DIVERSE ROLES OF DEAD/DEAH-BOX HELICASES IN INNATE IMMUNITY AND DISEASES

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INTRODUCTION

DEAD-box and DEAH-box helicases (DEAD/DEAH-box helicases) are enzymes that bind and hydrolyze NTP to unwind double-stranded RNA molecules or remodel RNA-protein complexes [1]. They constitute the DEAD/H-box family, the largest group of helicases in the SF2 helicase superfamily [2]. Structurally, these enzymes are characterized by two tandem repeats of RecA globular domains, with nine conserved motifs: Q (only in DEAD-box helicases), I, Ia, Ib, II, III in the N-terminal domain, and IV, V, and VI in the C-terminal domain [2]. Among them, motifs Q, I (Walker A Motif), II (Walker B Motif), and IV are required for ATP binding and hydrolysis, motifs Ia, Ib, III, IV, and V participate in intramolecular rearrangement and interaction with RNA, and motifs III and V are implied in coordination between the ATP binding and nucleic binding sites [2]. The Walker B Motif comprises a distinctive amino acid sequence, D-E-A-D (asp-glu-ala-glu) or D-E-A-H (asp-glu-ala-his), hence giving the name to the entire protein family. In total, the human genome encodes for 42 DEAD-box and 16 DEAH-box helicases [3,4]. The nomenclature of DEAD/DEAH-box helicases uses DDX or DHX and a number for DEAD-box proteins and DEAH-box proteins, respectively.

DEAD/DEAH-box helicases are primarily involved in all facets of RNA metabolism, including pre-mRNA splicing, micro RNA processing, RNA export, RNA editing, storage and decay, ribosome biogenesis, transcription, and translation [5]. However, DEAD/DEAH-box helicases can perform important roles unrelated to RNA metabolism, for which they sometimes do not even require interaction with RNA [6]. Some of these include transcriptional coregulation [7], monitoring of cell cycle progression [8], regulation of protein localization [9] and protein activity [10,11]. Furthermore, an accumulating number of studies associate DEAD/DEAH-box helicases with multiple functions in innate immunity.

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Innate immunity is a component of bodily defense systems which, unlike its counterpart adaptive immunity, mounts a rapid and generic response against foreign infectious agents or endogenous harm (e.g., malignant cells). For this purpose, the innate immunity employs several elements that can be divided into innate immune proteins and innate immune cells [12]. Innate immune proteins—such as complement proteins, lipopolysaccharide-binding protein (LBP), pentraxins, collectins, and defensins—are humoral proteins that possess antimicrobial properties or aid in sensing and clearance of pathogens [12]. Innate immune cells are responsible for the recognition of pathogens, initiation of immune response (often manifested as inflammation), elimination of pathogens or unhealthy cells, and activation of the adaptive immune system [12]. The cells which perform these tasks are of hematopoietic lineage like macrophages, dendritic cells, neutrophils, natural killer cells, and other leukocytes. In part, the epithelial cells located in skin and respiratory, gastrointestinal, and genitourinary tracts also participate in the innate immune responses.

The most prominent feature of pathogen recognition by the innate immune system is the so-called pattern recognition receptors (PRRs). These genetically predetermined receptors with broad specificity (as compared to the diverse and highly specific receptors of the adaptive immunity) are able to distinguish between the self and nonself by specifically detecting either the microbial structures or common biological consequences of infection. The microbial structures, usually termed pathogen-associated molecular patterns (PAMPs), incorporate highly conserved molecules that are essential for pathogen's viability or virulence, but are not typical of host organism. Examples of PAMPs are bacterial lipopolysaccharides, peptidoglycans, endotoxins, and viral nucleic acid variants such as double-stranded RNA (dsRNA) or unmethylated CpG motifs in DNA [13−15]. The common biological consequences of infection, on the other hand, refer to the release of molecules known as damage-associated patterns (DAMPs). DAMPs are released upon infliction of cell damage during infection or sterile conditions [16]. In addition, PRRs can also detect abnormalities such as the presence of host DNA or cleaved RNA in cytoplasm.

