viral protein proteolysis by fusion with ubiquitin results in the presentation of viral antigen to CD8 T cells (39). Further studies using cells with a temperature-sensitive defect in ubiquitin conjugation demonstrated that ubiquitin-mediated protein degradation is required for presentation of antigen to MHC I restricted CD8 T cells (40). Meanwhile, type I interferon induces a subclass of proteasomes that contain two MHC-encoded subunits, LMP2 and LMP7 to promote peptide antigen presentation by MHC I (41, 42). The first evidence to indicate that ERAD is involved in regulating the antigen presentation by MHC I is the observation of MHC I protein co-localization with artificial antigen in the ER (43). Huang *et al* showed for the first time that the ER-resident E3 ubiquitin ligase HRD1 functions as a positive regulator for the peptide antigen presentation by MHC I molecules (44). MHC class I heavy chains that fail to achieve their native conformation in complex with both β2-microglobulin and peptide are targeted for ER-associated degradation. In addition, HRD1 and its E2 ubiquitin conjugation enzyme UBE2J1 regulate the homeostatic regulation of MHC class I assembly and expression by directly promoting ubiquitin-conjugation onto the misfolded MHC I molecules (45, 46). Therefore, ERAD-mediated MHC I degradation plays an important role in the homeostatic regulation of MHC class I assembly and expression by dendritic cells (Fig. 2). In addition to HRD1, the E3 ubiquitin ligase TMEM129 has recently joined in the action of ERAD-mediated regulation MHC I expression through its recruitment onto ER by Derlin 1 (47).

Surprisingly, analysis of the phenotypes of CD11c-restriced HRD1 deficient mice, Yang *et al* observed a selective reduction of MHC II expression by CD11c+ dendritic cells (DCs) (36). Interestingly, HRD1 directly recognizes Blimp1, a transcription co-suppresser that inhibits the MHC II transcription activator (CIITA) transcriptional activity (48, 49), as a substrate for ubiquitination and degradation (36). As a consequence, loss of HRD1 functions leads to the elevated Blimp1 expression to suppress MHC-II transcription and MHC-II mediated antigen presentation to CD4 T cells (36) (Fig. 2). Therefore, HRD1 appears to regulate

antigen presentation through two distinct molecular mechanisms: First to regulate MHC-I assembly in the ER by destructing the misfolded β2-microglobulin through ERAD, and second to control MHC II gene transcription through catalyzing Blimp1 ubiquitination and degradation in an ERAD-independent manner (Fig. 2).

HRD1 is an E3 ligase that positively regulates T cell activation.

It has been reported that Xbp-1, a transcription factor of HRD1(30), is induced and activated by TCR and IL-2 stimulation in CD8 T cells. Inactivation of Xbp-1 resulted in impaired CD8 T cell immune response to viral infection (50). More recently, Kemp *et al* has observed that targeted deletion of IRE1α, an ER stress sensor that activates Xbp-1, impairs CD4 T cell differentiation toward Th2 (51). As Xbp-1 is a transcription factor in promoting HRD1 gene expression, these studies imply a possibility that HRD1 functions as a possible positive regulator of T cell immunity. Indeed, Xu *et al* recently discovered that genetic suppression of HRD1 impairs T cell activation and differentiation. HRD1 appears to positively regulate T cell clonal expansion by targeting $p27^{Kip1}$, a cyclin-dependent kinase inhibitor for ubiquitination and degradation. Loss of HRD1 expression results in accumulated $p27^{kip1}$ protein expression and G1/0 cell cycle arrest upon TCR/CD28 ligation (37). Therefore, HRD1 is a TCR/CD28-dependent E3 ubiquitin ligase of $p27^{Kip1}$ in promoting the clonal expansion during early T cell activation (Fig. 2).

