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Hippo kinase NDR2 inhibits IL-17 signaling by promoting Smurf1-mediated MEKK2 ubiquitination and degradation

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ABSTRACT

NDR/LATS kinase family are conserved from yeast to man and their roles in inflammation remains largely unknown. In the present study, we show that knockdown of NDR2 significantly increases IL-17-induced IL-6, CXCL2 and CCL20 expression in Hela and HT-29 cells. Knockdown of NDR2 enhances IL-17-induced MAPK and NF-κB activation. NDR2 interacts with E3 ubiquitin protein ligase Smurf1, promotes Smurf1-mediated K48-linked ubiquitination of MEKK2 and inhibits expression of MEKK2. Consistently, knockdown of Smurf1 increases IL-17-induced IL-6, CXCL2 and CCL20 expression. On the other hand, overexpression of MEKK2 increases IL-17-induced IL-6 expression. These results suggest that NDR2 may play important roles in IL-17-associated inflammation by promoting Smurf1-mediated MEKK2 ubiquitination and degradation.

1. Introduction

Interleukin 17 (IL-17) is originally considered to be mainly produced by Th17 cell subset in adaptive immunity. Recent studies show that some innate cell types, including $\delta\gamma$ T cells, iNKT cells, LTi-like cells, NK cells, myeloid cells and epithelia cells, also can produce IL-17, as the early sources of IL-17 in response to stress, injury or pathogens (Zhu et al., 2010). Among IL-17 family's six members (IL-17 A to IL − 17 F), IL-17 A, commonly called as IL-17, is the first identified and the most intensively studied member in this family (Iwakura et al., 2011). IL-17 induce production of proinflammatory cytokines, chemokines, antimicrobial peptides and metalloproteinases. IL-17 deficient mice are highly susceptible to bacterial Infection (Ishigame et al., 2009). IL-17 deficiency also leads to increased susceptibility to fungus infection (Bar et al., 2014; Taylor et al., 2014). In another hand, IL-17 contributes to the development of many autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis and inflammatory bowel disease (Bedoya et al., 2013). IL-17 promotes tumor angiogenesis by inducing vascular endothelial growth factor (VEGF) expression and promotes tumor resistance to anti-angiogenic therapy (Chung et al., 2013; Numasaki et al., 2003). IL-17 deficiency significantly inhibits spontaneous intestinal tumorigenesis in $Apc^{Min/+}$ mice, suggesting that endogenous IL-17 promotes intestinal tumorigenesis (Chae and Bothwell, 2011; Wang et al., 2014).

IL-17 binds to a heterodimeric receptor complex of IL-17RA and IL-17RC subunits, which recruits adaptor proteins Act1 (also known as TRAF3 interacting protein 2, TRAF3IP2) and TNF receptor associated factor 6 (TRAF6), and ultimately activates MAPK and NF-κB to regulate proinflammatory cytokines and chemokines expression, such as Interleukin 6 (IL-6), C-X-C motif chemokine ligand 2 (CXCL2) and C-C Motif Chemokine Ligand 2 (CCL2) (Gaffen, 2009). Act1 also can recruit TRAF2 and TRAF5 to stabilize mRNA transcripts of chemokines and cytokines (Sun et al., 2011). Meanwhile, several negative regulators of IL-17 signaling have been revealed. $SCF^{\beta-TRCP}E3$ ubiquitin ligase facilitates K48-linked ubiquitination and degradation of Act1 to restrict IL-17 signaling (Shi et al., 2011). A20 (also known as TNF Alpha Induced Protein 3) inhibits IL-17-induced NF-κB activation and proinflammatory cytokine production by deubiquitinating TRAF6 (Garg et al., 2013). Ubiquitin Specific Peptidase 25 (USP25) inhibits IL-17 signaling by removing Lys63-linked ubiquitination in TRAF5 and TRAF6 (Zhong et al., 2012). TRAF3 inhibits IL-17 signaling by blocking the interaction between Act1 and TRAF6 (Zhu et al., 2010). Although the signal mechanism of IL-17 has been intensively investigated, there are still unknown molecules that play important roles in modulating IL-

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17 signaling.

Serine/threonine kinases are a large group of kinase enzymes that phosphorylates the hydroxyl (OH) group of serine or threonine, which play a significant role in a wide range of cellular processes. Serine/threonine kinase 38/38 L (Stk38/38 L), also known as nuclear Dbf2p-related kinase 1/2 (NDR1/2), belong to NDR/LATS kinase family of serine-threonine kinases protein, are conserved from yeast to man. NDR1/2 are important for the regulation of centrosome duplication, cell cycle progression, autophagy and apoptosis. As NDR/LATS family members, NDR1/2 inhibit Yes Associated Protein 1 (YAP1) expression by phosphorylating YAP1 in intestinal epithelium and prevents development of colon tumor (Zhang et al., 2015). Recently, evidence emerges that NDR1/2 might play an important role in inflammation. NDR1/2 are required to limit inflammation by dampening cytokine secretion and to control T cell motility and homeostasis (Tang et al., 2015). NDR1/2 inhibit CpG-induced proinflammatory cytokine production (Wen et al., 2015). However, NDR1 potentiates IL-17-induced inflammation (Ma et al., 2017). Meanwhile, the role of NDR2 in IL-17-induced inflammation remains unknown.

In the present study, we demonstrate that NDR2 inhibits IL-17-induced inflammation by promoting Smurf1-mediated K48-linked ubiquitination of Mitogen-Activated Protein Kinase Kinase Kinase 2 (MEKK2).