PRRs are interspersed across cell membrane, endosomes, and cytoplasm of the innate immune cells, especially macrophages and dendritic cells. They can be classified into Toll-like receptors (TLRs) [13], C-type lectin receptors (CLRs) [17], nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) [18], cytosolic DNA sensors [19] and RIG-I-like receptors (RLRs) [20]. Of them, the cytoplasmic DNA sensors and RLRs along with their corresponding signaling pathways are of particular interest for this chapter because of their relation to DEAD/DEAH-box helicases.

The presence of DNA in the cytoplasm of mammalian cells is commonly associated with the presence of viral, bacterial, or protozoan DNA, or the release of host DNA to cytosol following the cell damage [21]. Cytosolic DNA sensors that propagate response against such events involve a number of proteins specialized in detection of different DNA variants or secondary messengers such as cyclic dinucleotides (CDNs) [22]. The examples of CDNs are cyclic di-guanosine monophosphate (c-di-GMP), cyclic di-adenosine monophosphate (c-di-AMP), and cyclic GMP−AMP (cGAMP). c-di-GMP and c-di-AMP are two common bacterial messengers, whereas cGAMP is produced in mammalian cells by cyclic cGAS (cyclic GMP-AMP synthase) upon detection of cytosolic DNA [23]. The cytosolic DNA sensors include cGAS, Z-form DNA-sensing DAI (DNA-dependent activator of IRF protein) [24], B-form DNA- and CDN-sensing DDX41 (discussed below), as well as dsDNA-sensing IFI16 [25] and AIM2 (absent in melanoma 2) [26].

RIG-I-like receptors are the main group of cytoplasmic viral RNA sensors [20]. Although they also belong to the DEAD/H-box family of helicases, RLRs have been extensively studied and thus

won't be the main focus of this chapter, but will be discussed due to their central role in RNA sensing and interaction with other DEAD/DEAH-box helicases. This group consists of three members, namely retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) [20]. Among them, RIG-I and MDA5 are specialized for sensing different types of viral RNA. These two sensors contain two structural motifs known as caspase activation and recruitment domains (CARDs), which facilitate interactions with downstream proteins involved in the innate immune signaling. By contrast, LGP2 does not contain the CARD domains and thus cannot promote downstream signaling. Instead, it serves as a positive regulator of MDA5 signaling [27].

Upon detection of nucleic acids, the RLRs and cytosolic DNA sensors activate their respective downstream signaling cascades. A number of cytosolic DNA sensors (including cGAS, DDX41, DAI and IFI16) transduce the signal to the stimulator of interferon genes (STING) located on the membrane of endoplasmatic reticulum [28]. This leads to the generation of functional STING dimers, which mediate phosphorylation of the TBK1/IKKε (tank binding kinase 1/ inhibitor of nuclear factor kappa-B kinase subunit epsilon) kinase complex and the IKK (inhibitor of nuclear factor kappa-B kinase) [29−31]. TBK1/IKKε and IKK respectively activate interferon regulatory factor 3 (IRF3) and NF-κB, which translocate to nucleus in order to instigate the transcription of innate immune response genes.

RLRs transduce the signal to the mitochondrial antiviral-signaling protein (MAVS) through interaction of the CARD domains present in both proteins [32]. The signal causes the formation of massive MAVS aggregates on the mitochondrial membrane, which interact and activate tumor necrosis factor (TNF) receptor associated factors (TRAFs) such as TRAF2, TRAF3, TRAF5, and TRAF6 [33−35]. These E3 ligases initiate synthesis of ubiquitin chains that recruit the NF-κB essential modulator (NEMO) and TBK1/IKKε to the MAVS aggregate. Afterwards, TRAFs activate TBK1/IKKε, whereas NEMO phosphorylates IKK, which further enhances the activation of TBK1/IKKε [35]. Similarly to the STING pathway, TBK1/IKKε and IKK then activate IRF3, IRF7, and NF-κB to stimulate the transcription of response genes.

Signaling via STING and MAVS culminates in the production of type I interferons (IFNs) and proinflammatory cytokines [36]. The former primarily include numerous subtypes of IFN-α and a single IFN-β, whereas the latter include TNF-α, interleukin-1β (IL-1β), IL-6, and IL-18. The secreted type I IFNs trigger the expression of a myriad of response genes known as IFN-inducible genes through the activation of the JAK-STAT signaling pathway in the receptor cells [36]. Collectively, all these signaling events broadly activate immune cells, induce inflammation and raise the defenses of host cells.