In addition to promoting T cell growth, HRD1 functions are essential for IL-2 production and CD4 T cell differentiation toward both Th1 and Th17 (37). However, HRD1 appears to regulate cytokine production by CD4 T cells independent of its activity in catalyzing $p27^{Kip1}$ ubiquitination and degradation, because further deletion of $p27^{Kip1}$ in HRD1-null T cells, while rescued T cell proliferation, failed to restore IL-2, IFN-γ and IL-17 production (37). It has also been shown that the transcriptional co-suppresser Blimp1 inhibits T cell production of cytokines including IL-2, IFN-γ and IL-17(52, 53). Given the fact that HRD1 targets Blimp1 for ubiquitination and degradation in DCs (36), it is speculated that HRD1 may regulate T cell cytokine production through Blimp1 ubiquitination and degradation.

HRD1 fine-tunes T cell immunity through maintaining Treg stability.

In the inflammatory environment, the suppressive regulatory T cells (Tregs) are often unstable and fail to maintain their suppressive functions (54). Since inflammatory cytokines induce the ER stress responses, in particular the activation of IRE1α pathway (55), we reasoned whether the ER stress response is involved in Treg instability. Indeed, treatment with a pharmacological ER stress inducer dramatically destabilized Treg cells while an ER stress inhibitor largely blocked inflammatory cytokine-induced Treg instability. The HRD1 ERAD pathway plays a critical role in FoxP3 expression, stability, and immune suppressive functions. Conditional genetic deletion of HRD1 specifically in Tregs results in a significant reduction in FoxP3 expression during polarization in $HRD1^{fl/fl}$-$FoxP3^{cre}$ Treg with an increase in IRE1α, but not in PERK or ATF6, activity. More importantly, treatment with either the ER stress inhibitor or the IRE1α inhibitor could rescue HRD1-null Tregs from inflammatory cytokine-induced Treg destabilization. Therefore, HRD1 fine-tunes T cell immune homeostasis through promoting T cell activation and Treg stabilization (56).

HRD1 plays critical role at two distinct stages in B cell immunity.

Activation of IRE1α-Xbp-1 pathway has been detected during B cell development and activation stages (57). Recent studies by Ji *et al* report that B cell-specific loss of SEL1L, an ER adaptor that forms a complex with HRD1 for ERAD (58), leads to a severe developmental block during transition from large to small pre-B cells. Mechanistically, SEL1L selectively recognizes and targets the pre-B cell receptor (pre-BCR) for proteasomal degradation. The pre-BCR complex accumulates both intracellularly and at the cell surface in SEL1L-deficient pre-B cells, leading to persistent pre-BCR signaling and pre-B cell proliferation. Our laboratory has observed a similar B cell developmental defect in B cell-specific HRD1 knockout mice (33). Therefore, the SEL1L-HRD1 complex recognizes pre-BCR complex as an ERAD substrate in regulation B cell development (Fig. 3).

During the activation phase, HRD1 plays an important role in protecting B cells from activation-induced apoptosis because loss of HRD1 functions results in the increased B cell death upon either BCR or LPS stimulation (57). While HRD1 has been defined as an anti-apoptotic factor to suppress ER stress-induced cell death, HRD1 appears to inhibit activation induced B cell death through an ER stress-independent mechanism. HRD1 deletion does not cause increased ER stress response and further deletion of CHOP (59, 60), a downstream transcription factor in regulating ER stress-induced cell death, could not rescue HRD1-null B cells from the activation-induced apoptosis (57). Also, further IRE1α deletion could not rescue HRD1-null B cells from activation-induced B cell apoptosis (57, 61). Importantly, the expression of Fas, the death receptor that is required for the activation-induced B cell death, is upregulated at the protein but not mRNA levels in HRD1-null B cells, implying that HRD1 targets the death receptor Fas for degradation to protect B cells from activation induced B cell apoptosis. In fact, HRD1 interacts with Fas and catalyzes Fas ubiquitination and degradation. HRD1 recognizes pre-BCR complex and Fas through two distinct regions. Interaction with pre-BCR complex is mediated by the N-terminal region of HRD1, which binds to the misfolded proteins for ubiquitination and degradation. In contrast, the C-terminal proline-rich region of HRD1 is required for its interaction with Fas (57) (Fig. 1). It is likely that HRD1 regulates B cell development and activation through two distinct molecular mechanisms (Fig. 3).