2. Materials and methods

2.1. Antibodies and reagents

Antibodies specific for NDR2 (sc-46185), NDR1/2 (H-100) (sc-66998), MEKK2 (sc-1088), ERK1/2 (sc-93), p38 (sc-535), Smurf1 (sc-100616), Actin (sc-1616), mouse-normal-IgG (sc-202), rabbit-normal-IgG (sc-2028) were obtained from Santa Cruz (Santa Cruz Biotechnology, Santa Cruz, CA). Antibodies for p-ERK1/2 (#9101), p-JNK (#9251), JNK (#9252), pp38 (#9216), pp65 (#3033), p65(#8242), K48-Ubiquitin (#4289), Ubiquitin (#3936), Myc-Tag (#2278) were purchased from CST (Cell Signaling Technology, Beverly, MA). Antibodies for Flag-tag (F1804) and HA-tag (H3663) were obtained from Sigma (Sigma-Aldrich, St. Louis, MO). Recombinant human IL-17 (200-17) was obtained from PeproTech (PeproTech inc. Rocky Hill, USA).

2.2. Cell culture

Hela, HT-29, HEK293 and HEK293 T cells were obtained from American Type Culture Collection (Manassas, VA), and were cultured as suggested by suppliers.

2.3. Plasmids, transfection and RNA interference

The vectors of pCMV6-XL4, pCMV6-XL4-NDR2 encoding human NDR2, pCMV6-Kan/Neo-Smurf1 encoding mouse Smurf1 and pCMV6-Kan/Neo were purchased from (OriGene Technologies Inc. Rockville, MD). pCMV-Myc and pCMV-HA were purchased from Clontech Laboratories, Inc. These various vectors (with Myc-tag or HA-tag) encoding human NDR2 and human MEKK2 were constructed in our laboratory. Flag-NDR2 and Flag-Smurf1 were gifts from Professor Xiaojian Wang (Institute of Immunology, Zhejiang University). For transient transfection of various plasmids DNA in HEK293 and HEK293 T cells, JetPEI regents were used (Polyplus 101-40 N). The human NDR2 specific siRNA was 5′-GGAUAAGAGGAAUCUUUAUTT-3′, and human Smurf1 specific siRNA sequence was 5′−CCUUGCAAAGA AAGACUUCTT-3′. The non-sense sequence 5′-UUCUCCGAACGUGUCA CGUTT-3′ was used as negative control siRNA.

2.4. Real-Time Quantitative-PCR

Total cellular RNA was extracted with RNA extraction kit and cDNA was synthesized using the M-MLV Reverse Transcriptase kits (Takara 2641 A) according to the manufacturer's instructions. Real-time PCR was performed with SYBR Premix Ex-Taq (Bio-Red 1,725,125) on ABI-7500. The primer sequences for Q-PCR were as followed:

hActin-F (5′-CGTGGACATCCGTAAAGACC-3′),
hActin-R (5′-ACATCTGCTGGAAGGTGGAC-3′),
hNDR2-F (5′-ATCGGGATATTAAGCCAGACAACC-3′),
hNDR2-R (5′-CTTGGTGGGTTGTGTGTGAGA-3′),
hIL-6-F (5′-ATGAACTCCTTCTCCAACAAGCGC-3′),
hIL-6-R (5′-GGGAAGGCAGCAGGCAACAC-3′),
hCCL20-F (5′-GCGCAAATCCAAAACAGACT-3′),
hCCL20-R (5′-CAAGTCCAGTGAGGCACAAA-3′),
hCXCL2-F (5′-CTCAAGAATGGGCAGAAAGC-3′),
hCXCL2-R (5′-AAACACATTAGGCGCAATCC-3′).

2.5. ELISA assay of cytokines and chemokines

The concentrations of IL-6 in culture supernatants were measured with ELISA kits according to the manufacturer's instructions. (eBioscience, MN, USA).

2.6. Immunoprecipitation and immunoblot analysis

Antibodies for immunoprecipitation were anti-Smuf1, anti-MEKK2 and anti-Myc. The anti-rabbit IgG HRP antibody (Rockland 18-8816-33) as secondary antibody was used for the immunoblot analysis of immunoprecipitation lysates. Immunoprecipitation and immunoblot analysis were performed as previously described (Wen et al., 2015). Briefly, cells were lysed with M-PER Protein Extraction Reagent (Pierce 78505) supplemented with protease inhibitor cocktail, and protein concentrations of the extracts were measured with BCA assay according to the manufacturer's instructions (Pierce 23225). Equal amounts of extracts were used for immunoprecipitation with antibodies and Protein A/G magnetic beads (Sigma-Aldrich, St. Louis, MO), or loaded for SDS–PAGE, transferred onto nitrocellulose membranes and then blotted with indicated antibodies. Finally, signal intensity was determined with the Tanon 5200S Chemiluminescent Imaging System.

2.7. Ubiquitination assays

The ubiquitination assays were performed as previously described (Wen et al., 2015). Briefly, HEK293 T cells were transfected with plasmids expressing MEKK2, NDR2, Smurf1 and ubiquitin. 12 h later, cells were treated with proteasome inhibitors 20um MG132 and MG115 for another 12 h. Samples were collected and boiled for 10 min after adding 1% SDS. The cell lysate was diluted to 0.1% SDS with lysis buffer. Protein concentrations of the extracts were measured, and equal amounts of extracts were used for immunoprecipitation of target protein. Prepared samples were resolved on 6% SDS–PAGE. Detection of polyubiquitination was performed with indicated antibodies.

