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Autophagy dysfunction in autoinflammatory diseases

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Abstract

Autoinflammatory diseases (AUIDs) are a genetically heterogeneous group of rheumatic diseases characterized by episodic inflammation linked with dysregulated innate immune responses. In this review, we summarize the molecular mechanisms altered by disease-associated variants in several AUIDs, including *NOD2*-associated diseases, TNF receptor-associated periodic syndrome (TRAPS), familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), and highlight the roles dysregulated autophagy plays in disease pathogenesis. Autophagy is a conserved eukaryotic pathway for the elimination of cellular stressors, such as misfolded proteins, damaged organelles, or intracellular microorganisms. It is now recognized that autophagy also functions to control inflammation through regulatory interactions with innate immune signaling pathways. AUID-associated genetic variants are known to directly activate inflammatory signaling pathways. Recent evidence also indicates that these variants may also cause impairment of autophagy, thus augmenting inflammatory responses indirectly. Intriguingly, these variants can impair autophagy by different mechanisms, further implicating the autophagic response pathway in AUIDs. These discoveries provide evidence that autophagy could be investigated as a new therapeutic target for AUIDs.

Keywords

Autoinflammatory diseases; Autophagy; *NOD2*-associated diseases; TNF receptor-associated periodic syndrome; Familial mediterranean fever; Hyperimmunoglobulinemia D and periodic fever syndrome

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1. Introduction

Autoinflammatory diseases (AUIDs) were originally termed by Dr. Kastner's research group in 1999 to describe several heritable rheumatic disorders that present as self-limited episodes of fever and serosal, synovial, or cutaneous inflammation [1]. The term *autoinflammatory* disease is preferable to *autoimmune* disease as it is now understood that AUIDs result from dysregulated innate immune responses and generally lack the presence of autoanti-bodies. Classic members of this disease family include familial Mediterranean fever (FMF), TNF receptoreassociated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS) and hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) (Table 1) [2]. Presently, AUIDs represent a large spectrum of rheumatic and inflammatory disorders, including more than 40 monogenic diseases [3], as well as polygenic diseases including Crohn's disease (CD), adult onset Still's disease (AOSD), Behçet's disease, gout, and systemic juvenile idiopathic arthritis (sJIA) [4].

The genetically defined AUIDs can be classified into 5 groups based on the predominant pro-inflammatory cytokines or inflammatory pathway driving the disease [3]. These groups include: (1) Interleukin (IL)-1-mediated AUIDs; (2) Interferon (IFN)-mediated AUIDs; (3) NF- κ B-mediated diseases; (4) AUIDs caused by persistent macrophage activation; (5) AUIDs with yet uncharacterized pivotal pro-inflammatory mediators. As our understanding of detailed pathogenic mechanisms has increased, it has laid a foundation for the investigation and selection of more effective therapies for these relatively rare diseases. For instance, patients with CAPS spectrum, an IL-1-associated AUID, therapeutically respond to IL-1 blockade by Anakinra, Rilonacept and Canakinumab [5]. Similarly, the classic AUIDs like FMF, TRAPS and HIDS are also currently classified as IL-1-mediated AUIDs, yet they tend to have a more variable response to IL-1 inhibition, indicating that other pathways in these diseases may play more important roles in their pathogenesis. Therefore, a more complete understanding of underlying disease mechanisms may provide newer and more effective therapeutic choices.

2. Candidate molecular mechanisms of the disease pathogenesis in AUIDs

2.1. General pathogenesis of AUIDs

The mechanisms by which disease-causing genetic variants lead to the flares of AUIDs vary significantly, but they all primarily impact pattern recognition receptors (PRRs) that trigger innate immune responses [3,6]. PRRs are located either on the cell surface or in the cytosol, recognizing pathogen-associated molecular patterns (PAMPs) in bacteria, viruses and fungi. PRRs also recognize danger-associated molecular patterns (DAMPs) elicited by cell injury [7]. Most PRRs can be classified into one of five families consisting of the Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid inducible gene I (RIG-I)-like receptors (RLRs), and absent in melanoma 2 (AIM2)-like receptors (ALRs) [8]. PRRs on the cell surface include most TLRs and CLRs, while the intracellular receptors include NLRs, ALRs, RLRs and TLR3, 7, 8, and 9. The AUID-associated mutants of PRRs and related adaptors are all intracellular. For example, variants in NLR family member *NLRP3* (NLR family pyrin domain containing 3) are found in CAPS [9], *NLRP4* (NLR family CARD

domain containing 4) mutations are linked to macrophage activation syndrome (MAS) [10], *NOD2* variants are associated with Blau syndrome (BS) [11], and mutations in RLR family member *MDA5* (melanoma differentiation gene 5) are found in Aicardi-Goutières syndrome 7 [12].