HRD1 in regulating the innate immune response:

In addition to its important roles in antigen presentation, HRD1 was identified to function as a critical positive regulator that enhances TLR-induced inflammatory cytokine production in macrophages during bacterial infection. At the molecular level, HRD1 specifically targets the deubiquitinase USP15 to attenuate USP15-mediated iKBα stabilization and consequently leads to NF-kB activation, linking, for the first time, ERAD functions to microbial infection (62). In addition, HRD1 has been shown as an ubiquitin ligase for degradation of CD155, the ligand of CD226 in tumor microenvironment in hepatic cell carcinoma. Since, CD226 is a critical receptor for NK cell functions, HRD1-mediated suppression of CD155 expression impairs the NK cell immunity to liver cancer (63).

HRD1 IN AUTOIMMUNE INFLAMMATORY DISEASES.

Rheumatoid Arthritis:

Through an immunoscreening using antirheumatoid synovial cell antibody, Amano *et al* observed that HRD1 expression is significantly uprogelated in synovial fibroblasts from patients with rheumatoid arthritis (RA) and renamed HRD1 to Synoviolin. They further showed that mice overexpressing this HRD1 developed spontaneous arthropathy. Conversely, reduced expression of HRD1 protected mice from collagen-induced arthritis (64). Further studies by our laboratory demonstrated that the proinflammatory cytokines IL-1β and TNF-α are responsible for inducing HRD1 expression in mouse synovial fibroblasts (65, 66). In addition, both IL-17 and IL-26, two pathogenic cytokines in RA disease development and progression were found to induce HRD1 expression during RA development (65, 67). Therefore, cytokine-induced HRD1 expression is a critical pathogenic factor in RA through the anti-apoptotic functions of HRD1.

While the underlying molecular mechanisms remain largely unknown, it has been speculated that elevated HRD1 expression promotes RA development and progression through its anti-apoptotic activity of suppressing the death of synovial fibroblasts during synovitis (64). HRD1 achieves its anti-apoptotic functions through at least three distinct molecular mechanisms: First, our laboratory has discovered that HRD1 protects ER stress induced cell death through targeting the ER stress sensor IRE1α for ubiquitination and degradation (31, 61). Since IRE1α leads to caspase-12 cleavage and triggers cell apoptosis (68), HRD1 suppresses synovial cell apoptosis through targeting IRE1α for degradation. Second, HRD1 promotes cell cycle progression and survival by targeting tumor suppressor gene p53 for ubiquitination (20). Recently, our laboratory has shown that HRD1 protects the activation-induced B cell apoptosis through its E3 ligase activity in marking the death receptor Fas for ubiquitination-mediated degradation. Given that both HRD1 and Fas are ubiquitously expressed and involved in regulating the death of a variety types of cells, HRD1-mediated Fas degradation could be a common molecular mechanism in the death pathway unrestricted to B cells (57). In addition, HLA-B27 misfolded heavy chain dimers is involved inflammatory arthritis by inducing the unfolded protein response. Interestingly, HRD1 ERAD can recognize the misfolded HLA-B27 for degradation and consequently suppresses HLA-B27 induced inflammation (69, 70).

A partial suppression of HRD1 protects mice from collagen-induced arthritis, implying that HRD1 is a potential therapeutic target for RA. Interestingly, a HRD1 specific inhibitor, LS-102, which inhibits the E3 ligase catalytic activities of HRD1 has been identified by a high throughput screening (71). Of note, LS-102 suppresses the proliferation of rheumatoid synovial cells, and significantly reduces the severity of disease in a mouse model of RA (71). Therefore, even though further investigations are needed, it is an optimistic expectation for the use of HRD1 inhibitors to treat human RA as well as other types of autoimmune inflammatory diseases.