2.8. Statistical analysis

Comparisons between two groups were determined with Student's *t*-test. All experiments were independently repeated at least three times. $P < 0.05$ were considered statistically significant.

3. Results

3.1. NDR2 negatively regulates IL-17-induced inflammation in Hela and HT-29 cells

To characterize the role of NDR2 in IL-17-induced inflammation, we

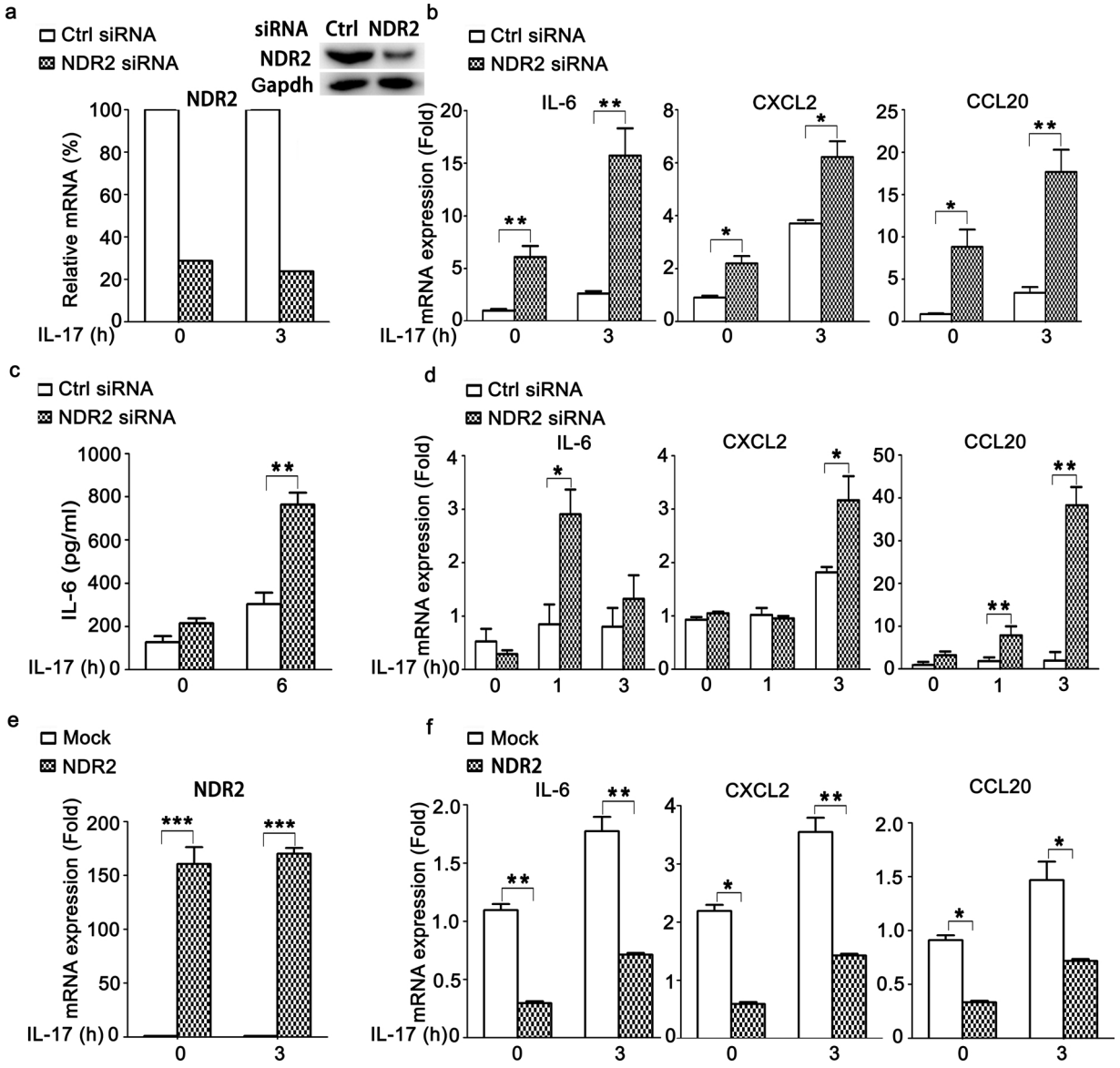

Fig. 1. NDR2 suppresses the inflammation responses induced by IL-17 in Hela and HT-29 cell lines.
Hela cells **(a–c)** and HT-29 cells **(d)** were transfected with 10 nM control (Ctrl) RNA and NDR2 siRNA for 48 h. (a) The interfering efficiency of NDR2 siRNA was evaluated by quantitative PCR (Q-PCR) and western blot in transfected Hela cells treated by IL-17 for 3 h. **(b)** Transfected Hela cells were treated by IL-17 for 3 h, then the mRNA of IL-6, CXCL2 and CCL20 were evaluated by quantitative PCR. **(c)** IL-6 was examined by ELISA in transfected Hela cells treated by 50 ng/ml IL-17 for 6 h. **(d)** HT-29 cells were treated as described in **(b)**, then the mRNA of IL-6, CXCL2 and CCL20 were evaluated by quantitative PCR. **(e, f)** Quantitative PCR assay of NDR2, IL-6, CXCL2 and CCL20 mRNA expression in Hela cells transfected with flag-PCDNA3.1(-) (Mock) and flag-NDR2 for 24 h, then treated with 50 ng/ml IL-17 for 3 h. Data are shown as mean ± SD. (n = 3), $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ (Student's *t*-test). The results shown are representative of three independent experiments.