However, what are the functions of DEAD/DEAH-box helicases in STING and MAVS signaling pathways? Apart from the abovementioned RLRs and DDX41, other DEAD/DEAH-box helicases have been reported to act as sensors of cytosolic DNA/RNA, adapter molecules, or regulators of signaling and gene expression (Table 9.1). In addition, DEAD/DEAH-box helicases are also hijacked and exploited by viruses to circumvent detection and aid in viral replication. To demonstrate the known range of their activities in innate immunity (especially in STING and MAVS pathways), this chapter will introduce exemplar DEAD/DEAH-box helicases and their interactions with viruses or other pathogens. We also give an outline of diseases in which DEAD/DEAH-box helicases are, or may be involved in the context of immunity.

Table 9.1 Known DEAD/DEAH-Box Helicases in Innate Immunity and Their Evasion or Exploitation by Viruses

DEAD/H-Box Helicase	Function in Innate Immunity	Cell Type	Evaded or Hijacked By	Relation to Other Proteins in Innate Immunity
DDX1	Component of the cytosolic RNA-sensing DDX1-DDX21-DHX36 complex that sensitizes TRIF adapter. Known to sense long and short poly I:C, reovirus and influenza A virus [37].	dendritic cells [37]	HIV-1 [38,39] coronavirus [40,41] JC virus [42]	DDX21 [37] — DDX1 interacts with DDX21 in the DDX1-DDX21-DHX36 complex and transduces the signal to DDX21-DHX36 upon sensing viral dsRNA
DDX3 (DDX3X)	Positively regulates translation of PACT [43]. Binds RLRs or directly recognizes viral RNA and binds MAVS to augment or sensitize downstream signaling. Known to sense poly I:C, viral stem-loop RNA and VSV [44]. Scaffolding adaptor in the MAVS signaling pathway. Interacts with MAVS, TRAF3 and IKKε [45,46]. Direct transcription factor for IFN-β upon *Listeria monocytogenes* infection [47]. Regulation of NF-κB pathway [48,49]. Assembly of processing bodies and stress granules [50,51]. Participates in DAI-dependent sensing of viral dsDNA [52]. Inhibition of hepatitis B virus polymerase [53].	hepatocyte lineage cells [43–46,48,49,53] A549 cells [45,46] RAW264.7 macrophages [47] THF cells [52]	hepatitis C [54–57] HIV-1 [55,58,59] norovirus, West Nile virus, Japanese encephalitis virus [55]	MAVS — DDX3 can activate MAVS and act as a scaffolding adaptor in downstream signaling TRAF3 [46] — Interaction between DDX3 and TRAF3 triggers K63-linked polyubiquitination and oligomerization of TRAF3 IKKε [45,46] — IKKε and DDX3 phosphorylate each other to promote downstream signaling in the MAVS pathway TBK1 [47] — DDX3 undergoes phosphorylation by TBK1 before it can act as a transcription factor for IFN-β PP2A [48] — Positive regulation of NF-κB transcriptional activity by modulation of PP2A activity NF-κB subunit p65 [49] — Suppression of NF-κB transcriptional activity eIF4E and PABP1 [50] — Promotion of stress granule formation and inhibition of translation

Table 9.1 Known DEAD/DEAH-Box Helicases in Innate Immunity and Their Evasion or Exploitation by Viruses
Continued

