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Beyond autophagy: New roles for ULK1 in immune signaling and interferon responses

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Abstract

The human serine/threonine kinase ULK1 is the human homolog of the *Caenorhabditis elegans* Unc-51 kinase and of the *Saccharomyces cerevisiae* autophagy-related protein kinase Atg1. As Unc-51 and Atg1, ULK1 regulates both axon growth and autophagy, respectively, in mammalian cells. However, a novel immunoregulatory role of ULK1 has been recently described. This kinase was shown to be required for regulation of both type I interferon (IFN) production and induction of type I IFN signaling. Optimal regulation of IFN production is crucial for generation of effective IFN-immune responses, and defects in such networks can be detrimental for the host leading to uncontrolled pathogen infection, tumor growth, or autoimmune diseases. Thus, ULK1 plays a central role in IFN-dependent immunity. Here we review the diverse roles of ULK1, with special focus on its importance to type I IFN signaling, and highlight important future study questions.

Keywords

ULK1; Interferon; signal transduction; immune signaling; innate immunity

1. Introduction

ULK1 (Unc-51-like kinase 1) is a highly conserved serine/threonine kinase mainly known for its regulatory role in autophagy in response to nutrient deprivation [1, 2]. However, recent findings have revealed a prospective role for ULK1 in regulation of innate immunity of interferons (IFNs) [3, 4]. This opens a new field of investigation that could have important implications for the advancement of the IFN research field and change our overall understanding of the mechanisms behind IFN-mediated immune responses. In this review

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Conflict of interest statement

None.

we present our current understanding on the different roles of ULK1 with special attention to its role in type I IFN production and type I IFN-induced responses.

2. Interferons

IFNs were first described in 1957 by Alick Isaacs and Jean Lindenmann [5] as secreted factors capable of inducing viral interference. In 1965, Wheelock identified the synthesis of another IFN-like protein with anti-viral properties [6]. Few years later (1972), Falcoff [7] demonstrated that lymphocytes are capable of producing two distinct types of IFNs in response to different inducers and suggested calling virus IFN the protein secreted by any type of cell in response to a virus infection, and immune IFN the protein secreted by immunocompetent cells during an immune response. One year later, Youngner and Salvin [8] decided to classify these IFNs as type I and type II IFNs, respectively. It wasn't until 1980 that a group of renowned scientists in the field agreed upon the definition of IFN and decided to classify the IFNs based on their antigenic specificities using Greek letters: IFN α , IFN β (for the classical virus-induced or type I IFNs) and IFN γ (for the type II, immune IFN) [9]. However, the terms type I, type II, and, more recently, type III IFNs are still used today to group IFNs based on their protein structure, receptor binding and/or biological functions [10–12]. Currently, in humans, type I IFN family comprises 13 human IFN α species (and allelic forms) encoded by 14 human genes, IFN β , IFN ϵ , IFN κ , and IFN ω , whereas IFN γ is the only type II IFN known [10, 11, 12]. IFN δ [13], IFN τ [14], and the IFN-like cytokine limitin [15] are part of the type I IFN family, but are not found in humans [12]. In 2003, a new IFN family, type III, was established and comprises IFN-like cytokines, which, although resembling interleukin-10 (IL-10)-related cytokines, possess antiviral properties [16–18]. These are classified as IFN λ 1, IFN λ 2, and IFN λ 3 (nomenclature currently used) or IL-29, IL-28A, and IL-28B, respectively [16, 17]. More recently, a new member was added to this family, IFN λ 4, which possesses antiviral properties *in vitro* [19]. However, through mechanisms that are not yet understood, IFN λ 4 activity is inversely correlated to hepatitis C virus and cytomegalovirus clearance [19, 20, 21, 22].

2.1. IFN signaling and functional responses

The expression of IFNs is triggered by activation of pattern recognition receptors (PRRs) and cytokine receptors signaling pathways [23–25]. IFNs are then secreted and bind heterodimeric cell surface receptors [11]. Type I IFNs are produced by most cell types and bind the type I IFN receptor (IFNAR), which is composed by IFNAR1 and IFNAR2 subunits and expressed in almost all cell types [23, 24]. IFN γ is mainly produced by natural killer cells, T cells and antigen presenting cells (APCs) and binds to type II IFN receptor that is composed by two ligand binding IFNGR1 chains and two signal-transducing IFNGR2 chains [10, 26]. Whereas IFNGR1 is constitutively expressed in most cells, the expression of IFNGR2 is cell type- and signal-dependent [26]. Type III IFNs are produced by nearly all cells, however the expression of the ligand binding IFN λ R1 (or IL-28RA) subunit of the type III IFN receptor is restricted to few cell types, mostly of epithelial origin [25, 27]. The other type III receptor subunit, IL-10R2, is also part of IL-10, IL-22, and IL-26 receptor complexes [25, 27]. The different IFN receptor subunits are each constitutively associated with tyrosine kinases of the Janus family (Jaks) [11, 23]. IFNAR1 and IL-10R2 are