Variants associated with AUIDs drive pathogenesis by both direct and indirect effects on PRR function. One mechanism is that the result of a genetic variant causes the hyperactivation of a PRR directly. Activated PRRs generate various innate immune responses, including transcription of proinflammatory mediators and non-transcriptional functions, such as induction of phagocytosis, autophagy, cell death, and cytokine maturation [13]. The inflammasome, a highly organized complex induced by activated intracellular PRRs, such as NLRP3, NLRC4 and AIM2, proteolytically process the inactive form pro-IL-1 β into mature, active IL-1 β [14], which is the key cytokine resulting in the symptoms of group 1 AUIDs. The structure of canonical inflammasomes, such as NLRP3 and AIM2 inflammasome, usually consist of 3 parts: PRR, an adaptor protein ASC [apoptosis-associated speck-like protein containing CARD (caspase recruitment domains)] that contains a Pyrin domain (PYD) and CARD, as well as the protease caspase-1 which mediates the processing of IL-1 β [14]. The ASC adaptor acts as a molecular bridge binding to PRRs via PYD-PYD interactions and interacting with caspase-1 through CARD-CARD binding. Some CARD containing PRRs (such as NLRC4) can directly recruit caspase-1 without the adaptor ASC (Fig. 1). Mutations in PRRs may constitutively activate inflammasomes in the absence of activating signals from PAMPs or DAMPs, resulting in high levels of IL-1 β secretion.

Alternately, increased PRR activation can result from indirect mechanisms, such as the accumulation of intracellular stressors that trigger PRR activation, or the loss of a negative regulator of inflammation. A number of diverse intracellular stressors can activate inflammasomes, of which NLRP3 inflammasome has been most extensively studied [15]. The NLRP3 inflammasome can be activated by ion fluxes (potassium efflux or calcium influx) or mitochondrial dysfunction. These chemical signals are thought to result from damage by a wide range of indirect, structurally dissimilar agonists, including both exogenous and endogenous molecules, such as crystalline molecules (alum, silica, asbestos, monosodium urate), viral infections, bacterial pore-forming toxins, ATP, or endoplasmic reticulum (ER) stress [16–22]. These stressors can also be generated due to variants that result in defective enzymes leading to accumulation of unprocessed substrates (e.g. HIDS), misfolded proteins (e.g. TRAPS), or endogenous nucleotides (e.g. some IFN-mediated AUIDs), which trigger a common intracellular stress response called autophagy. When autophagy is defective or cannot keep up with the production of intracellular stressors, inflammation results.

2.2. Overview of autophagy

The process of canonical autophagy has been extensively described [23–25], thus only a brief overview will be provided here. Autophagy is induced by cellular stressors, such as starvation, infection, or organelle damage, stimulating the formation of the isolation membrane to capture intracellular cargo in an initial, cup-like, sequestering compartment.

Closure of the isolation membrane results in the formation of a cytosolic double membrane vesicle that targets intracellular cargo for degradation called the autophagosome. The autophagosome subsequently fuses with lysosomes to deliver lysosomal hydrolases and degrade the contents of the autolysosome (Fig. 2).

The core proteins required for autophagy are called autophagy related ('ATG') proteins. Approximately 40 genes encoding ATG proteins have been identified in yeast, of which 15 genes are conserved in mammals. These mammalian core ATG proteins can be classified into several subgroups: (1) ULK1 complex (composed of ULK1, mATG13, FIP200 and ATG101) that is negatively regulated by mTOR (mammalian target of rapamycin) and is required for the recruitment of the autophagy-specific class III PI3K (phosphoinositide 3-kinase) complex to forming autophagosomes; (2) the class III PI3K complex (composed of VPS34, Beclin-1, ATG14L and VPS15) generates phosphatidylinositol 3-phosphate that provides binding sites for other autophagy effectors, such as DFCP1 (double FYVE domain-containing protein 1) and members of the WIPI (WD-repeat protein interacting with phosphoinositides) family to the forming phagophore; (3) ATG2-WIPI complex: the WIPI family (WIPI1-4) forms a complex with ATG2 and recruits additional ATG complexes to the forming autophagosome; (4) the ATG16L1 complex (a ubiquitination-like conjugation system) is composed of ATG16L1, ATG5, and ATG12. The ubiquitin-like protein ATG12 is conjugated to ATG5 by ATG7 (an E1-like enzyme) and ATG10 (an E2-like enzyme), and this ATG16L1 complex functions as the E3-like enzyme for the LC3 conjugation system; (5) LC3 (microtubule-associated protein 1A/1B-light chain 3) conjugation system acts to conjugate phosphatidylethanolamine (PE) to LC3. It is comprised of ATG7 (an E1-like enzyme), ATG3 (an E2-like enzyme) and the ATG16L1 complex (an E3-like complex). The addition of PE to LC3 alters the subcellular localization of LC3 from the cytosol (LC3-I form) to insertion in the autophagosomal membrane (LC3-II form). LC3-II on the autophagosome has been proposed to drive a number of essential processes, but is best known to act as a docking molecule for capture of substrates into the autophagosome (Fig. 2).