DEAD/H-Box Helicase	Function in Innate Immunity	Cell Type	Inhibited or Exploited By	Relation to Other Proteins in Innate Immunity
DDX21	Component of the cytosolic RNA-sensing DDX1-DDX21-DHX36 complex [37]. Enhances inflammation through expression of S100A9 during infection [60]. Directly obstructs the lifecycles of influenza A virus, Hantaan virus and Borna disease virus [61−63]. Interacts with dengue virus and subsequently initiates innate immune response (pathway unknown) [64].	Dendritic cells macrophages (innate immune signaling) [37,60]	influenza A virus [61] HIV-1 [63]	DDX1, DHX36, and TRIF [37,60] — Downstream signal transduction resulting in the activation of NF-κB and IRF3 S100A9 (DAMP) [60] — Expressed after DDX21 signaling in macrophages during infection
DDX24	IFN-inducible, STAT1-dependent negative regulator of the RLR-MAVS pathway [65].	Ubiquitously expressed [65]	N/A	RIG-I and MDA5 [65] — Competes for binding their RNA ligands FADD/RIP1 complex [65] — Interferes with the formation of the complex to inhibit the activation of IRF7 p300 [66] — DDX24 suppresses p300-mediated stabilization of the tumor suppressor p53 (putative role in negative regulation of innate immune signaling [67,68])
DDX46	Negative regulation of antiviral innate immune response by retention of *Mavs*, *Traf3* and *Traf6* mRNA in nucleus [69].	Macrophages [69]	N/A	ALKBH5 [69] — Demethylation of the m6A modification on the mRNA transcripts containing CCGGUU motif
DDX60L	Effector protein in the type I, II and III IFN response against HCV. Enhances activation of IRF3 dependent on RIG-I [71].	Primary human hepatocytes [71]	N/A	N/A

Table 9.1 Known DEAD/DEAH-Box Helicases in Innate Immunity and Their Evasion or Exploitation by Viruses *Continued*

DEAD/H-Box Helicase	Function in Innate Immunity	Cell Type	Inhibited or Exploited By	Relation to Other Proteins in Innate Immunity
DDX41	Reviewed in detail by Jiang et al [70]. Cytosolic DNA sensor in the STING pathway. Known to sense B- form DNA, *L. monocytogenes*, HSV-1, adenoviruses, CDNs and retroviral reverse transcripts. [72−74]	Dendritic cells, macrophages, and neutrophils [72,73,75]	N/A	STING [72,73] — Downstream signal transduction BTK [76] — Positive regulation of DDX41 by phosphorylation TRIM 21 [77] — Sequestration and degradation of DDX41 by K48-linked ubiquitination C3a and C5a [78] — Suppression of DDX41 expression cGAS, APOBEC3 [74,79] — IFN-inducible genes dependent on DDX41 signaling
DDX60	Cell-type-specific, upstream viral RNA (possibly DNA) sensor and activator of RIG-I and MDA5. Known to sense poly I:C, VSV, Sendai virus, hepatitis B and C virus, HSV-1 [80,81]. Degradation of hepatitis B and hepatitis C virus RNA as a component of RNA exosome complex in hepatocytes [81].	Macrophages, splenic CD11c$^+$ cells, and fibroblasts [80,81] Hepatocytes [81]	virus-mediated EGFR activation [81−83] Hantaan virus [84]	RIG-I and MDA5 [80,81] — Activated by interaction with DDX60 during virus infection RNA exosome — Degradation of viral RNA EGF, EGFR [81−83] — Negatively regulate antiviral activities of DDX60
DHX33	Sensor of bacterial and viral RNA, activates the NLRP3 inflammasome in macrophages. [85,86]. RLR-independent viral dsRNA sensor in the MAVS pathway in myeloid dendritic cells. Known to sense poly I:C and reovirus [87].	Macrophages [85,86] Myeloid dendritic cells [87]	N/A	NLRP3 [85,86] — DHX15 interacts with NLRP3 to activate the NLRP3 inflammasome TRIM33 [86] — Promotes interaction between DHX33 and NLRP3 by K63-linked ubiquitination MAVS [87] — Downstream signal transduction

Table 9.1 Known DEAD/DEAH-Box Helicases in Innate Immunity and Their Evasion or Exploitation by Viruses *Continued*