associated with TYK2; IFNRA2, IFNGR1, and IFN λ R1 are associated with JAK1; and IFNGR2 is associated with JAK2 [11, 23]. Engagement of either IFN receptor leads to activation of Jaks, followed by tyrosine phosphorylation of the receptor cytoplasmic domains creating docking sites for STAT (signal transducer and activator of transcription) proteins, which are then phosphorylated by Jaks [11, 23, 25]. Upon phosphorylation, STATs form either homodimers (under type I, II, and III stimulation) or heterodimers (under type I and III stimulation) that can either bind other transcription factors or directly translocate into the nucleus, where they initiate transcription of interferon stimulated genes (ISGs) [11, 23, 25, 28, 29]. For example, STAT1 homodimers bind IFN γ activation site (GAS) elements, which are defined as the palindromic consensus sequence TTCN₂₋₄GAA found in the promoter region of ISGs [30]. In contrast, STAT1–STAT2 heterodimers bind IRF9 (interferon regulatory factor 9) forming the ISGF3 (interferon-stimulated gene factor 3) complex, which travels into the nucleus and binds IFN-stimulated response elements (ISRE) present in the promoter region of other ISGs [31]. Interestingly, non-canonical and more complex models, involving STAT activation, for both type I and II pathways have been described [32, 33, 34]. Upon IFN γ treatment, both the ligand and the IFNGR1 subunit were found to be internalized by endocytosis and then translocate into the nucleus in a form of a complex with STAT1, where they bind GAS elements [32, 33]. Similarly, IFNAR1, IFNAR2, TYK2, STAT1, STAT2, and type I IFN were found to localize in the nucleus of IFN treated cells [34]. However, further studies are needed to better understand the impact of these findings on gene transcription and IFN responses.

Besides activation of the canonical Jak-Stat signaling cascades [35], IFNs also modulate several other signaling pathways, such as mitogen-activated protein kinases (MAPKs) (e.g, p38 MAPK, ERK1/2, Mnk) [29, 36, 37, 38, 39], phosphatidylinositol 3-kinase (PI3K)-AKT [37, 40, 41], and mammalian target of rapamycin complex 1 (mTORC1) [36, 42] and mTORC2 signaling cascades [43, 44]. Recent studies have demonstrated that these pathways can act independently and/or cross-regulate each other [3, 45, 46]. Nevertheless, the coordinated activation of these multiple signaling pathways upon engagement of IFNRs is required for optimal transcription and/or mRNA translation of a broad range of ISGs that are required to mount appropriate IFN-responses [11].

As discussed, IFNs are characterized by their antiviral properties [26], however these cytokines exert multiple other functions [47, 48]. These include antibacterial, immunomodulatory, anti-proliferative, pro-apoptotic, autophagic, and anti-angiogenic properties [23, 24, 48, 49, 50]. As such, IFNs have been approved for use as therapeutic agents against chronic viral infections (e.g., human papillomavirus, hepatitis C and hepatitis B virus), cancer (e.g., melanoma, renal cell carcinoma, chronic myeloid leukemia (CML), hairy cell leukemia, multiple myeloma, non-hodgkin lymphoma, and AIDS-related Kaposi's sarcoma), and multiple sclerosis [26, 48, 51]. However, constitutive IFN production can be also harmful in mammals and lead to type I interferonopathies, which are monogenic disorders characterized mostly by neurological and dermatological symptoms, such as systemic lupus erythematosus (SLE) and Aicardi-Goutières syndrome [52]. Moreover, IFNs can also be detrimental during specific bacterial or viral infections [53]. In fact, recently, Ng et al. [54] demonstrated that, although binding the same receptor, IFN β delays clearance of lymphocytic choriomeningitis virus (LCMV) *in vivo*, whereas IFN α prevents early viral

dissemination. Given the complexity of the IFN signaling it is fundamental to completely understand the mechanistic events behind it, in order to design better treatments against pathogen infection and several immune-related diseases.