Similar to HRD1, the E3 ubiquitin ligase Ro52/Trim21 is targeted as an autoantigen in systemic lupus erythematosus, rheumatoid arthritis and Sjögren’s syndrome. Polymorphisms in the Ro52 gene have been linked to these autoimmune conditions (72–76). Of note,

TRIM21 has been indented as binding partner of Fc fragment and it functionally interacts with IgG1 and regulates its quality control via the ERAD system (77–79). It will be interesting to further elucidate the crosstalk between TRIM21 and HRD1 in autoimmune pathogenesis.

Other types of autoimmune inflammatory diseases:

A possible link between HRD1 and human multiple sclerosis is seen in the increase of HRD1 expression in T cells from patients with multiple sclerosis (MS) (37). This elevated HRD1 expression plays critical roles in human T cell activation and is possibly involved in immune tolerance. In mice, targeted deletion of HRD1 specifically in T cells largely protects mice from myelin-oligodendrocyte-glycoprotein-induced experimental autoimmune encephalomyelitis, a mouse autoimmune central nervous system disease that resembles human MS. In addition, the reduced expression or loss-of-function mutations in the Fas protein or its ligand lead to lupus-like systemic autoimmune diseases in mice and humans (80–83). Fas-mediated cell death has been known as a critical mechanism to eliminate unwanted autoreactive B cells. The fact that HRD1 targets Fas to protect B cells from activation induced apoptosis, provides a possible link between HRD1 and lupus pathogenesis. Important work is waiting to be done in elucidating HRD1-mediated Fas ubiquitination and degradation in lupus and other B cell-mediated autoimmune diseases.

PERSPECTIVES AND FUTURE DIRECTIONS.

How isHRD1-mediated ubiquitination regulated?

Much progress has been made during the last few decades to understand how HRD1-mediated ubiquitination and degradation of misfolded proteins after translocation from ER lumen to cytoplasmic compartment during ERAD occurs. Interestingly, several recent studies have revealed that HRD1-mediated ubiquitination of certain proteins, including p53 (20), Nrf2 (84), Blimp1 (36), $p27^{Kip1}$(37) and Fas (57), uncouples with extensive UPR response, implying an ERAD-independent molecular mechanism in protein degradation. The N-terminal ER lumen domain is often required for the recognition of the misfolded protein substrates during ERAD. In contrast, HRD1 recognizes p53, Nrf2, Blimp1, p27Kip1 and Fas through its C-terminal cytoplasmic region (Fig. 1A). In this case, the specific extracellular stimuli rather than pharmacological ER stress inducers such as tunicamycin can induce HRD1 interaction with its targeting proteins. For example, TCR and CD28 stimulation enhances HRD1 interaction with $p27^{Kip1}$ in T cells, and LPS stimulation triggers Blimp1 interaction with HRD1 in DCs in regulating MHC-II transcription (36, 37). It remains a molecular puzzle underlying how extracellular signaling regulates HRD1 interaction with its non-ERAD substrates to achieve its physiological functions.

How does HRD1 target nuclear transcription factors for ubiquitination?

