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ABSTRACT

IL-17 activates NF-κB and induces expression of proinflammatory genes. IL-17 drives disease in autoimmune conditions, and anti–IL-17 Abs have shown impressive success in the clinic. Although produced by lymphocytes, IL-17 predominantly signals in fibroblasts and epithelial cells. IL-17–driven inflammation is kept in check by negative feedback signaling molecules, including the ubiquitin editing enzyme A20, whose gene TNFAIP3 is linked to autoimmune disease susceptibility. The A20 binding inhibitor of NF-κB activation 1 (ABIN-1) is an A20-binding protein encoded by the TNIP1 gene, which is also linked to autoimmune disease susceptibility including psoriasis. Accordingly, we hypothesized that ABIN-1 might play a role in negatively regulating IL-17 signaling activity. Indeed, ABIN-1 enhanced both tonic and IL-17–dependent NF-κB signaling in IL-17–responsive fibroblast cells. Interestingly, the inhibitory activities of ABIN-1 on IL-17 signaling were independent of A20. ABIN-1 is a known NF-κB target gene, and we found that IL-17–induced activation of NF-κB led to enhanced ABIN-1 mRNA expression and promoter activity. Surprisingly, however, the ABIN-1 protein was inducibly degraded following IL-17 signaling in a proteasome-dependent manner. Thus, ABIN-1, acting independently of A20, restricts both baseline and IL-17–induced inflammatory gene expression. We conclude that IL-17–induced signals lead to degradation of ABIN-1, thereby releasing a constitutive cellular brake on NF-κB activation.

INTRODUCTION

Interleukin 17A (IL-17) is produced by lymphocytes and acts on tissue fibroblasts and epithelial cells to activate inflammatory gene expression. IL-17 is required to clear extracellular pathogens, particularly fungi such as Candida albicans. However, excessive IL-17 signaling is associated with autoimmune diseases such as psoriasis, psoriatic arthritis, and ankylosing spondylitis, among others. IL-17 blocking therapies have shown considerable efficacy in treating psoriatic patients, and are being evaluated for various other conditions (2).

The mechanisms of signaling mediated by IL-17 are incompletely defined. Produced by Th17 cells and a variety of innate lymphocyte subsets, IL-17 and its receptor belong to a subclass of
cytokines with distinct structural properties compared with other cytokine superfamilies. After IL-17 binds to its receptor, numerous signaling intermediates are engaged to transduce downstream signaling. One key early event is activation of the Act1 and TRAF6 E3 ubiquitin ligases. These in turn lead to degradation of the NF-κB transcription factor (3–5). Consequently, genes with promoters containing NF-κB–binding elements are upregulated by IL-17 stimulation, with IL-6 (Il6) and Lipocalin-2 (Lcn2) being prototypical IL-17 target genes (6).

To date, the mechanisms that constrain the IL-17 pathway are not well understood, which is an important issue in light of the autoimmune potential of this cytokine. Recently, we showed that the ubiquitin editing enzyme A20 inhibits IL-17 signaling by de-ubiquitinating TRAF6 and thereby limiting NF-κB and MAPK activation (7). Moreover, IL-17 upregulates A20 expression, establishing a negative feedback loop that restricts IL-17–driven inflammation. A20 is encoded by TNFAIP3, a genetic locus frequently associated with human autoimmune diseases. In seeking to understand how IL-17 controls autoimmunity, we evaluated other genetic loci connected to IL-17-driven autoimmune conditions. The A20-binding inhibitor of NF-κB activation 1 (ABIN-1) is an A20-binding protein coded by the TNIP1 gene. ABIN-1 single nucleotide polymorphisms are associated with psoriasis in human genome–wide association analyses (8–11). Additionally, mice with keratinocytes lacking ABIN-1 are more sensitive to imiquimod-induced dermatitis, a model of psoriasis (12). Because IL-17 signaling is associated with psoriasis and inhibited by A20, we hypothesized that ABIN-1 might also serve as a downstream inhibitor of the IL-17 signaling pathway.