synthesized small interfering RNA specific to NDR2 and observed the effect of NDR2 knockdown on IL-17-induced proinflammatory cytokine and chemokine mRNA expression. The NDR2 siRNA can efficiently inhibit endogenous NDR2 mRNA and protein expression in Hela cells (Fig. 1a). As shown in Fig. 1b, NDR2 knockdown significantly increases IL-17-induced IL-6, CXCL2 and CCL20 mRNA expression in Hela cells. Consistently, NDR2 knockdown increases IL-17-induced IL-6 production in Hela cells (Fig. 1c). Similarly, NDR2 knockdown also increases IL-17-induced IL-6, CXCL2 and CCL20 mRNA expression in HT-29 cells (Fig. 1d). Furthermore, NDR2 overexpression decreased IL-17-induced IL-6, CXCL2 and CCL20 mRNA expression in Hela cells (Fig. 1e–f). These results suggest that NDR2 functions as a negative regulator in IL-17-induced inflammation.

3.2. NDR2 inhibits ERK, p38 and NF-κB activation in IL-17 signaling

IL-17 induces inflammatory cytokines and chemokines through activating MAPK and NF-κB signal pathways. To reveal the signaling events that are regulated by NDR2 to inhibit IL-17-induced inflammation, effects of NDR2 knockdown on IL-17-induced MAPK and NF-κB activation in Hela cells were observed. NDR2 knockdown increases IL-17-induced phosphorylation of ERK1/2, p38 and NF-κB p65 in Hela cells (Fig. 2a). In HT-29 cells, NDR2 knockdown also increases IL-17-induced phosphorylation of ERK1/2, p38 and NF-κB p65 (Fig. 2b). These results demonstrate that NDR2 could inhibit IL-17-induced inflammatory cytokine and chemokine production possibly by negatively regulating ERK1/2 and NF-κB p65 in IL-17 signaling pathway.

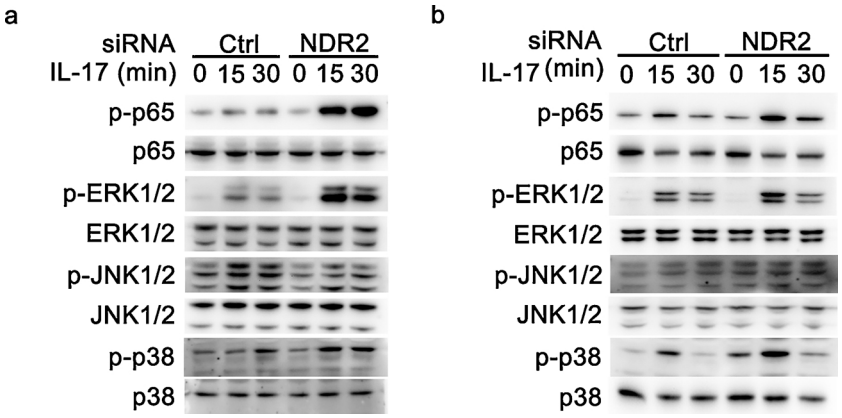

Fig. 2. NDR2 inhibits ERK, p38 and NF-κB activation in IL-17 signaling **(a)** Hela cells were transfected with 10 nM indicated siRNA (Ctrl, NDR2) for 48 h, then were treatment with 50 ng/ml recombined human IL-17 for 0 min, 15 min and 30 min. Immunoblot analysis were performed to examine the indicated proteins phosphorylation level or total proteins of MAPKs and NF-κB signaling in lysates of treated cells. **(b)** HT-29 cells were transfected with 10 nM indicated siRNA (NC, NDR2) for 48 h, then were treated with 50 ng/ml IL-17 for 0 min, 15 min and 30 min. The phosphorylation level and total protein of NF-κB p65, ERK1/2, JNK1/2 and p38 were detected by western blot. The results shown are representative of three independent experiments.

3.3. NDR2 promotes Smurf1-mediated MEKK2 ubiquitination

NDR1 inhibits TLR9-activated inflammation by promoting Smurf1-mediated MEKK2 ubiquitination (Wen et al., 2015). MEKK2 is also required for TNF-α-induced NF-κB activation (Schmidt et al., 2003). These studies prompted us to investigate the interaction between NDR2, MEKK2 and Smurf1. As shown in Fig. 3a and b, NDR2 is constitutively associated with Smurf1, and IL-17 stimulation increases the association between NDR2 and MEKK2. Overexpression of NDR2 and Smurf1 alone remarkably inhibits MEKK2 expression, and combination of NDR2 and Smurf1 overexpression synergistically inhibits MEKK2 expression (Fig. 3c). NDR2 overexpression dose-dependently increases K48-linked ubiquitination of MEKK2 (Fig. 3d), suggesting that NDR2 inhibits MEKK2 expression by promoting MEKK2 ubiquitination synergistically with Smurf1.