One of the interesting recent discoveries is that the ER spanning E3 ubiquitin ligase targets several transcription factors for ubiquitination-mediated degradation. p53 was the first identified transcription factor substrate of HRD1, which predominantly co-localizes with HRD1 in the perinuclear regions of cells, but not in their nuclei, suggesting a cytoplasmic recognition of p53 by HRD1. The subcellular interactions of HRD1 with other nuclear

factors including Nrf1, Nrf2, Blimp1 and PGC-1β has not been studied further. Considering the fact that HRD1 is an ER transmembrane protein (Fig. 1), it is unlikely that HRD1 interacts with these transcription factors in the nucleus. However, bioinformatics analysis of the HRD1 amino acid sequence reveals two putative cleavage sites for both Site-1 protease (S1P) and Site-2 protease (S2P) (Fig. 1), two ER resident proteases that cleave ATF6 in regulating ER stress response. Importantly, both sites are located in the region between the RING finger and the 6th transmembrane domain of HRD1, where cleavage results in the production of a protein with an E3 ligase catalytic RING finger and a long C-terminal proline-rich cytoplasmic tail. Therefore, it is possible that this cleaved HRD1 may function as a nuclear E3 ligase for degradation of its nuclear substrates. More recently, ERAD machinery has been shown to control inner nuclear membrane protein quality, suggesting a possibility that HRD1 targets nuclear proteins at the inner nuclear membrane (85).

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Abbreviations:

HRD1	Hydroxymethylglutaryl reductase degradation protein 1
ER	Endoplasmic reticulum
ERAD	ER-associated degradation
IL-1β	Interleukin 1 beta
TNF-α	Tumor necrosis factor alpha
BiP	Binding immunoglobulin protein
XBP-1	X-box protein 1
RING	Really interesting new gene
SEL1	Suppressor/enhancer of Lin-1-like
HFD	High fat diet
POMC	pro-opiomelanocortin
IRE1α	Inositol-requiring enzyme 1 alpha
PERK	Protein kinase R-like endoplasmic reticulum kinase
ATF6	Activating transcription factor 6
CREBH	cAMP-responsive element-binding protein H
FGF21	Fibroblast growth factor 21

RA	Rheumatoid arthritis
LMP2	Latent membrane protein 2
MHC	Major histocompatibility complex
CIITA	Class II transcription activator
TCR	T cell receptor
BCR	B cell receptor
Skp2	S-phase kinase associated protein 2
CD28	Cluster of differentiation 28
DC	Dendritic cells
Blimp1	Beta-interferon gene positive regulatory domain I-binding factor
Tfh	T follicular help cells
Treg	T regulatory cells
FoxP3	folk head box protein 3
TRAF2	(tumor necrosis factor receptor (TNFR)-associated factor-2)
JNK	c-Jun n-terminal kinases
MS	Multiple sclerosis
IFN-γ	Interferon gamma
Nrf2	Nuclear factor erythroid 2–related factor 2
T2D	type 2 diabetes

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Highlights

- HRD1 is an ER-resident ubiquitin ligase known to regulate ERAD.
- HRD1 regulates both T cell and B cell immunity
- HRD1 is involved in antigen presentation process
- The altered HRD1 expression is associated with autoimmune inflammatory diseases