In this study, we demonstrate that ABIN-1 constitutively restricts the basal expression of IL-17 target genes such as Il6 in fibroblasts and stromal cells. ABIN-1 also negatively regulates IL-17–induced production of Il6, Lcn2, and other NF-κB–dependent genes, although not all IL-17–inducible genes are affected. Although ABIN-1 is known to interact with A20, we found that A20 is not needed for ABIN-1–mediated inhibition of IL-17 signaling. Additionally, IL-17 induced expression of ABIN-1 (Tnip1) mRNA, driven through its proximal promoter. Surprisingly, however, ABIN-1 protein levels were reduced following IL-17 signaling; an event that was mediated by proteasomal degradation. Thus, IL-17 signaling serves to release the ABIN-1–controlled brake on inflammation, revealing a new regulatory circuit in the IL-17 inflammatory pathway.

MATERIALS AND METHODS

Abs and reagents

Abs. Abs used were ABIN-1 (SC134660; Santa Cruz Biotechnology, Santa Cruz, CA or 4664; Cell Signaling, Beverly, MA), IκBα (SC371; Santa Cruz Biotechnology), α-tubulin (ab40742; Abcam, Cambridge, MA), and β-actin (ab49900; Abcam). Secondary Abs were from Thermo Fisher Scientific. Inhibitors were MG132 (474790–100UG, 20 μM), staurosporine (569396, 100 nM), and inhibitor of NF-κB kinase (IKK) inhibitor VII (401486-1MG, 10 μM; EMD MilliporeSigma, Billerica, MA).

HEK293T cells were cultured in DMEM and ST2 cells and murine embryonic fibroblasts (MEFs) were cultured in α-MEM (Sigma-Aldrich, St Louis, MO) containing 10% FBS with l-glutamine and antibiotics (Invitrogen). Transfections were performed with Fugene HD (Promega, Madison, WI) or Lipofect (SigmaGen, Rockville, MD). Plasmids expressing ABIN-1, the ABIN-1 promoter, and the Lcn2 promoter were previously described (13–15). Luciferase assays were performed as described (7, 14). Small interfering RNAs (siRNAs) were from Dharmacon (GE, Lafayette, CO): Tnip1 (ABIN-1) (L-047652-01), Tnfaip3 (A20) (L-058907-02), and nontargeting mock (D-001810-10-20). siRNA transfections were performed 48 h prior to stimulation. In all cases efficiency of knockdown was confirmed by quantitative PCR (qPCR).

RNA isolation, qPCR, and ELISA

RNA was extracted using RNAeasy Kits (74106; Qiagen) and cDNA was made to perform qPCR. Primers were from Qiagen: Tnfaip3 (QT00134064), Lcn2 (QT00113407), Ccl20 (QT00098875), Lcn2 (QT00134064), Gapdh (QT00143934), and Nfkbia (QT00142394). Relative gene expression was normalized to Gapdh. ELISA kits were from eBioscience.

Immunoprecipitation and immunoblotting

Cells were lysed on ice for 20 min in lysis buffer (1% NP40, 150 mM NaCl, 50 mM Tris pH 8.0, 2 mM NaF) supplemented with 1 mM Na2VO4, 50 mM PMSF, 10 mM β-glycerophosphate disodium salt, and a protease inhibitor mixture (Sigma-Millipore). Samples were boiled in running buffer and immunoblotted. Band intensity was analyzed using AlphaView SA Version 3.4.0 (Protein Simple, San Jose, CA).

Statistics

To assess significance, we used the Student t test, ANOVA with post hoc Tukey analysis, or linear regression. A p value < 0.05 was considered significant. Error bars reflect the mean ± SEM of replicates within individual experiments or pooled data, as indicated in the figure legends. All experiments were repeated at least twice.