As autophagy involves dramatic subcellular membrane remodeling, certain subcellular systems, including the membrane trafficking system and the cytoskeletal network, also undertake essential functions in autophagy [24,26]. Of note, the Ras-related small GTPases superfamily plays a key role as regulators. The Ras superfamily is divided into five main families (Ras, Rho, Ran, Rab, and Arf GTPases) [27]. Rab GTPases serve as master regulators in virtually all steps of membrane traffic [28], while Rho GTPases act as molecular switches for cytoskeleton dynamics [29], either in an active state (GTP-bound) or inactivate state (GDP-bound). Indeed, several Rab GTPases play extensive roles in autophagy [30]. For example, the late endosomal Rab7 has been shown to be involved in the late stages of autophagosome maturation by facilitating fusion of autophagosomes with late endosomes [31,32]. Additionally, Ras proteins are post-translational modified by geranylgeranyl transferase. This prenylation is essential for the functions of Ras proteins, since prenylation localizes these proteins to membranes [33]. Defective prenylation has been observed to result in impaired autophagy [34], possibly indirectly due to dysfunction of Rab GTPases.

Although bulk cytosol can be turned over through autophagy as a starvation response, usually autophagy targets specific substrates to remove cellular stressors [24], such as misfolded proteins, damaged organelles, or protein aggregates. This process is called selective autophagy or precision autophagy. Specific terms are used to classify autophagy according to the degradative cargo, like mitophagy (mitochondria) [35], or pexophagy (peroxisomes) [36]. Intracellular pathogens can also be eliminated by autophagy and is called xenophagy [37]. The specificity of autophagy is commonly determined by E3-like enzymes, which conjugate ubiquitin to the targeted substrate. One example is Parkin, an E3 ubiquitin ligase responsible for mitophagy which recognizes PINK1 (PTEN-induced putative kinase 1), a mitochondrial resident protein on the outer mitochondrial membrane (OMM). PINK1 is constitutively degraded in healthy mitochondria and accumulates in damaged and depolarized mitochondria. Parkin recognizes PINK1 and ubiquitinates multiple proteins on the OMM, then leads to autophagic degradation of mitochondria [38,39]. Autophagy adaptors, such as SQSTM1 (p62) [40], are sensors for ubiquitinated substrates that contain ubiquitin-binding domains and LC3-interacting regions (LIR). These adaptor proteins act as molecular bridges to recruit the LC3 machinery to ubiquitinated substrates. Some sensors can directly recognize substrates and recruit autophagic machineries. For example, NOD2, a cytosolic PRR directly senses invasive bacterial infection through peptidoglycan and recruits ATG16L1 to the bacterial entry site to initiate xenophagy [41]. Another example is TRIM (tripartite motif) family proteins, which typically contain an N-terminal RING domain, a B box, and a coiled-coil domain, and a variable C-terminal domain [42]. TRIM proteins broadly affect autophagy, since TRIMs can assemble autophagic machinery (ULK1, Beclin 1, and LC3). They also recognize their cognate targets without requiring ubiquitin tagging via its variable C-terminal domain, and thus determine the autophagic selectivity [43].

2.3. Potential links between autophagy and AUIDs

Autophagy influences nearly all aspects of the innate immunity and can effectively control activities of inflammasomes [44–46]. First, aforementioned activating PAMPs and DAMPs, such as infections, damaged organelles, and accumulated aberrant substrates within the cell, can be eliminated via autophagy. Therefore, by removing activating signals, autophagy blocks further stimulation of inflammasomes. Second, inflammasome components, such as the inflammasome adaptor protein ASC, can be targeted for degradation by selective autophagy [47]. Third, autophagy can target pro-IL-1 β for degradation, removing the substrate for the inflammasome, and reducing production and secretion of the mature inflammatory cytokines [48].

Pathogenic variants identified in AUIDs may impair the autophagic function at different levels, and thus lead to over-secretion of pro-inflammatory mediators. These genetic defects are briefly summarized as follows based on different autophagic components: (1) variants in autophagy receptors that fail to recognize specific substrates; (2) variants in autophagy adaptors that block recruitment of downstream autophagic machinery; (3) variants in autophagy related proteins; (4) variants of metabolism enzymes that lead to post-translational modification of autophagy related proteins; (5) variants that lead to

accumulation of misfolded proteins that saturate the autophagic machinery and can cause the accumulation of ineffective, enlarged autophagic vacuoles within the cells.

3. Autophagy in classic AUIDs

3.1. Autophagy and NOD2-associated diseases

NOD2-associated diseases represent several diseases associated with specific, disease-associated variants in *NOD2* [49]. *NOD2*, also known as *CARD15*, is an intracellular bacterial sensor protein of the NLR family. Upon sensing bacteria, it induces signal transduction cascades that result in activation of autophagy and transcription of pro-inflammatory and immune modulating genes [50]. Specific *NOD2* variants are linked to several AUIDs that include [49]: CD, BS, and Yao syndrome (YAOS; formerly known as *NOD2*-associated autoinflammatory disease). Although all of these diseases are AUIDs, they are associated with a different spectrum of genetic variants that target distinct regions of *NOD2*. In CD, the three major disease-associated variants, R702W, L1007fs, and G908R are clustered near or in the ligand-sensing, leucine rich repeat (LRR) domain and are thought to reduce *NOD2* function. In contrast, BS variants are found in the central NBD region and are thought to increase *NOD2* activity. The variants most strongly associated with YAOS [51] are either intronic (IVS8⁺¹⁵⁸) or near the LRR domain (R702W) and the functional effects of these variants are still under investigation.