3.4. Smurf1 and MEKK2 oppositely regulates IL-17-induced inflammation

To investigate whether NDR2 regulates IL-17-induced inflammation by modulating Smurf1-mediated MEKK2 ubiquitination, we tested the role of Smurf1 in IL-17-induced IL-6 production in Hela cells. Smurf1-specific small interfering RNA efficiently inhibits Smurf1 expression

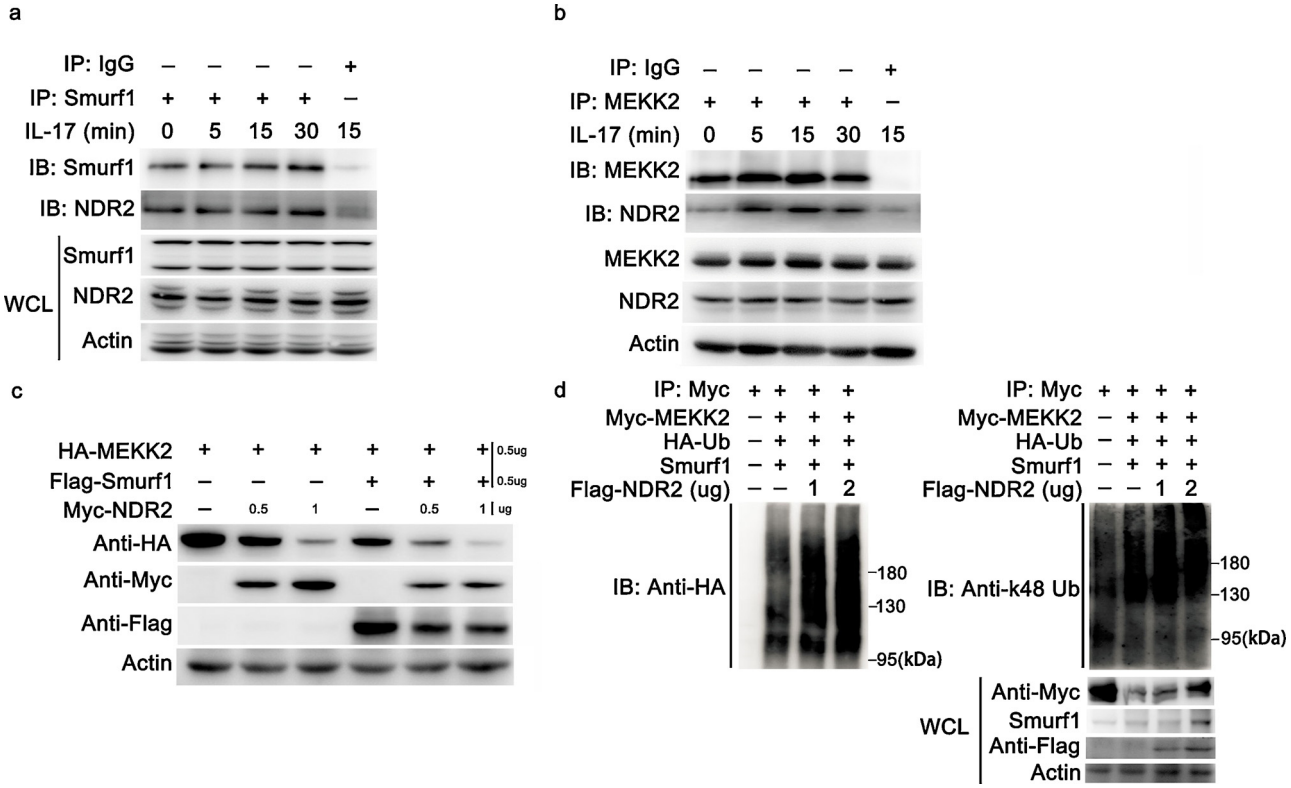

Fig. 3. NDR2 interacts with Smurf1 and MEKK2, and promotes the MEKK2 ubiquitination and degradation. **(a)** and (**b**) Hela cells were treated with 50 ng/ml IL-17 for various times (0 min, 5 min, 15 min, 30 min), and then whole-cell lysates (WCL) were collected. After pre-clearing of whole-cell lysates by incubation with normal IgG and protein A/G beads, immunoprecipitation was performed sequentially with normal control antibody (IgG 15 min), anti-Smurf1 (0 min, 5 min, 15 min, 30 min) **(a)**, anti-MEKK2 (0 min, 5 min, 15 min, 30 min) **(b)**. Component of immunoprecipitation complex and WCL were examined by western blot. **(c)** HEK293 T cells were transfected with various plasmids (as above). 24 h later, the WCL were collected and examined by western blot for indicated proteins. **(d)** Immunoblot analysis of MEKK2 ubiquitylation. HEK293 T cells were transfected with various plasmids (as above) for 12 h, and then treated with 20 μM MG132 and 20 μM MG115 for another 12 h. After heat denaturing in lysis buffer containing 1% SDS for 10 min, immunoprecipitation of the WCL from treated HEK293 T cells was performed with anti-Myc antibody. MEKK2 ubiquitylation was analyzed by immunoblot with anti-HA antibody (left) and anti-k48-Ub antibody (right). Data are from one experiment representative of three independent experiments.