RESULTS

ABIN-1 inhibits both basal and IL-17 induced gene expression

To delineate the role of ABIN-1 in IL-17–mediated signaling, we assessed IL-17 signaling in immortalized MEFs lacking ABIN-1 (16). Cells were treated with IL-17 over a 24 h period, and IL-6 in culture supernatants was assessed by ELISA. At baseline, ABIN-1−/− fibroblasts secreted significantly more IL-6 than ABIN-1+/+ cells (Fig. 1A). Similarly, ABIN-1−/− cells treated with IL-17 expressed more IL-6 than IL-17–stimulated ABIN-1+/+ cells. Consistent with these findings, elevated expression of Il6 mRNA was observed in ABIN-1−/− MEFs, both at baseline and after IL-17 stimulation (Fig. 1B). These results indicate that ABIN-1 restricts
FIGURE 1. ABIN-1 inhibits tonic and IL-17–dependent gene expression in mesenchymal cells.
(A) Kinetics of ABIN-1–mediated inhibition of IL-6 expression. ABIN-1+/+ or ABIN-1−/− fibroblasts were treated with IL-17 (200 ng/ml) for the indicated times, and IL-6 in conditioned supernatants was measured by ELISA. Data are representative of three experiments. Data are presented as mean values; *p < 0.05, two-way ANOVA with Sidak multiple comparisons test analyzing all groups.
(B) ABIN-1 restricts Il6 basal expression. ABIN-1+/+ or ABIN-1−/− fibroblasts were treated with IL-17 for 3 h, and Il6 mRNA was assessed by qPCR and normalized to Gapdh. *p < 0.05, two-way ANOVA with Sidak multiple comparisons test compared with untreated ABIN-1+/+ sample.
(C) ABIN-1 reconstitution inhibits Il6 expression. (Continued)
both tonic and IL-17-dependent IL-6 expression. To confirm that ABIN-1 limits IL-6 expression levels and to rule out the possibility that this effect was restricted to a particular MEF line, ABIN-1−/− fibroblasts were reconstituted with ABIN-1 by transfection. Cells were then stimulated with IL-17 for 3 h and Il6 mRNA was measured by qPCR. Consistent with its role as an inhibitor of inflammatory signaling, reconstitution with ABIN-1 decreased Il6 production compared with cells transfected with a control vector (Fig. IC).

To verify the inhibitory activity of ABIN-1 in another setting, we silenced ABIN-1 with siRNA in ST2 cells, a mouse bone marrow stromal cell line that responds robustly to IL-17 (Fig. 1D) (14). Indeed, knockdown of ABIN-1 led to increased expression of IL-6 at baseline and following IL-17 stimulation (Fig. 1E). Il6 mRNA was similarly enhanced upon ABIN-1 knockdown, as was expression of other IL-17 target genes including Lcn2 and Cxcl1 (Fig. IF). However, not all IL-17-induced genes were impacted by ABIN-1 deficiency; for example, Ccl20 and Nfkbia (encoding IκBα) are IL-17 target genes that are restricted by A20 but not by ABIN-1 (Fig. IF) (7). Together, these results demonstrate that ABIN-1 is a negative regulator of tonic and IL-17–induced signaling, selectively controlling expression of a subset of IL-17 target genes.