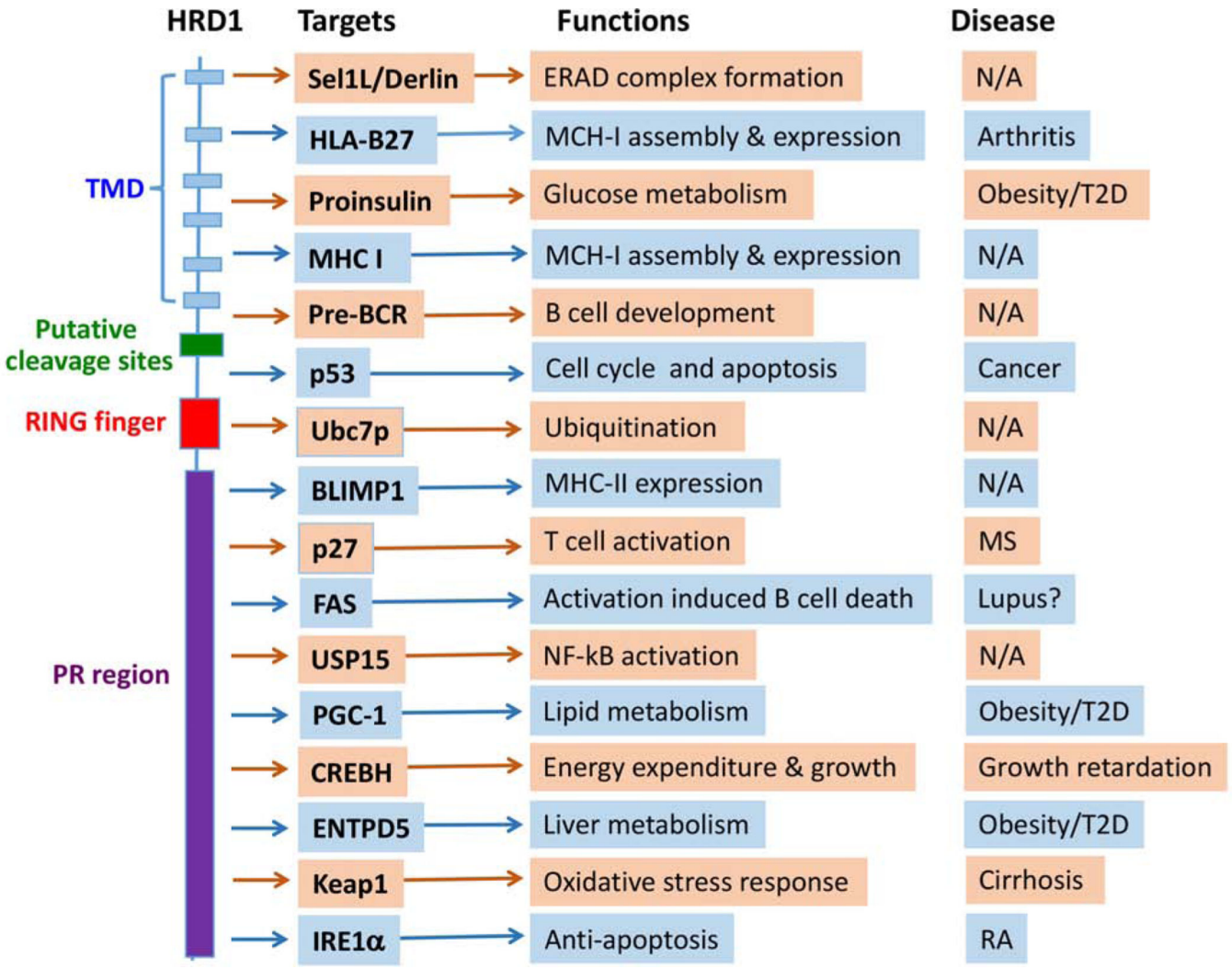

Figure 1. HRD1 structure and its substrates.

HRD1 protein has six N-terminal transmembrane domains (TMDs), a RING finger domain, and C-terminal proline-rich (PR) cytoplasmic tail. The HRD1 binding proteins, functional consequences of their interactions and possible disease associations are highlighted.