The functional effects of AUID-associated *NOD2* variants on autophagy have been only significantly investigated in the context of CD; there are no reports of autophagic roles in other *NOD2*-associated diseases like BS and YAOS. Impaired autophagy is well accepted as a pathogenic mechanism in CD. Besides *NOD2*, several other autophagy-related genes have genetic variants linked to increased susceptibility of CD that include *ATG16L1* [52], *IRGM* [53], and *ULK1* [54]. Functional studies demonstrate that CD-associated variants in these autophagy-related genes impair autophagy. For example, *NOD2* can recruit *ATG16L1* directly and induce xenophagy. The CD-associated *NOD2* L1007fs polymorphism, or *ATG16L1* T300A mutation disrupts the *NOD2*-*ATG16L1* interaction and as a result fails to induce bacterial clearance via autophagy [41]. Besides directly degrading pathogens, autophagy inhibits inflammation at different levels. As numerous inflammasomes have been shown to promote disease activity in CD [55], dysfunctional autophagy may accelerate disease pathogenesis through an inability to downregulate inflammation generated by activated inflammasomes (Fig. 3). It is noteworthy that *NOD2* signaling may also be targeted by the autophagy protein *ATG16L1* in an autophagy-independent manner [56]. *ATG16L1* can interfere with and recruit *RIPK2* (receptor-interacting serine-threonine-kinase 2), the central downstream signal of *NOD2*. As a result, mutated *ATG16L1* may fail to down regulate *NOD*-driven inflammatory responses.

3.2. Autophagy in TRAPS

TRAPS is caused by the variants in *TNFRSF1A* (tumor necrosis factor receptor superfamily member 1A), which encodes TNF receptor 1 (TNFR1). TNFR1 is a type 1 transmembrane protein that contains 4 N-terminal extracellular cysteine-rich domains (CRDs), a transmembrane domain, and a C-terminal cytoplasmic death domain (DD) [57]. TNFR1 is

activated by binding its ligand TNF α , and leads to the activation of transcription factors, like NF- κ B or AP-1, to induce transcription of pro-inflammatory genes, or results in stimulation of death processes, such as apoptosis or necroptosis, depending on cellular contents and the microenvironment conditions [58,59]. Also, the extracellular domain of TNFR1 can be cleaved and shed from the cell surface to generate soluble receptors. This shedding may attenuate TNF- α activity because soluble TNFR are able to bind ligands and function as competitive antagonists for soluble TNF α [60,61].

TNFR1 is multifunctional, and different variants of *TNFRSF1A* in TRAPS patients can cause inflammation via different mechanisms. Therefore, clinical phenotypes and therapeutic responses vary significantly [62]. *TNFRSF1A* variants can cause impaired TNF- α binding, abnormal apoptosis that may prolong pro-inflammatory cell survival, altered NF- κ B activation, or defective receptor shedding [1,63e68]. For example, the p.V173D variant (near the metalloproteinase cleavage site) significantly reduces shedding of TNFR1 and patients are strikingly responsive to Etanercept treatment, as compared with other mutants [68]. In contrast, some variants are associated with anti-inflammatory effects (weaker binding of TNF- α , lower cell-surface expression, or decreased TNF-induced NF- κ B activation), indicating that the pro-inflammatory effects of these variants are indirect and may have different mechanisms beyond the alterations in TNFR1-dependent pathways. To date, both *in vitro* and *in vivo* studies have unveiled that some TRAPS-associated variants may cause protein misfolding that lead to defective TNFR1 trafficking and their retention in the ER [66,69], which may in turn increase the intracellular stress with autophagy involved in the pathogenesis.