**ABIN-1 inhibits IL-17R signaling independently of A20**

Because ABIN-1 was identified based on its ability to bind A20, we asked whether ABIN-1–mediated inhibition of IL-17R signaling is dependent on A20 (17). Accordingly, we knocked down ABIN-1 in A20−/− fibroblasts by RNA silencing. As shown, reduced expression of ABIN-1 led to enhanced Il6 and Lcn2 expression, both at baseline and after IL-17 stimulation, similar to wild-type MEFs and ST2 cells (Fig. 2A). In an independent approach to address the role of A20 in ABIN-1 activity, we cotransfected A20−/− MEFs with ABIN-1 together with a luciferase reporter driven by the Lcn2 promoter (18). Cells were stimulated with IL-17 for 6 h and Luc activity assessed. As we previously reported, A20−/− fibroblasts showed only a modest responsiveness to IL-17, probably because baseline NF-κB is constitutively high in the absence of A20 (7). Nonetheless, Lcn2-promoter activity was markedly reduced upon transfection of ABIN-1 or A20, confirming that A20 is dispensable for the inhibitory function of ABIN-1 (Fig. 2B). As a third method to assess the role of A20, we transfected ST2 cells with the Lcn2 luciferase reporter with either a full-length ABIN-1 or a truncated mutant lacking the A20-binding domain (but retaining the NF-κB–inhibitory C-terminal domain) (Fig. 2C) (15). In response to IL-17, both the full-length and truncated forms of ABIN-1 inhibited IL-17–dependent Lcn2-promoter activation (Fig. 2C). Collectively, these findings demonstrate that ABIN-1 suppresses IL-17 activity and tonic inflammatory signaling independently of A20.

**ABIN-1 regulates IL-17–activated NF-κB signaling**

ABIN-1 is known to inhibit NF-κB in the context of TNF-α stimulation, and the above results suggested ABIN-1 suppressed NF-κB–dependent genes in the IL-17 pathway as well (19–22). An early step in the canonical NF-κB signaling pathway is phosphorylation of the inhibitor IκBα, which leads to its degradation by the proteasome, releasing NF-κB for nuclear translocation. Moreover, the gene encoding IκBα is induced in an NF-κB–dependent manner, establishing a negative feedback loop (23). To determine whether ABIN-1 targets NF-κB in the IL-17 signaling cascade, we assessed IL-17–dependent IκBα degradation in ABIN-1−/− fibroblasts. In ABIN-1−/− cells transfected with a control empty vector (EV), IκBα was degraded within 15 min following IL-17 stimulation and remained at low levels for as long as 60 min poststimulation (Fig. 3A, lanes 5–8). In contrast, in ABIN-1−/− fibroblasts reconstituted with ABIN-1, IκBα was restored to basal levels by 60 min (Fig. 3A, lane 4). Therefore, there is prolonged activation of NF-κB signaling when ABIN-1 is deficient. These data indicate that ABIN-1 inhibits IL-17–dependent NF-κB signaling upstream of IκBα degradation.

To confirm that ABIN-1 inhibits NF-κB, we knocked down ABIN-1 in ST2 cells and evaluated NF-κB activation by IL-17. In ST2 cells transfected with a control (mock) siRNA IκBα returned to normal levels 60 min after IL-17 stimulation (Fig. 3B, lane 4). However, when ABIN-1 was reduced, cells deficient in this molecule could not re-establish pretreatment levels of IκBα (Fig. 3B, lane 8). These data suggest that ABIN-1 is required to inhibit IL-17–dependent NF-κB signaling upstream of IκBα.

To further define the mechanism by which ABIN-1 inhibits IL-17 signaling, we measured IL-17–dependent Lcn2 promoter activation in ST2 cells transfected with full-length ABIN-1 or a mutant with a nonfunctional ubiquitin binding domain (UBAN) (15). Whereas the full-length ABIN-1 inhibited IL-17–dependent Lcn2 promoter activation, the UBAN mutant did not impair basal