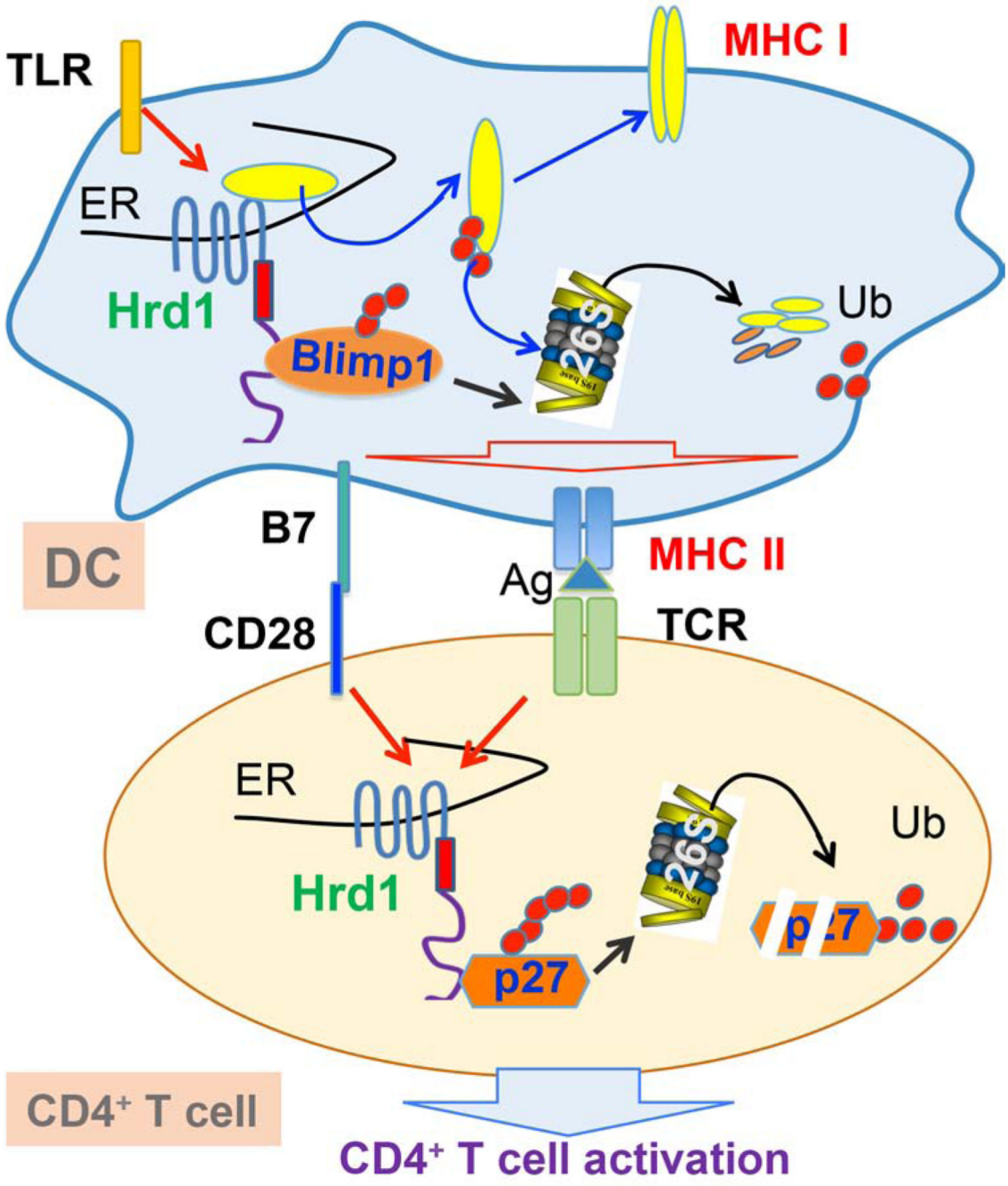

Figure 2. Illustration of HRD1 functions in DCs and T cells.

HRD1 targets MHC class I proteins for degradation as a quality control mechanism for MHC class I cell surface expression. Meanwhile, dendritic HRD1 C-terminus interacts with the transcription suppresser Blimp1 for ubiquitination-mediated degradation, which consequently activates CIITA for MHC class II transcription. HRD1 also functions as an E3 ubiquitin ligase to promote p27kip1 destruction for T cell clonal expansion upon TCR and CD28 stimulation.