3. ULK1, a regulator of axon growth and autophagy

The human serine/threonine-protein kinase ULK1 was identified as the human homolog of the *C. elegans* Unc-51 kinase [55] and of the *S. cerevisiae* autophagy-related protein kinase Apg1p/Atg1 [56] in 1998 [57]. Sequence analysis showed that, at the amino acid level, ULK1 is 57%, 20%, and 27% similar to the kinase (located in the N-terminus), the proline/serine-rich, and the C-terminal domains of Atg1, respectively [57]. Compared to the same domains of Unc-51, ULK1 presents 74%, 22%, and 46% similarity, respectively [57]. Although presenting high homology with Unc-51, which is expressed exclusively in neurons, ULK1 was found to be ubiquitously expressed in human adult tissues, suggesting that this evolutionary conserved serine/threonine kinase may have acquired a diversity of functions during vertebrate evolution [57]. In later studies, four orthologs of ULK1 were identified in mammals: ULK2, ULK3, ULK4, and STK36 (or fused) [58, 59]. The overall sequence of ULK2 is 55% identical to that of ULK1, presenting 79.1% similarity to its kinase domain and 55.9% to its conserved C-terminal domain [59]. In contrast, ULK3, ULK4 and STK36 have lower sequence similarity to that of ULK1 and do not present the conserved C-terminus [59].

Mutation of the *unc* (uncoordinated movement)-51 gene in *C. elegans* affects the outgrowth and guidance of axons resulting in abnormal cell distribution (in particular the positioning of neurons and muscle cells), and in uncoordinated/paralyzed, egg-laying defective and dumpy phenotypes [55, 60, 61]. Similarly, both ULK1 and ULK2 were shown to be important during neuronal development [58]. ULK1 was shown to be required for neurite elongation and differentiation of cerebellar granule neurons [62]. This process seems to be regulated by the interaction of ULK1 with SynGAP and Syntenin, two synaptic proteins, and consequent regulation of Ras-like GTPase cascade and Rab5-induced endocytic trafficking in neurons [63]. In fact, the knockdown of either one or both ULK1 and ULK2 by RNAi reduced the size of axons and increased their branching and the number of long filopodia in sensory neurons, possibly due to defective endocytosis of the nerve growth factor (NGF) and its receptor TrkA, resulting in prolonged TrkA/NGF-mediated signaling [64]. Additionally, ULK1 directly phosphorylates Syntenin-1 impeding its binding to ubiquitin [65] and plays a cytoprotective role in neurons [2].

On the other hand, mutation of *apgl/atg1* gene in *S. cerevisiae* resulted in an autophagy-defective strain, with absence of autophagosome formation in the cytosol and faster loss of viability under starvation conditions, when compared to the wild-type strain [56, 66]. Likewise, ULK1 has been implicated in regulation of the autophagic response upon nutrient starvation in higher eukaryotes [1, 2]. Interestingly, ULK1 and ULK2 present redundant autophagic functions in fibroblasts [2], but not in human embryonic kidney 293 (HEK293) cells [1] and in cerebellar granule neurons [2]. This suggests that ULK2 might compensate ULK1-driven responses in a cell-type specific manner [2]. In fact, ULK1 or ULK2 knockout (KO) mice are viable and do not exhibit any developmental defects [67, 68]. However,

ULK1/2 double knockout (DKO) mice die within a day after birth [68, 69]. Similarly, autophagy induced by amino acid deprivation occurs in ULK1- and ULK2-deficient mouse embryonic fibroblasts (MEFs), but not in ULK1/2 DKO MEFs [67, 68]. However, reticulocyte maturation is impaired in ULK1 KO mice, which present delayed mitochondrial and ribosomal clearance during erythroid differentiation [67, 70].

The role of ULK1 in the autophagic processes has been extensively studied and has been reviewed elsewhere [58, 59, 71]. In brief, and in a very simplified way, the amino acid and nutrient sensor mTORC1, via Raptor, binds the ULK1-ATG13-FIP200-ATG101 complex and phosphorylates ULK1 on serine 757 (Ser757) preventing its association with AMP activated protein kinase (AMPK) and inhibiting initiation of autophagy under nutrient-rich conditions [72]. Upon nutrient deprivation, the energy sensor AMPK becomes active and inhibits mTORC1, leading to de-phosphorylation of mTORC1 phospho-sites in ULK1. Under these conditions, AMPK binds to and directly phosphorylates ULK1, which then triggers formation of autophagosomes [58, 59, 71, 72, 73, 74, 75, 76].