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ABIN-1−/− fibroblasts were transiently transfected with an ABIN-1–expressing plasmid or EV. After 24 h, cells were treated with IL-17 for 3 h and Ifnα was assessed by qPCR. Data are presented as the fold-induction of Ifnα in IL-17–stimulated cells compared with unstimulated samples. Data are normalized to untreated cells transfected with the same plasmid. *p < 0.05, two-way ANOVA with Sidak multiple comparisons test compared with untreated. (D) ABIN-1 knockdown efficiency. ST2 cells were transfected with siRNA targeting ABIN-1 or a scrambled siRNA (mock) control. ABIN-1 (Tnip1) expression was assessed by qPCR (left) and ABIN-1 protein by immunoblotting (right). *p < 0.05, two-way ANOVA with Sidak multiple comparisons test compared with mock, unstimulated cells. (E) ABIN-1 silencing enhances tonic and IL-17–induced IL-6 production. ST2 cells were transfected with the indicated siRNAs. After 48 h cells were stimulated with IL-17 for 3 h, and secreted IL-6 was assessed by ELISA. *p < 0.05, two-way ANOVA with Sidak multiple comparisons test compared with mock unstimulated cells. (F) ABIN-1 silencing enhances tonic and IL-17–induced expression of some but not all IL-17 target genes. ST2 cells from (E) were analyzed for the expression of the indicated genes by qPCR. *p < 0.05, two-way ANOVA with Sidak multiple comparisons test compared with mock unstimulated cells. (B–F) Data are representative of three independent experiments.
signaling and partially inhibited IL-17 signaling (Fig. 3C). This may suggest that ABIN-1 restricts NF-κB activity by different mechanisms, with the IL-17–dependent activity being UBAN dependent. Thus, ABIN-1 is a negative regulator of NF-κB activation in response to IL-17 signaling. Additionally, the UBAN of ABIN-1 is required to inhibit both tonic and IL-17–induced signaling.

**IL-17 signaling differentially regulates ABIN-1 mRNA and protein**

IL-17 induces several known signaling inhibitors to establish feedback signaling loops, including IkBα, A20, and Regnase-1/MCP1-induced protein 1, all of which are regulated by NF-κB. ABIN-1 is also a known NF-κB target gene, raising the possibility that IL-17 might also induce its expression (24). Accordingly, we measured ABIN-1 mRNA by qPCR following IL-17 stimulation. A linear regression model showed that IL-17 significantly, albeit modestly, induced ABIN-1 (Tnip1) mRNA over time, resulting in ~2-fold increased levels over 2 h (Fig. 4A). This induction was NF-κB dependent, as expression was blocked in the presence of an IKK inhibitor (Fig. 4B). Moreover, IL-17 induction of ABIN-1 occurred at the level of the promoter, as verified in ST2 cells transfected with the Lcn2-promoter reporter together with FL or 444–647 forms of ABIN-1. Then 24 h posttransfection, cells were stimulated with IL-17 for 6 h and luciferase activity measured. *p < 0.05, two-way ANOVA with Tukey multiple comparisons test compared with cells transfected with E.V. and treated with IL-17 in (C) and (B), or with cells treated with mock siRNA and stimulated with IL-17 (A). Data are representative of three independent experiments.

![Image](https://doi.org/10.4049/immunohorizons.1700035)
zero) time point (Fig. 4C). A similar trend was seen in MEFs (Supplemental Fig. 2A, 2B). To determine whether the reduced ABIN-1 levels were due to proteasomal degradation, cells were treated with IL-17 in the presence of the proteasome inhibitor MG132. Blocking proteasome function prevented ABIN-1 protein degradation after IL-17 treatment, which was most notable at the early (15 min) time point (Fig. 4D). These data indicate that, even though the ABIN-1 promoter is activated by IL-17, ABIN-1 is inducibly degraded in an IL-17–dependent manner. This unexpected finding suggests that IL-17 signaling releases a brake in inflammation that is normally controlled by ABIN-1.