DEAD/H-Box Helicase	Function in Innate Immunity	Cell Type	Inhibited or Exploited By	Relation to Other Proteins in Innate Immunity
DHX9	Senses class B CpG motifs and stimulates MyD88-dependent activation of NF-κB in plasmacytoid dendritic cells [88]. Viral dsRNA sensor in the MAVS pathway in myeloid dendritic cells. Known to sense long and short poly I:C, reovirus and influenza A virus [89]. Senses short dsRNA and activates the NLRP9b inflammasome in the intestinal epithelial cells. Known to sense rotavirus [90]. Assembly of RISC (speculated role in the innate immunity) [91].	Plasmacytoid, dendritic cells [88] Myeloid dendritic cells [89] intestinal epithelial cells [90]	HIV-1 [92,93] myxoma virus [94] influenza B virus (nature of interaction unknown) [95]	MyD88 [88] — Downstream signal transduction leading to the activation of NF-κB subunit 50 MAVS [89] — Downstream signal transduction NLRP9b [90] — DHX9 interacts with NLRP9b to activate the NLRP9b inflammasome
DHX15	Directly senses viral dsRNA (1.5−8 kb poly I:C, Sendai virus and reovirus) in tandem with DHX9 and sensitizes MAVS in myeloid dendritic cells. Essential for the activation of IRF3, NF-κB and MAPK [96]. Forms complex with MAVS and interacts with TRAF6 to activate NF-κB and MAPK upon EMCV and Sendai virus infection and trigger apoptosis [97]. Associates with NLRP6 to sense long viral dsRNA, induces IRF3/ IRF7-mediated type I and III IFN response [98].	Myeloid dendritic cells [96] HeLa and HEK 293 cells [97] intestinal epithelial cells [98]	N/A	DHX9 — Pairs with DHX9 to sense viral dsRNA MAVS — Downstream signal transduction NLRP6 [98] — DX15 pairs with NLRP6 to sense long viral dsRNA NKRF and RMB5 [99,100] — Regulation of apoptosis in nucleus (possible overlapping function with the immune-mediated stimulation of apoptosis in cytosol)
DHX36	Component of the cytosolic RNA-sensing DDX1-DDX21-DHX36 complex [37]. Senses class A CpG motifs and stimulates MyD88-dependent activation of IRF7 in plasmacytoid dendritic cells [88]. Senses viral RNA and then augments RIG-I signaling by mediating the assembly of PKR-dependent antiviral stress granules. Known to sense poly I:C, influenza A virus and Newcastle disease virus [101].	Dendritic cells [37] Plasmacytoid dendritic cells [88] mouse embryonic fibroblasts [101]	N/A	DDX21 and TRIF [37] — Downstream signal transduction resulting in the activation of NF-κB and IRF3 MyD88 [88] — Downstream signal transduction leading to the activation of IRF7 PKR [101] — Phosphorylated by DHX36 to induce the formation of PKR-mediated antiviral stress granules RIG-I [101] — Physical interaction with RIG-I in antiviral stress granules

(*Continued*)

Table 9.1 Known DEAD/DEAH-Box Helicases in Innate Immunity and Their Evasion or Exploitation by Viruses
Continued

DEAD/H-Box Helicase	Function in Innate Immunity	Cell Type	Inhibited or Exploited By	Relation to Other Proteins in Innate Immunity
DDX6	Represses activation of interferon-stimulated genes in the absence of infection [102]. Integral component of the processing bodies [103].	N/A	hepatitis C virus [104–106] HIV-1 [107] adenovirus [108] West Nile virus [109] dengue virus [110]	LSM1 [102] − DDX6-mediated suppression of ISGs is dependent on mRNA degradation by LSM1
DDX17	Counters Rift Valley fever virus infection by specifically binding stem loops in the viral RNA [111]. ZAP-mediated degradation of retroviral RNA [112] Putative role in the RLR-mediated antiviral response [113].	N/A	HIV-1 [114–116] influenza A virus [117]	ZAP [112] − DDX17 is a cofactor in the ZAP-mediated RNA degradation complex DHX9 [118] interaction between DDX17 and DHX9 (not studied in the context of innate immunity)
DDX25	Negative regulator of the IFN signaling pathway. Inhibits NF-κB and IRF3 activation [119].	Ubiquitously expressed [119]	dengue virus, VSV and Zika virus [119]	DDX25 inhibits NF-κB and IRF3 [119]
DHX29	Upstream viral RNA sensor and activator of RIG-I [120].	Human airway epithelial cells and fibroblasts [120]	salivirus [121]	RIG-I and MAVS [120] − DHX29 directly interacts with RIG-I and MAVS to transduce signal