Two important reports recently revealed that ULK1 can be phosphorylated in multiple sites spread through its three highly conserved domains, indicating that ULK1 functions might be controlled by several kinases, including AMPK, AKT, and mTOR [77, 78]. Moreover, Bach et al. [78] suggested that ULK1 kinase could act as a central node that integrates “information” coming from different signaling pathways involved in the control of autophagic responses. We go farther. Given the ubiquitous expression of ULK1 in higher eukaryotes and the potential for its kinase activity to be controlled by several other kinases, we have hypothesized that ULK1 might have other biological role(s) beyond the regulation of axon growth and autophagy, and that its activity can be stimulated by different signaling molecules. Consistent with this idea, non-autophagic roles have been previously described for other autophagy-related proteins (reviewed in [79]). Additionally, ULK1 activity was shown to be required for insulin-mediated glucose uptake and lipid metabolism in adipocytes [80], for the completion of the life cycle and infection of the intracellular bacterium *Brucella abortus* [81], and for reactive oxygen species-induced cell death by promoting poly (ADP-ribose) polymerase 1 (PARP1) activity [82].

3.1. ULK1 as a regulator of IFN production

Pathogenic nucleic acids, such as DNA, RNA, or nucleotides, are detected by host sensing mechanisms, which include toll-like receptors, RIG-I like receptors, AIM2-like receptors, and intracellular DNA receptors [83]. These sensors regulate activation of several downstream effectors that lead to the transcription of type I IFNs and pro-inflammatory cytokines that regulate innate and adaptive immune responses [83, 84]. Recently, Sun and colleagues [85] identified a cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS) and showed that this can bind cytoplasmic DNA, triggering the synthesis of cGAMP [86], and consequently inducing IRF3 activation and IFN β production in a STING (stimulator of interferon genes)-dependent manner. In another report, Konno et al. [4] demonstrated that cGAS, via synthesis of cGAMP, is required for dephosphorylation of AMPK on Thr172 and of ULK1 on Ser556 in human and Ser555 in murine cells (AMPK phospho-site in ULK1). ULK1 is then capable of phosphorylating STING on Ser366

blocking its kinase activity towards IRF3, and consequent transcription of IFN β [4]. Consonantly, RNAi suppression of ULK1 led to increased levels of type I IFN production in response to both dsDNA and cGAMP's treatments [4]. However, it is still unclear whether cGAMP can directly or indirectly control both ULK1 and AMPK dephosphorylation events. It would be interesting to determine whether cGAMP can bind one or both kinases, as it was shown to bind STING [87, 88]. Nevertheless, ULK1 was shown to suppress sustained transcription of innate immune genes [4], which could be fundamental to prevent the development of STING-dependent pro-inflammatory diseases [89]. A recent study focused on the mechanism behind the fact that solar ultraviolet (UV) exposure exacerbates the symptoms of patients with autoimmune diseases, such as systemic lupus erythematosus, supports this idea [90]. In their report, Kemp et al. [90] observed that UV exposure causes high levels of cellular DNA damage, which triggers caspase/calpain-mediated apoptosis and consequent loss of ULK1 protein levels. As a result, STING remains highly active in response to cytosolic DNA and cyclic dinucleotides, resulting in constant IRF3 activation and IFN α/β production that could explain why patients with autoimmune diseases are more susceptible to UV light exposure [90].