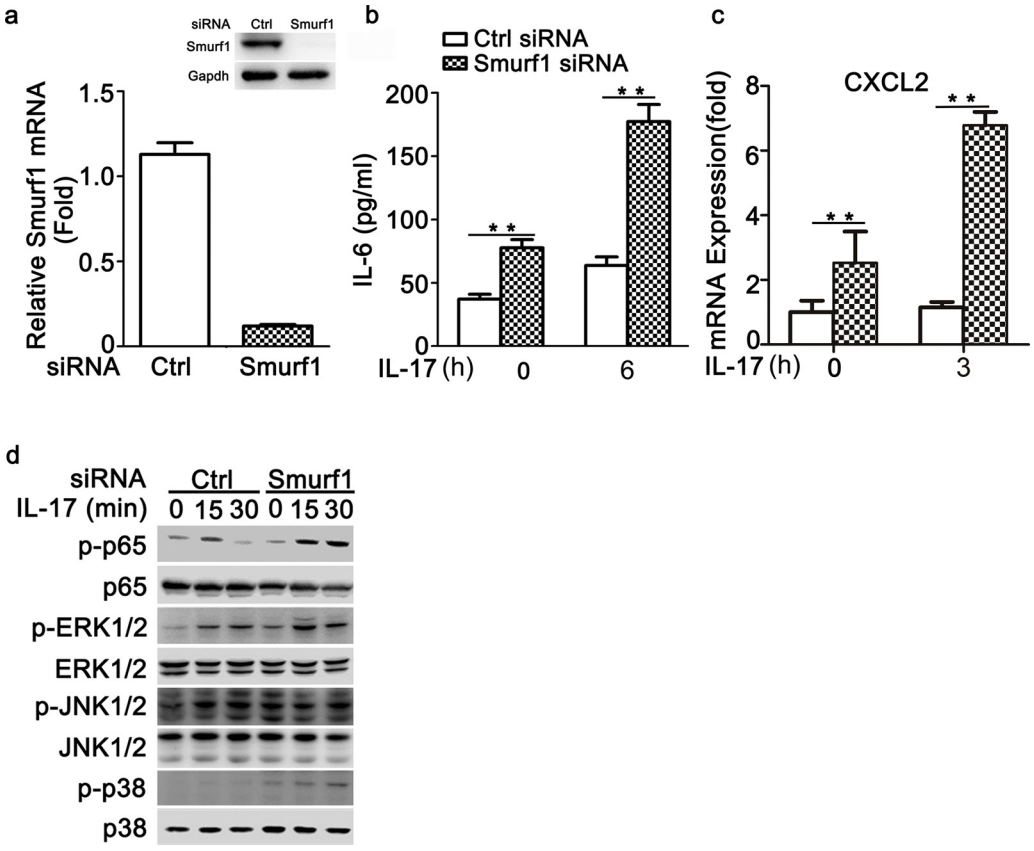

Fig. 4. Smurf1 significantly inhibits IL-17-induced IL-6 production and ERK1/2, p38 and NF-κB p65 activation. **(a)** Quantitative PCR and immunoblot assay of Smurf1 expression in Hela cells transfected with 10 nM control RNA and Smurf1-specific siRNA for 48 h. **(b)** ELISA assay of IL-6 production in the supernatant of Hela cells transiently transfected with 10 nM Control RNA and Smurf1-specific siRNA for 48 h, stimulated with 50 ng/ml IL-17 for 6 h. (c) Transfected Hela cells were treated by IL-17 for 3 h, then the mRNA of CXCL2 was evaluated by quantitative PCR. **(d)** Hela cells were transfected with 10 nM indicated siRNA (Ctrl, Smurf1) for 48 h, then were treated with 50 ng/ml recombined human IL-17 for 0 min, 15 min and 30 min. Immunoblot analysis were performed to examine the indicated proteins phosphorylation level or total proteins of MAPKs and NF-κB signaling in these treated lysates. Data are shown as mean ± SD. ** $P < 0.01$ (Student's *t*-test). Similar results were obtained in three independent experiments.

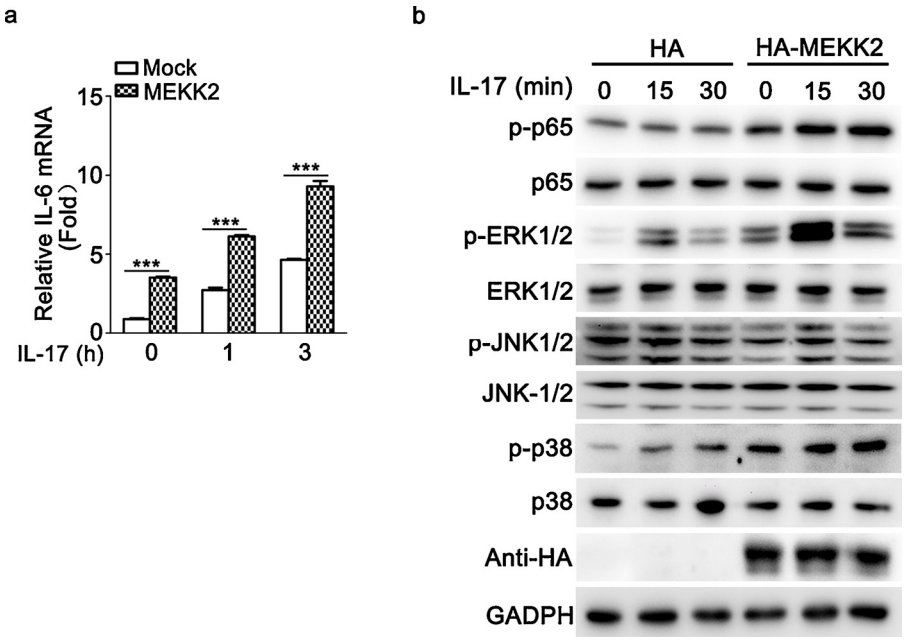

Fig. 5. MEKK2 overexpression significantly enhances IL-17-induced IL-6 expression and ERK1/2, p38 and NF-κB p65 activation. Quantitative PCR assay of IL-6 mRNA expression in Hela cells transfected with indicated plasmids (PCMV-HA, MEKK2-HA) for 24 h, treated with 50 ng/ml IL-17 for 1 h and 3 h. Data are shown as mean ± SD, ***$P < 0.001$ (Student's *t*-test). Similar results were obtained in three independent experiments. **(b)** Immunoblot (IB) assay of MEKK2 overexpression in Hela cells, transfected with indicated plasmids (PCMV-HA, MEKK2-HA) for 24 h, then treated with 50 ng/ml IL-17 for 0 min, 15 min and 30 min. The phosphorylation level and total protein of NF-κB p65, ERK1/2, JNK1/2 and p38 were detected by western blot. Similar results were obtained in three independent experiments.