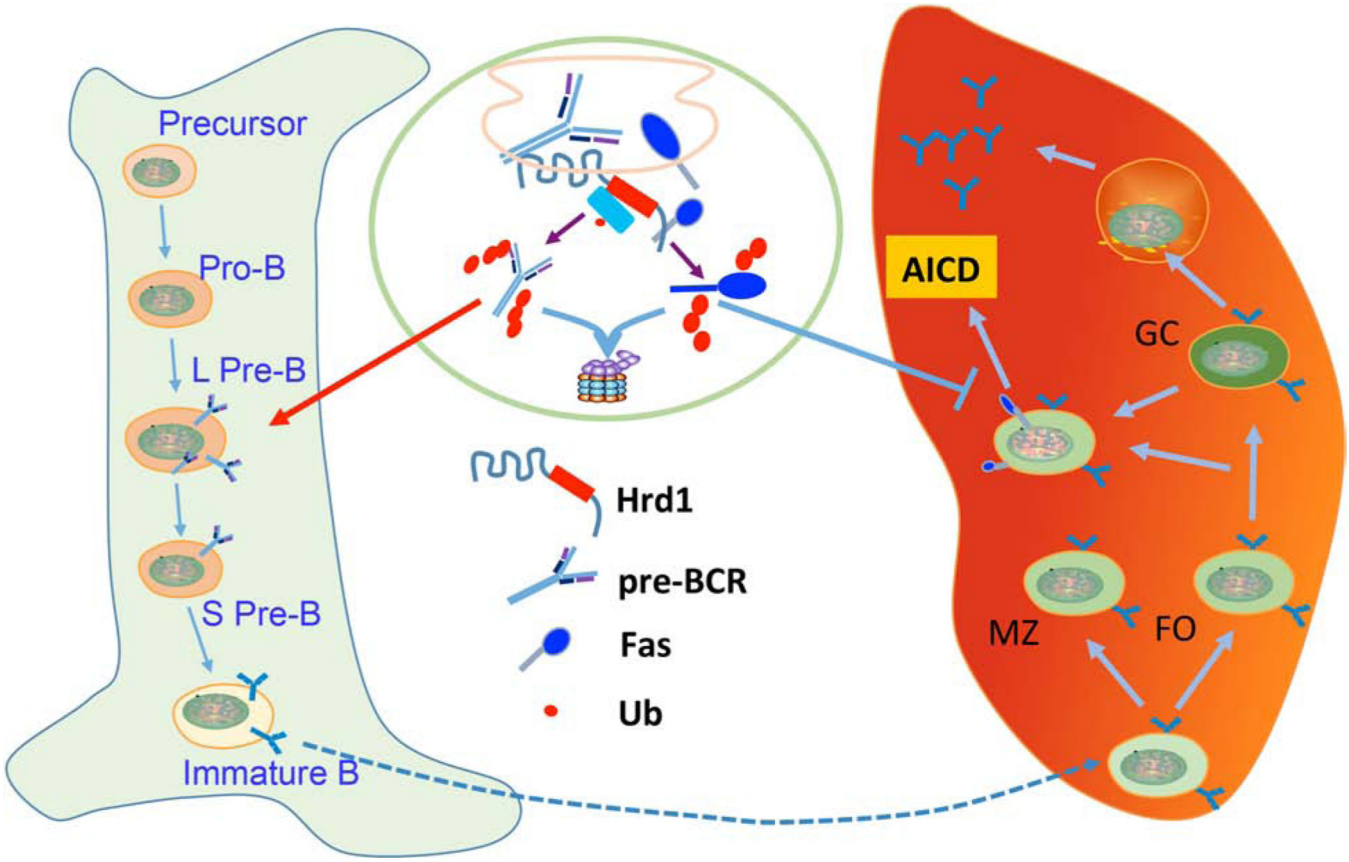

Figure 3. HRD1 regulates B cell immunity at two distinct stages.

HRD1 ERAD plays a critical role in quality control of pre-BCR processing, specifically during the transition from large (L-) to small pre-B (S PreB) cell stage during B cell development in bone marrow. The immature B cells then home to the spleen and HRD1 protects B cells from the activation-induced apoptosis through targeting the death receptor Fas for ubiquitination and proteasomal degradation.