The correlation between autophagy and NF- κ B pathway has been well studied and these data may help understand the role of autophagy in TRAPS. The TNFR1-induced activation of the classical NF- κ B pathway has been elegantly reviewed [70]. Upon binding TNF α , TNFR1 recruits adaptor TRADD (TNF receptoreassociated death domain) to nucleate 'Complex I' [71] comprised of TRADD, TRAF2 (TNF receptoreassociated factor 2), RIPK1, cIAP1 (cellular inhibitor of apoptosis 1), cIAP2, and LUBAC (linear ubiquitin chain assembly complex). RIPK1 is poly-ubiquitinated via cIAP1/2 and TRAF2 [72,73], and this non-degradative ubiquitin chain serves as scaffold to recruit the TAK1 (TGF- β -activated kinase 1) kinase complex, consisting of TAK1 and TABs (TAK1-binding protein) [74]. TAK1 then phosphorylates IKK1 (I κ B kinase 1) and IKK2, which in turn leads to phosphorylation and proteasomal degradation of I κ B (inhibitor of kappa B) [75], and NF- κ B activation. Several components in the NF- κ B pathway also have important functions in autophagy separate from their role in NF- κ B activation. IKK1/2 is essential for inducing of canonical autophagy in response to various autophagy inducers, (including starvation, rapamycin and TNF- α), and this process is independent of NF- κ B activation [76,77]. In resting conditions, TAB2 and TAB3 bind the essential autophagic factor Beclin-1 and inhibit autophagy activation. Upon induction by pro-autophagic stimuli, TAB2 and TAB3 dissociate from Beclin-1 to engage in stimulatory interactions with TAK1, and facilitate autophagy through induction of PI3P-containing vesicles via the action of the Beclin-1 containing class III PI3K complex [78]. TBK1 (TANK-binding kinase 1), an important innate immunity regulator, is necessary for autophagosome maturation rather than autophagy induction and mediates IL-1 induced autophagy [79]. This can be an important negative feedback

controlling the inflammation in AUIDs. Additionally, intact autophagy function is also essential for NF- κ B activation induced by TNF- α [77], suggesting an intimate inter-relationship between autophagy and NF- κ B pathway exists. While more research needs to be done to fully understand the inter-relationship of NF- κ B and autophagy, it appears that NF- κ B can be either pro-autophagic (promote Beclin-1 transcription) [80] or anti-autophagic [81,82], possibly depending on different microenvironment.

By studying the autophagy in TRAPS patients, Bachetti's group [69] demonstrated that autophagy is the main cellular mechanism for the clearance of TNFR1 proteins of both wild type and mutant (C55Y or DEL27) forms. Monocytes from TRAPS patients or cells exogenously expressing mutant C55Y TNFR1 showed impaired autophagy. While these cells had normal initiation of autophagy, they had substantially impaired lysosomal clearance of autophagosomal contents, possibly due to the overload of misfolded proteins, resulting in the accumulation of enlarged autophagic vacuoles within the cells. Additionally, these mutant TNFR1 proteins triggered enhanced NF- κ B activation, but expression of Beclin-1 was not altered, indicating that the pro-autophagic effects of NF- κ B activation mentioned above may not operate in this case. TRAPS may act as a model of other protein aggregation diseases, such as cystic fibrosis (CF), Alzheimer's disease (AD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS), linking autophagy to inflammation [83]. Drugs targeting HSP90 like geldanamycin, by increasing protein refolding may rescue the autophagic functions already impaired by misfolded proteins loads [69]; however, the detailed effects of geldanamycin on autophagy need to be further investigated since geldanamycin can have negative effects on the activation of NF- κ B by inducing IKK subunit degradation [84] and potentially suppressing autophagic initiation through TAK1-IKK axis (Fig. 3).

3.3. Autophagy in FMF

FMF is caused by *MEFV* gene variant encoding pyrin (also called TRIM20), which is the only TRIM family member with an N-terminal PYD instead of a RING domain. Such variants as M680I, M694V, and V726A [85] mostly affect the C-terminal B.30.2/SPRY domain. Historically, the function of both wild-type and mutated pyrin was highly controversial as both pro- and anti-inflammatory roles have been suggested for pyrin [86]. In some studies, pyrin negatively regulates NLRP3 inflammasome activity by directly binding to ASC (via Pyrin domain) and caspase-1 (via SPRY domain) [87]. Thus, mutated pyrin loses the ability to negatively regulate the NLRP3 inflammasome, resulting in higher inflammasome activity and more IL-1 β production. Other studies suggest pyrin can assemble a 'pyrin inflammasome' together with ASC and caspase-1 to facilitate IL-1 β processing independently of NLRP3 [88–90], and in the mutated form, the caspase-1 activity is constitutively activated. Recently, both of these contrasting models have gained support, implicating a complex regulatory network. Pyrin can sense signal changes of cytoskeletal organization by bacterial toxins via RhoA [91]. Further studies demonstrated that activated RhoA induces downstream kinases like PKN, phosphorylates pyrin and leads to inhibitory binding of pyrin by 14-3-3 proteins [92]. Toxins of some bacteria, such as *Clostridium difficile*, *Burkholderia cenocepacia* and *Vibrio cholera*, can inactivate RhoA and lead to actin depolymerization. In this manner, pyrin senses bacterial infection and responds by

nucleating an inflammasome to defend against bacteria. Pypin with the three frequent FMF-associated B30.2 variants (M680I, M694V, and V726A) substantially reduces the binding affinity to PKN, and thus escapes from the inhibitory phosphorylation [92]. This may explain why colchicine, as a microtubule-depolymerizing agent and a potent RhoA activator [93], can be used as one of the most effective drugs for FMF treatment.