(Fig. 4a). Smurf1 knockdown significantly increases IL-17-induced IL-6 production (Fig. 4b) and CXCL2 (Fig. 4c) expression. Consistently, Smurf1 knockdown increases IL-17-induced ERK1/2, p38 and NF-κB p65 activation (Fig. 4d). We also observed the effect of MEKK2 overexpression on IL-17-induced cytokine production. As shown in Fig. 5a, MEKK2 overexpression significantly increases IL-17-induced IL-6 expression (Fig. 5a). Consistently, MEKK2 overexpression enhances IL-17-induced ERK1/2, p38 and NF-κB p65 activation (Fig. 5b). These results suggest that Smurf1 negatively regulates IL-17-induced inflammation via inhibiting MEKK2.

4. Discussion

Upon IL-17 binding, IL-17R recruits adaptor proteins Act1 and TRAF6, and ultimately activates MAPK and NF-κB to regulate proinflammatory cytokines and chemokines expression (Amatya et al., 2017). However, the exact mechanism by which IL-17 signaling is transduced remains largely unclear. MEKK2 increases TLR9-mediated

proinflammatory cytokine production by activating ERK1/2 pathway, enhances TNF-α-induced NF-κB activation and inflammation (Wen et al., 2015). Here our results demonstrate that MEKK2 positively regulates IL-17-induced proinflammatory cytokines and chemokines expression, suggesting that MEKK2 is involved in the signal transduction of IL-17, possibly by regulating MAPK and NF-κB activation.

IL-17 is required for host immune defense to pathogens. However, abnormal activation of IL-17 signal pathway has high potential to induce pathological inflammatory conditions. Thus, IL-17 signaling is strictly regulated to avoid pathogenic conditions. Several negative regulators have reported to inhibit IL-17-induced inflammation by targeting known molecules functioning in IL-17 signaling (Sun et al., 2011; Wen et al., 2015; Zhang et al., 2015). In the present study, knockdown of NDR2 and Smurf1 significantly increases IL-17-induced proinflammatory cytokines and chemokines expression, NDR2 and Smurf1 synergistically promote MEKK2 ubiquitination, demonstrating that both of NDR2 and Smurf1 negatively regulate IL-17-induced inflammation by targeting MEKK2.

NDR1/2 are conserved from yeast to man and originally found to be important for the regulation of centrosome duplication, cell cycle progression, autophagy and apoptosis. Recent studies show that NDR1/2 might play important role in inflammation. NDR1/2 inhibit CpG-induced proinflammatory cytokine production (Wen et al., 2015). These reports suggest that NDR1 and NDR2 have similar functions in most biological processes they regulated. However, NDR1 potentiates IL-17-induced inflammation (Ma et al., 2017), and meanwhile NDR2 inhibits IL-17-induced inflammation. Our study show that NDR1 and NDR2 might have different function.

NDR1 and NDR2 are generally believed to compensate for each other, which has been demonstrated during development. While, NDR1/2, the two mammalian isoforms, differ mainly in their tissue and cell type specific expression patterns. Different functions were also reported between NDRs. Due to their distinct subcellular localization, NDR2, but not NDR1, plays a critical role in the formation of primary cilia (Abe et al., 2017).

In conclusion, the present study identifies NDR2 and Smurf1 as novel negative regulators and MEKK2 as a novel positive regulator of IL-17-induced inflammatory cytokine and chemokine production. This study brings new insight into the mechanism by which IL-17 signaling is regulated, and also provides new targets for the therapy of inflammatory diseases.

Declaration of interest

The authors have declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.molimm.2018.10.005.

References

Abe, S., Nagai, T., Masukawa, M., Okumoto, K., Homma, Y., Fujiki, Y., Mizuno, K., 2017. Localization of protein kinase NDR2 to Peroxisomes and its role in Ciliogenesis. J. Biol. Chem. 292, 4089–4098.

Amatya, N., Garg, A.V., Gaffen, S.L., 2017. IL-17 signaling: the yin and the yang. Trends Immunol. 38, 310–322.

Bar, E., Whitney, P.G., Moor, K., Reis e Sousa, C., LeibundGut-Landmann, S., 2014. IL-17 regulates systemic fungal immunity by controlling the functional competence of NK cells. Immunity 40, 117–127.

Bedoya, S.K., Lam, B., Lau, K., Larkin 3rd, J., 2013. Th17 cells in immunity and autoimmunity. Clin. Dev. Immunol. 2013, 986789.

Chae, W.J., Bothwell, A.L., 2011. IL-17F deficiency inhibits small intestinal tumorigenesis in ApcMin/+ mice. Biochem. Biophys. Res. Commun. 414, 31–36.