3.2. ULK1 as a regulator of IFN signaling

Interestingly, although involved in a negative feedback mechanism to prevent STING hyperactivation and type I IFN overproduction [4], we recently found that ULK1 is required for type I IFN signal transduction [3]. Our report established that IFN β treatment leads to AKT-dependent ULK1 phosphorylation on Ser757 [3], previously identified as a mTORC1 phospho-site in ULK1 [72, 76]. In contrast, no changes were observed on phosphorylation levels of Ser555 (or Ser556), the AMPK phospho-site [3]. Furthermore, we showed that engagement of type I IFNR requires ULK1 kinase activity for optimal phosphorylation of p38 MAPK and transcription of ISGs with both ISRE and GAS elements in their promoter regions [3]. As such, ULK1 expression was shown to be required for optimal type I IFN-induced anti-viral and anti-proliferative responses [3]. Notably, ULK1 expression levels were found to be elevated in patients with myeloproliferative neoplasms (polycythemia vera, essential thrombocytosis, and myelofibrosis) when compared to healthy individuals, and suppression of ULK1 expression blocked the anti-neoplastic functions of type I IFNs against malignant erythroid precursors from patients with polycythemia vera [3]. These results suggest that increased ULK1 expression could correlate with favorable responses to type I IFN therapy in MPNs and other types of IFN-responsive cancers, but this remains to be further explored. Our findings revealed a novel autophagy-independent role for ULK1, whose activity is critical for type I IFN-mediated immune responses by controlling, at least in part, p38 MAPK signaling and transcription of ISGs [3]. However, given the fact that AKT activity is only required for mRNA translation of ISGs [41], it is likely that ULK1 could be regulated by other(s) upstream kinase(s) activated by engagement of type I IFNR and that these kinases could be required for the role of ULK1 in transcription regulation. Thus, further research is warranted to clearly identify the signaling events upstream and downstream of ULK1 in type I IFN signal transduction pathways (Fig. 1).

4. Implications and future directions

The involvement of ULK1 activity on both regulation of type I IFN production [4] and of type I IFN-induced signaling responses [3] suggests that ULK1 could act as a central player that, depending on the stimuli, can undergo different phosphorylation events regulating distinct downstream effectors required for the proper control of type I IFN responses [91]. These observations raise several interesting questions. Is ULK1 regulated downstream of other DNA/RNA sensors, besides cGAS, in response to pathogen infection? Could ULK1 mutations or mutations leading to dysregulated ULK1 activation underlie type I interferonopathies and/or familial autoinflammatory syndromes? Given the fact that different patients respond differently to IFN therapy, could ULK1 mutations or expression levels in each patient correlate with success or failure of IFN-treatment against different types of cancer? Could ULK1 status explain why IFN treatment can be unfavorable for specific bacterial or viral infections? Does engagement of type II and/or type III IFN receptors also lead to activation of ULK1 kinase function? Moreover, is ULK1 kinase activity required for signaling by other cytokines or even growth factors? Or is it “the kinase” that distinguishes IFN-mediated responses from other stimuli-driven responses that use the same downstream signaling cascades, such as mTORC1, mTORC2, and MAPK pathways? Answering these questions and unraveling the mechanistic details behind the role of ULK1 in type I IFN signaling may enable the clinical manipulation of ULK1 expression in order to improve IFN-based therapies.

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Biographies

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Ewa M. Kosciuczuk, PhD, is a postdoctoral fellow at Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Dr. Platanius laboratory. Her research focus on studying signal transduction pathways in malignant leukemia and myeloid cells in order to develop novel therapeutic strategies targeting such malignancies. She completed her PhD at the Institute of Genetics and Animal Breeding, Polish Academy of Sciences, in Warsaw, Poland. Her PhD studies focused on gene expression profiling in mammary gland pathophysiology.

Leonidas C. Platanius, MD, PhD, is the Director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and the Jesse, Sara, Andrew, Abigail, Benjamin and Elizabeth Lurie Professor of Oncology. Dr. Platanius's laboratory has been working for many years in the field of interferon and cytokine signaling. Work from his lab was the first to establish the activation of multiple STAT-independent signaling pathways that play essential roles in the generation of IFN-responses, including the p38 MAPK and mTOR signaling cascades. His laboratory also focus on the therapeutic targeting of several signaling cascades that promote tumorigenesis in various types of cancer. Dr. Platanius received the 2013 Seymour & Vivian Milstein Award for Excellence in Cytokine Research and has served as President of the International Cytokine and Interferon Society in 2010–2011.

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Highlights

- Discussion of the novel immunoregulatory role of ULK1 in IFN-dependent immunity and of important future study questions.

Fig. 1. Putative roles of ULK1 in type I IFN signaling

Engagement of type I IFN receptor (IFNR) results in activation of multiple kinases, including ULK1. However, many interesting questions remain unanswered. Does ULK1 engagement in type I IFN signaling require activation by other upstream kinase(s)? Does ULK1 regulate engagement of other downstream effector(s) required for transcription and/or translation of ISGs? What is the impact of ULK1 expression and activation/inactivation in type I IFN-mediated responses?

Abbreviations: ULKK, ULK1 kinase; UE, ULK1 effector.