As mentioned previously, TRIM proteins can mediate selective autophagy, and so does pypin (TRIM20). Under stimulation of IFN- γ , the SPRY domain of pypin recognizes and binds to NLRP3, while the middle portion (including B-box and CCD) is mainly responsible for recruiting autophagic apparatus, including ULK1, Beclin1, ATG16L1 and some paralogues of LC3, and thus leads to precision autophagy of NLRP3 [94]. The disease-associated variants in the SPRY domain of pypin perturb autophagic degradation of NLRP3 and hence may contribute to the inflammatory phenotype [94]. Beyond acting as a pro- or anti-inflammation regulator, the roles of pypin may also depend on the stimulating factor (IFN- γ , drugs or bacterial toxins), or the mutant status. Undoubtedly, the precision autophagy may provide an important mechanism by which inflammasome activation is inhibited (Fig. 3).

3.4. Autophagy in HIDS

HIDS, also called mevalonate kinase deficiency (MKD), is caused by autosomal recessive variants in the *MVK* (mevalonate kinase) gene [95]. *MVK* is a key component in mevalonate pathway that produces isopentenyl 5-PP (pyrophosphate), which is involved in cholesterol synthesis. Statins, the drugs used to decrease cholesterol levels, can inhibit HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme-A) reductase that are also within the mevalonate pathway, and thus they are often used as drug development tools to establish research models for HIDS. Isopentenyl 5-pyrophosphate is also involved in the non-cholesterol pathway that produces farnesyl-PP or geranylgeranyl-PP, and further induces prenylation of small GTPase, either farnesylation or geranylgeranylation [33].

The mechanism of *MVK* deficiency leading to autoinflammation has been elucidated. Surprisingly, this has led to a connection between HIDS and FMF, which were previously considered as unrelated AUIDs [92]. Chae's group reported that similar to FMF, the pypin inflammasome also mediates IL-1 β release in HIDS, and this is triggered by dysfunctional RhoA [92]. Defects of geranylgeranylation at the C-terminus of RhoA, as a result of *MVK* deficiency, cannot induce RhoA translocation from the cytosol to the plasma membrane, an essential step for its biological function. RhoA acts as a negative regulator of pypin inflammasome, and thus inactivated RhoA will fail to suppress the pypin inflammasome. This may also explain why there is little inhibitory effect of colchicine for patients with HIDS, probably because colchicine could not activate RhoA that was not localized to the cell membrane.

Since defects in the post-transcriptional modification of prenylation can affect a wide range of small GTPases, the RhoA-pypin inflammasome axis may not be the only pathogenic pathway in HIDS. Van der Burgh's group reported that damaged mitochondria were accumulated in the cytosol of isoprenoid deficient monocytes, and this was due to impaired autophagy, both in peripheral blood mononuclear cells (PBMCs) from HIDS patients and simvastatin treated monocytes. Oxidized mitochondrial DNA further contributes to the

IL-1 β hypersecretion via the NLRP3 inflammasome [34]. It should be remembered that the same group also demonstrated that defective prenylation of RhoA had no effect on autophagy [96], indicating that impaired autophagy might act as a different pathway from RhoA-pyrin inflammasomes axis. It is possible that other small GTPases, in particular of the Rab family, may be involved in impaired autophagy when prenylation is absent. Rab GTPases serve as regulators of membrane traffic and are more important in autophagy processes. Yet, the exact GTPase that leads to impaired mitophagy remains to be identified (Fig. 3).

4. Autophagy in other AUIDs and differences between AUIDs and autoimmune disorders

4.1. Autophagy in recently reported monogenic AUIDs

Dysregulation of IFN signaling has been linked to inflammatory diseases, including STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutieres syndrome (AGS) 1–7, proteasome-associated autoinflammatory syndromes/chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (PRAAS/CANDLE), and Spondyloenchondrodysplasia with immune dysregulation (SPENCDI) [3]. Although scanty literature can be found to study these rare diseases, the regulation of type I IFN has been broadly investigated [97]. Type I IFN is one of the most important mediators of antiviral signaling. For RNA viruses, double-stranded RNA in the cytosol is sensed by RIG-I and MDA5, and signals through the adaptor protein mitochondrial antiviral-signaling protein (MAVS) [98], a transmembrane protein localized in mitochondria. Oligomerization of MAVS can activate transcription factors IRF3 and IRF7 and induce type I IFN production. AGS7 is caused by gain-of-function variants in *IFIH1*, the gene encoding MDA5, which lead to enhanced IFN- β transcription [99]. Autophagy can regulate the activation of mitochondrion-tethered MAVS by mitophagy [100] or other mechanisms [101,102], thus suppressing type I IFN production. For DNA viruses, cyclic di-nucleotides generated by cyclic GMP–AMP synthase (cGAS) in the presence of dsDNA activate the adaptor protein stimulator of interferon genes (STING) to induce type I IFN expression [97]. Gain-of-function variants in *TMEM173*, which encodes STING, are found in SAVI patients [103]. STING trafficking and activation are controlled by autophagy protein ATG9L1, possibly via a non-canonical autophagy pathway [104]. ULK1 activation also leads to inhibitory phosphorylation of STING and less type I IFN expression, and this process is autophagy independent [105]. All these studies suggest that autophagy or autophagy proteins can suppress type I IFN production by precise regulation and may represent a potential therapeutic target for this group of AUIDs.