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DDX41

The role of DDX41 as sensor of cytosolic DNA in STING pathway was first reported by Zhang et al. in 2011 after noticing that knockout of IFI16, another cytosolic DNA sensor, does not significantly decrease IFN-β levels [72]. Constitutively expressed in dendritic cells, macrophages and neutrophils, the cytosolic DDX41 is bound to the E3 ubiquitin ligase TRIM21, which keeps DDX41 in inactivated state [75,77]. Upon appearance of B-form DNA, DNA viruses or cyclic dinucleotides (CDNs), DDX41 dissociates from TRIM21, and is then phosphorylated by Bruton's tyrosine kinase (BTK), which enables its sensing function [76]. BTK kinase activity also facilitates the interaction between DDX41 and STING, which triggers downstream STING signaling via TBK1 and subsequently activates transcription factors such as IRF3 and NF-κB [72,73,76]. These transcription factors induce expression of type I IFNs and proinflammatory cytokines, including TNF and IL-6. Type I IFN signaling also stimulates the expression of interferon-stimulated genes, which further promote or regulate the immune response.

Among the interferon-stimulated genes, the expression of cGAS is dependent on the initial production of type I IFN mediated by basal DDX41 [79]. TRIM21 is responsible for negative regulation of DDX41 by inducing its degradation via K48-linked ubiquitination [77]. The expression of APOBEC3, a cytidine deaminase important in antiretroviral innate immunity, can also be induced by IFN signaling through DDX41/STING axis [74]. This suggests that DDX41 has a role in sensing retroviral reverse transcripts.

Negative regulation of DDX41 is essential because excessive expression of type I interferons may cause various pathological conditions, such as systemic lupus erythematosus [122], or lymphocyte apoptosis during *Listeria monocytogenes* infection. Besides TRIM21, the complement anaphylatoxins C3a and C5a have also been reported to negatively regulate DDX41 by suppressing its expression [78].

Structural analyses of DDX41 have given us a better insight into the mechanisms behind its roles in the innate immunity. DDX41 contains a disordered N-terminal region, a DEAD domain and a helicase domain. The N-terminal region of DDX41 was demonstrated to play a role in translocation of the protein to the nucleus [123]. This may explain the fact that DDX41 was found localized both in cytoplasm and nucleus of MCAT-293T (murine cationic amino acid transporter-expressing 293T) cells upon the infection with murine leukemia virus [74]. Such observation implies that DDX41 may participate in another, unknown pathway associated with innate immunity.

The DEAD domain plays the central role in DNA/CDN sensing, a feature specific for DDX41 among DEAD/DEAH-box helicases. Several highly conserved amino acid residues (Arg267, Lys304, Lys331, and Lys381; Lys331 only binds CDNs) are crucial for the ligand binding [124]. In addition, deletion of motif I or motif II impairs both DNA/CDN sensing and binding to STING [36]. Interestingly, the process of DNA/CDN sensing was also shown to be inhibited by the helicase domain [72,124]. The possible explanation is that the linker region between DEAD and helicase domain may position the helicase domain in a conformation which disturbs the interaction between DEAD domain and its ligands [124]. Moreover, Q motif, motif I, and motif II

collectively form an ATP binding and hydrolysis site, as predicted in the overall structures of the DEAD domain solved by Jiang et al. [123] and Omura et al. [124]. Omura et al. reported three different conformations of the N-terminal region, among which only the "closed form," characterized by Q motif adjacent to motif I, is predicted to bind ATP [124]. Contrarily, the two "opened forms" and a similar structure reported by Jiang et al. are all characterized by conformation that sterically clashes with the putative ATP binding site [123,124]. This is further supported by the fact that Jiang et al. did not detect any significant affinity of the protein for ATP in vitro [123]. Based on their findings, Omura et al. propose that the DEAD domain undergoes a structural transition between an ATP-bound closed conformation and an opened conformation after ATP hydrolysis and ADP release, thus playing a role in DNA/CDN sensing by accelerating the ligand turnover of DDX41 [124]. Lastly, phosphorylation of Tyr364 in the DEAD domain and Tyr414 from the linker region between the DEAD and helicase domain by BTK was demonstrated to be of key importance in DNA/CDN sensing and binding to STING [76]; however, a pull-down assay of phosphorylated full-length DDX41 from another study failed to validate the effect of BTK on DNA/CDN sensing [124].