**DISCUSSION**

Exacerbated IL-17R signaling is associated with psoriasis and other autoimmune conditions (2, 26–28). Accordingly, it is not surprising that there are negative regulators that act on the IL-17 signaling cascade to prevent the overexuberant inflammatory responses that underlie tissue pathology. Notably, many of these inhibitory pathways converge on NF-κB activation (3). The development of autoimmunity is associated with polymorphisms in genes that influence NF-κB activity, such as *TNFAIP3* (encoding A20), *NFKBIA* (encoding IκBα), and *TNIP1* (encoding ABIN-1) (29, 30). In prior work, we found that A20 is part of a feedback loop that restricts IL-17–mediated TRAF6 ubiquitination, which is required for NF-κB and MAPK activation; this finding prompted the present analyses of the A20-binding protein ABIN-1 (7). Because of its A20-binding capacity, it is frequently assumed that ABIN-1’s functions involve A20 (17, 31, 32). Indeed, ABIN-1 coexpression with A20 was shown to induce destabilization of the IKK complex and inhibition of NF-κB signaling in a lower chordate model organism (33). Similarly, ABIN-1 cooperates with A20 to inhibit antiviral signaling or TNF-regulated NF-κB signaling (20, 34). In contrast, our data show that ABIN-1 acts independently of A20 in the context of IL-17R signal transduction (Fig. 2).

Most of what is known about ABIN-1 comes from studies of TNF-α or LPS. ABIN-1 controls signaling by several reported mechanisms, including (1) inhibiting IKK complex activity by binding to NEMO (IKKγ) (20); (2) inhibiting ubiquitination and degradation of p105 to block p50 production in the noncanonical NF-κB pathway (21); and (3) by associating with and thus blocking TNF receptor adaptors such as RIP and TRAF2 (17). ABIN-1 requires its UBAN for its function, as a D485N mutation within the UBAN suppressed binding to K63 or linear polyubiquitin chains. In vivo, this mutation caused systemic inflammation and autoimmunity (35). This phenotype...
was considered to be an LPS-mediated response, but involvement of IL-17 was not explored. In this study, we demonstrate that a similar mutation in the UBAN eliminates ABIN-1–mediated inhibition of tonic and IL-17–dependent signaling (Fig. 3), raising the possibility that some effects of the D485N mutation could be ascribed to IL-17.

An unexpected finding in this study was the dichotomy by which IL-17 regulates ABIN-1 mRNA versus protein. We found consistently IL-17 triggers modest upregulation of ABIN-1 mRNA. Consistent with its mRNA induction, IL-17 activates the ABIN-1 proximal promoter (Fig. 4). NF-κB regulates the gene promoter activity of ABIN-1, inducing its mRNA as a late expression gene compared with the A20 expression after TNF-α stimulation (13, 24). These data thus suggested that ABIN-1 is part of a similar negative feedback loop, analogous to other IL-17 signaling inhibitors such as A20 and MCP1-induced protein 1/Regnase-1 (7, 36). Indeed, in HeLa cells NF-κB was found to induce expression of ABIN-1, whereas ABIN-1 in turn repressed NF-κB activity (13). However, the impact of IL-17 on ABIN-1 protein levels contrasted strikingly and unexpectedly with its transcriptional activation, because the net effect of IL-17 was to downregulate ABIN-1 protein levels (Fig. 4). Interestingly, the phenomenon of ABIN-1 degradation after an inflammatory stimulus is evident in the published literature, although to our knowledge it has never been remarked upon. For example, ABIN-1 levels decreased after TLR and TNF-α stimulation of bone marrow–derived macrophages with approximately the same kinetics as we observed with IL-17 signaling (35). Additionally, studies in human psoriatic skin lesion biopsies showed increased ABIN-1 mRNA but decreased protein, indicating that this phenomenon occurs in a setting where both IL-17 and ABIN-1 are known to be clinically relevant (11). Mice in which ABIN-1 is conditionally deleted in keratinocytes develop more severe skin inflammation than control mice after imiquimod-induced dermatitis, which is associated with increased expression of IL-17 target genes such as Cxcl1 and Ccl20 (12). These findings therefore confirm the physiologic connection between ABIN-1 and IL-17.