There is an unspecified type of AUIDs characterized by a pustular/psoriasis-like phenotype, including CARD14-mediated psoriasis (CAMPS), deficiency of IL-36 receptor antagonist (DITRA) and pustular psoriasis, caused by variants in the *CARD14*, *IL36RN* and *APIS3* gene [106–108], respectively. The enhanced IL-36 signaling in keratinocytes seems to be an important mechanism for this phenotype [109]. Recently Capon's group first reported that *APIS3* variants cause skin autoinflammation by disrupting keratinocyte autophagy and up-regulating IL-36 production [110]. *APIS3* is abundantly expressed in keratinocytes and

encodes a subunit of AP-1 complex which has been implicated in the formation of autophagosomes [111]. Variants in *AP1S3* may impair keratinocyte autophagy and leads to abnormal p62 accumulation, with activation of NF- κ B and up-regulation of IL-36 expression [110]. The study results from this special type of monogenic AUIDs may provide new perspectives that defective autophagy can be involved in certain cutaneous conditions.

4.2. Gouty arthritis and pro-inflammatory effects of autophagy

As is previously discussed in this article, we mainly focused on the anti-inflammatory effects of autophagy. However, as we know from studies on TRAPS, autophagy also facilitates TNF- α induced NF- κ B activation, which seems counterintuitive. This is not the only case for a pro-inflammatory effect of autophagy, and in some circumstances autophagy even promotes IL-1 β secretion [112]. Therefore, it is essential to understand the complexity of this system before a pro- or anti-autophagy therapy is applied to AUID patients to avoid unintended side effects as much as possible. Deretic's group reported that when inflammasome agonists such as LPS, alum, silica, amyloid- β or nigericin, are combined with stimulators of autophagy (i.e. starvation or mTOR inhibition with pp242/Torinib) this can strongly promote inflammasome-dependent cytokine secretion of IL-1 β and IL-18 [112]. Inhibition of autophagy flux by bafilomycin A1 (an antagonist of vacuolar H⁺ ATPase and prevents luminal acidification and autophagosomal cargo degradation) reduces this IL-1 β secretion [112]. Additional experiments demonstrated that, whereas basal autophagy inhibits IL-1 β secretion, induced autophagy augments IL-1 β secretion, and this is a type of autophagy-based unconventional secretory pathway. Further studies suggested that autophagosomes are involved in this process, and IL-1 β can be incorporated between the inner- and outer-membrane of the autophagosome and is released following the fusion with the plasma membrane [113]. As evidenced above, we may find a clue that in a chronic course of a disease, the basal autophagy function is anti-inflammatory; while in an acute phase, where pro-inflammatory stimuli usually exist, autophagy has synergistic effects with inflammatory responses.

This conclusion seems applicable in acute gouty arthritis, although there is little evidence. Ritis's group studied the proinflammatory neutrophil extracellular traps (NETs) [114], which are extracellular fibrous structures composed of chromatin and granule constituents of neutrophils. Release of NETs accompanied by neutrophil cell death (NETosis) after phagocytosis of pathogens or treatment with inflammatory stimuli are described as an extracellular antimicrobial process, critical for neutrophil physiology [115]. Formation of NETs during acute gout or following treatment of peripheral polymorphonuclear cells (PMNs) with monosodium urate (MSU) crystals is further associated with IL-1 signaling [114], and autophagy is required for NET-dependent cell death [116]. Treatment of PMNs with autophagy inhibitors 3-methyladenine (3-MA, a class III PI3K inhibitor) or bafilomycin A after the addition of MSU crystals significantly diminishes the percentage of cells releasing NETs [114]. This also demonstrates a different aspect for the pro-inflammatory function of autophagy.

4.3. Differences between AUIDs and autoimmune diseases

In contrast to autoimmune diseases, periodic occurrence of disease is generally more common in AUIDs, which have absence/low titers of antinuclear antibodies or antigen-specific T cells and primarily result from abnormal innate immunity. Autoimmune diseases are mainly related to adaptive immunity, which is less involved in AUIDs. Autophagy has been studied in both autoimmune and autoinflammatory disorders, and an autophagic role in T and B lymphocytes has been described in the autoimmune disease, systemic lupus erythematosus [117], whereas this type of study is rarely reported in AUIDs, perhaps due to the distinct immune responses in these two groups of rheumatic diseases.