Chung, A.S., Wu, X., Zhuang, G., Ngu, H., Kasman, I., Zhang, J., Vernes, J.M., Jiang, Z., Meng, Y.G., Peale, F.V., Ouyang, W., Ferrara, N., 2013. An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy. Nat. Med. 19, 1114–1123.

Gaffen, S.L., 2009. Structure and signalling in the IL-17 receptor family. Nat. Rev. Immunol. 9, 556–567.

Garg, A.V., Ahmed, M., Vallejo, A.N., Ma, A., Gaffen, S.L., 2013. The deubiquitinase A20 mediates feedback inhibition of interleukin-17 receptor signaling. Sci. Signal. 6 ra44.

Ishigame, H., Kakuta, S., Nagai, T., Kadoki, M., Nambu, A., Komiyama, Y., Fujikado, N., Tanahashi, Y., Akitsu, A., Kotaki, H., Sudo, K., Nakae, S., Sasakawa, C., Iwakura, Y., 2009. Differential roles of interleukin-17A and -17F in host defense against mucoepithelial bacterial infection and allergic responses. Immunity 30, 108–119.

Iwakura, Y., Ishigame, H., Saijo, S., Nakae, S., 2011. Functional specialization of interleukin-17 family members. Immunity 34, 149–162.

Ma C., Lin W., Liu Z., Tang W., Gautam R., Li H., Qian Y., Huang H. and Wang X., 2017. NDR1 protein kinase promotes IL-17- and TNF-alpha-mediated inflammation by competitively binding TRAF3. 18, 586–602.

Numasaki, M., Fukushi, J., Ono, M., Narula, S.K., Zavodny, P.J., Kudo, T., Robbins, P.D., Tahara, H., Lotze, M.T., 2003. Interleukin-17 promotes angiogenesis and tumor growth. Blood 101, 2620–2627.

Schmidt, C., Peng, B., Li, Z., Sclabas, G.M., Fujioka, S., Niu, J., Schmidt-Supprian, M., Evans, D.B., Abbruzzese, J.L., Chiao, P.J., 2003. Mechanisms of proinflammatory cytokine-induced biphasic NF-kappaB activation. Mol. Cell 12, 1287–1300.

Shi, P., Zhu, S., Lin, Y., Liu, Y., Liu, Y., Chen, Z., Shi, Y., Qian, Y., 2011. Persistent stimulation with interleukin-17 desensitizes cells through SCFbeta-TrCP-mediated degradation of Act1. Sci. Signal. 4 ra73.

Sun, D., Novotny, M., Bulek, K., Liu, C., Li, X., Hamilton, T., 2011. Treatment with IL-17 prolongs the half-life of chemokine CXCL1 mRNA via the adaptor TRAF5 and the splicing-regulatory factor SF2 (ASF). Nat. Immunol. 12, 853–860.

Tang, F., Gill, J., Ficht, X., Barthlott, T., Cornils, H., Schmitz-Rohmer, D., Hynx, D., Zhou, D., Zhang, L., Xue, G., Grzmil, M., Yang, Z., Hergovich, A., Hollaender, G.A., Stein, J.V., Hemmings, B.A., Matthias, P., 2015. The kinases NDR1/2 act downstream of the Hippo homolog MST1 to mediate both egress of thymocytes from the thymus and lymphocyte motility. Sci. Signal. 8 ra100.

Taylor, P.R., Roy, S., Leal Jr., S.M., Sun, Y., Howell, S.J., Cobb, B.A., Li, X., Pearlman, E., 2014. Activation of neutrophils by autocrine IL-17A-IL-17RC interactions during fungal infection is regulated by IL-6, IL-23, RORgammat and dectin-2. Nat. Immunol. 15, 143–151.

Wang, K., Kim, M.K., Di Caro, G., Wong, J., Shalapour, S., Wan, J., Zhang, W., Zhong, Z., Sanchez-Lopez, E., Wu, L.W., Taniguchi, K., Feng, Y., Fearon, E., Grivennikov, S.I., Karin, M., 2014. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. Immunity 41, 1052–1063.

Wen, M., Ma, X., Cheng, H., Jiang, W., Xu, X., Zhang, Y., Zhang, Y., Guo, Z., Yu, Y., Xu, H., Qian, C., Cao, X., An, H., 2015. Stk38 protein kinase preferentially inhibits TLR9-activated inflammatory responses by promoting MEKK2 ubiquitination in macrophages. Nat. Commun. 6, 7167.

Zhang, L., Tang, F., Terracciano, L., Hynx, D., Kohler, R., Bichet, S., Hess, D., Cron, P., Hemmings Brian, A., Hergovich, A., Schmitz-Rohmer, D., 2015. NDR functions as a physiological YAP1 kinase in the intestinal epithelium. Curr. Biol. 25, 296–305.

Zhong, B., Liu, X., Wang, X., Chang, S.H., Liu, X., Wang, A., Reynolds, J.M., Dong, C., 2012. Negative regulation of IL-17-mediated signaling and inflammation by the ubiquitin-specific protease USP25. Nat. Immunol. 13, 1110–1117.

Zhu, S., Pan, W., Shi, P., Gao, H., Zhao, F., Song, X., Liu, Y., Zhao, L., Li, X., Shi, Y., Qian, Y., 2010. Modulation of experimental autoimmune encephalomyelitis through TRAF3-mediated suppression of interleukin 17 receptor signaling. J. Exp. Med. 207, 2647–2662.