How do we reconcile the idea that IL-17 (and other stimuli) induces ABIN-1 transcription yet triggers protein loss? We speculate that the answer lies in the persistence of the stimulus and the kinetics of activation. In the early phase of inflammatory signals, ABIN-1 protein is degraded within 1–2 h, which serves to enhance inflammation. Simultaneously, ABIN-1 mRNA expression is upregulated by NF-κB and C/EBPβ, at least somewhat replenishing the pool of translated ABIN-1. In washout experiments, we found that ABIN-1 protein levels return to baseline ~4 h after IL-17 withdrawal (data not shown), thus returning the cell to a constitutively inhibited state. However, when IL-17 signals

**FIGURE 4. IL-17 signaling upregulates ABIN-1 mRNA but downregulates protein.**

(A) ABIN-1 (Tnip1) mRNA is upregulated by IL-17. ST2 cells were stimulated with IL-17 for the indicated times, and Tnip1 was analyzed by qPCR. Relative mRNA expression was assessed by linear regression modeling (p = 0.0085). Data are pooled from five independent experiments. (B) NF-κB regulates ABIN-1 mRNA. ST2 cells were pretreated with 10 μM IKK inhibitor VII for 30 min or DMSO and treated with IL-17 for 3 h. mRNA was analyzed by qPCR. Data are representative of three experiments. *p < 0.05 two-way ANOVA with Tukey multiple comparisons test compared to untreated sample. (C) ABIN-1 protein is downregulated upon IL-17 signaling. Left: ST2 cells were treated with IL-17 (200 ng/ml) and whole cell lysates were analyzed by immunoblotting. Lanes 7–8: cells were transfected with mock or ABIN-1 siRNA to confirm the identity of ABIN-1 band. Right: Relative protein band intensities were compared with the unstimulated time point (time zero) and analyzed by linear regression. Data are pooled from six independent experiments. (D) ABIN-1 is degraded by the proteasome. Left: ST2 cells were pretreated with MG-132 for 30 min or DMSO and treated with IL-17 for the indicated times. Whole cell lysates were analyzed by immunoblotting. Right: Relative protein band intensities were compared with the unstimulated time point and analyzed by linear regression. Data are pooled from four independent experiments.

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continuously, ABIN-1 degradation was maintained. Thus, the inhibitory activity of ABIN1 is compromised while there is ongoing stimulation. This might explain the observation that in patients with psoriasis there is elevated mRNA but decreased protein levels for ABIN-1 (24). Psoriasis is linked to several inflammatory cytokines, with a predominant role for IL-17A signaling, based in part on the success of anti–IL-17A and anti–IL-17RA biologic drugs (26, 37–39). Therefore, the idea that ABIN-1 is both a tonic inhibitor of inflammation and a negative regulator of IL-17 signaling fits well with our data and with findings in preclinical mouse models and human studies (10–12).

There are other examples of inhibitors that are downregulated by the signals that they regulate. In the case of IL-17R signaling, the proximal adaptor Act1 is degraded following phosphorylation to temper all downstream signaling events (40), and IkBα is degraded following phosphorylation to unmask the NF-κB nuclear import signal (41). IL-17 is just one of multiple immune effectors that can initiate ABIN-1 degradation and presumably thereby enhance inflammation. Moreover, IL-17 signals synergistically with many of these cytokines, particularly TNF-α (3, 42). Thus, ABIN-1 appears to regulate signaling at the intersection of these inflammatory stimuli, namely, the IKK complex.

These data have possible implications for therapeutic interventions. We show that ABIN-1 degradation is at least partially mediated by the proteasome, with no apparent contribution of caspases or the lysosome (data not shown). Therapeutics targeting the proteasome are used for cancer (43), and might be useful in diseases where ABIN-1 is implicated, i.e., those where TNIP1 single nucleotide polymorphisms are found. Another consideration is settings where overproduction of ABIN-1 activators such as IL-17 or TNF-α might lead to underexpression of ABIN-1 and hence chronic inflammation and associated harmful sequelae. Clearly, more work needs to be done to dissect the role of this important but enigmatic molecule in the context of inflammation.

DISCLOSURES

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