5. Concluding remarks

AUIDs primarily result from the dysregulation of innate immunity, and more molecular mechanisms underlying the immune abnormality have been unveiled in these disorders, including the relationship between autophagy and inflammation. Under normal conditions, autophagy can effectively control inflammasome activities, whereas autophagy alterations contribute to the pathogenesis of TRAPS, FMF and HIDS. As abundantly evidenced, augmenting autophagy by various means has reduced inflammasome activity and IL-1 β /activated caspase-1. However, autophagy-stimulating therapies need to be applied with caution, as autophagy also has pro-inflammatory effects under some circumstances, suggesting that proper balance of the pro- and anti-inflammatory actions may be delicately regulated. It is also suggested that autophagy-enhancing therapies may be avoided during acute inflammation. Certainly, further research is warranted to determine if autophagy inhibitors may be more effective for controlling excessive inflammation. It can be expected that an in-depth study of the role of autophagy in AUIDs may help design and develop better therapeutic strategy and approach for these diseases in the future.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jaut.2017.10.012>

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Fig. 1.

Inflammasomes. The structure of canonical inflammasomes, (such as NLRP3 and AIM2 inflammasomes), usually consist of 3 parts: PRR, adaptor protein ASC containing PYD and CARD, and protease caspase-1 which mediates the processing of IL-1 β . ASC is linked to PRR through PYD-PYD interaction, and caspase-1 is linked to ASC through CARD-CARD interaction. Some CARD containing PRRs (such as NLRC4) can directly recruit caspase-1 without the adaptor ASC. Inflammasomes can be activated by PAMPs (such as bacteria, viruses, fungi, etc.) or DAMPs (such as damaged organelles, accumulated aberrant substrates, etc.). Abbreviations: PRR, pattern recognition receptors; LRR, leucine-rich repeat; NBD, nucleotide-binding domain; HIN200, hematopoietic IFN-inducible nuclear protein with 200-amino-acid repeat; PYD, Pyrin domain; CARD, caspase recruitment domain; ASC, apoptosis-associated speck-like protein containing CARD; NLRP3, NLR family pyrin domain containing 3; AIM2, absent in melanoma 2; NLRC4, NLR family CARD domain containing 4; PAMPs, pathogen-associated molecular patterns; DAMPs, danger-associated molecular patterns.

Fig. 2.

The process of canonical autophagy. The autophagy inducing signals (like starvation) initiate formation of the isolation membrane. Closure of the isolation membrane results in formation of the autophagosome for further degradation. The subsequent lysosome-autophagosome fusion leads to degradation of the contents of the autophagosome by lysosomal hydrolases in the autolysosome. The ULK1 complex and class III PI3K complex are involved in the initiation process. The ATG16L1 complex facilitates LC3-PE conjugation.

Fig. 3.

Schematic diagram of several AUIDs pathogenesis. Mutated proteins and relevant changes (altered pathways, impaired combination with other components, etc.) are labeled in red. In CD, *NOD2* or *ATG16L1* disease-associated variants disrupt NOD2-ATG16L1 interaction and blocks bacteria clearance via autophagy. In TRAPS, accumulation of misfolded TNFR1 impairs the lysosomal digestion stage of autophagy and in turn causes decreased clearance of these misfolded proteins, which may lead to the stimulation of inflammasomes. Other TRAPS-associated *TNFRSF1A* variants (p.V173D) may lead to reduced shedding of TNFR1 and TNF- α activity cannot be attenuated by soluble receptors. In FMF, pyrin (TRIM20) binds to NLRP3 and at the same time recruits autophagic apparatus, leading to precision autophagy of NLRP3, under stimulation of IFN- γ . Toxins of some bacteria can inactivate RhoA and thus pyrin nucleates an inflammasome to defend against bacteria. Colchicine can activate RhoA then PKN and lead to inhibitory binding of pyrin by 14-3-3 proteins. FMF-associated B30.2 mutations of pyrin can reduce the binding affinity to PKN. In HIDS, prenylation of small GTPases such as Rabs can be absent, leading to impaired autophagy. Lack of prenylation on RhoA can lead to pyrin inflammasome activation. Abbreviations: CD, Crohn's disease; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; FMF, familial Mediterranean fever; NLRP3, NLR family pyrin domain containing 3; HIDS, hyperimmunoglobulinaemia D and periodic fever syndrome. (For

interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Classic members of monogenic autoinflammatory diseases.

Diseases	Gene	Protein	Inheritance	Prominent clinical features
FMF	<i>MEFV</i>	Pyrin	AR/AD	Episodic fever, serositis, oligoarthralgia, erysipelas-like eruption on the lower extremities, serositis, amyloidosis
TRAPS	<i>TNFRSF1A</i>	TNFR1	AD	Episodic fever, myalgia underlying rash, oligoarthralgia, periorbital edema, serositis, steroid response
HIDS	<i>MVK</i>	Mevalonate kinase	AR	Fever, rash, arthralgia, abdominal pain, diarrhea, conjunctivitis, cervical lymphadenopathy, splenomegaly
CAPS	<i>NLRP3</i>	Cryopyrin	AD	Fever, urticarial rash, cold intolerance, conjunctivitis, arthralgia, hearing loss and central nervous system involvement

FMF, familial Mediterranean fever; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; HIDS, hyper-gammaglobulinemia D syndrome; CAPS, cryopyrin-associated periodic syndromes; AR, autosomal recessive; AD, autosomal dominant.