Altogether, our understanding of DDX41 is insufficient to clearly explain the exact mechanisms behind DNA/CDN sensing, signal transduction via STING, and the regulation of DDX41 activity. However, the results of the abovementioned studies strongly indicate the existence of additional cofactors or posttranslational modifications involved in these mechanisms.

Mutations in DDX41 have been reported to be associated with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) [125,126]. A number of these mutations, namely p.M155I, p.R164W, p.F183I, p.A225D, p.E247K, p.P321L, and p.I396T, are located in the DEAD domain of DDX41 [123]. The presence of mutations in the DEAD domain suggests the role of deregulated innate immune signaling in MDS and AML. Furthermore, the whole STING signaling pathway is implicated in a number of inflammatory diseases and tumors, where it exhibits both pro- and anticancer functions. The topic has been reviewed in detail by He et al. [127]. Nevertheless, the involvement of DDX41 in the context of STING signaling pathway has not been reported in pathogenesis of these diseases, but it should be considered in future studies.

DDX3

Human DDX3 has two homologs, DDX3X and DDX3Y, which are located on chromosomes X and Y, respectively. Out of the two, DDX3X (here referred to as DDX3) is a nucleocytoplasmic helicase expressed in a wide range of tissues and involved in fundamental biological processes such as cell-cycle progression, lipid metabolism, gene expression, as well as transcription, mRNA splicing, mRNA export and translation [8,54,128−130].

Research on DDX3 in antiviral immunity conducted before 2015 has been reviewed in detail by Ariumi [131] and Valiente-Echeverría et al. [55]. In brief, DDX3 participates in a plethora of processes associated with immune responses, ranging from multiple functions in RLR-MAVS signaling pathway [44−47] and sensing of viral dsDNA via DAI [52], to constitution of cytoplasmic granules [50,51], and direct inhibition of hepatitis B virus polymerase [53]. Upstream of RLRs, DDX3 enhances the sensitivity of RLR-MAVS pathway by positively regulating translation of PACT, a dsRNA-binding protein that facilitates RIG-I sensing and activation [43]. Also, DDX3 can either bind RLRs or directly recognize viral RNA and bind MAVS to sensitize downstream

signaling [44]. While RLR binding could be important for intensifying the signal, direct RNA sensing may be essential during the initial antiviral response, when the IFN-inducible RLRs are present in low concentration. With no need for its enzymatic activity, DDX3 also serves as a scaffolding adaptor that interacts with important signaling molecules downstream of MAVS [46]. Upon infection, the interaction between DDX3 and TRAF3 triggers the K63-linked polyubiquitination and oligomerization of TRAF3. This event is important for the stabilization of MAVS-TRAF3 complex and recruitment of additional signaling molecules to the complex [46]. CK1ε, another kinase whose activity is regulated by DDX3, may also be recruited to the MAVS-TRAF3 complex to phosphorylate TRAF3 and thereby promote its autoubiquitination [132]. However, this notion needs to be further confirmed. Concurrently, DDX3 binds the scaffolding/dimerization domain of IKKε to induce the autophosphorylation of IKKε [45]. In turn, IKKε phosphorylates serine 102 in DDX3, leading to recruitment of IRF3 to the signaling complex. IKKε phosphorylates IRF3, which ultimately activates transcription of IFN-β [45]. In addition, DDX3 appears to directly act as a transcription factor for IFN-β after being phosphorylated by TBK1 [47].

Besides the stimulation of interferon production, DDX3 has been implied in the regulation of NF-κB pathway [48,49]. Interestingly, while one study showed the positive regulatory effect achieved by modulation of PP2A (a phosphatase that inactivates the NF-κB activator IKK-β and NF-κB subunit p65) [48], another study showed that DDX3 interacts with p65 to suppress its transcriptional activity [49]. The discrepancy between the effects is possibly due to different experimental conditions. The positive regulation was observed when the cells were stimulated by the synthetic dsRNA analog poly I:C [48], which resembles antiviral immune response, whereas the repression was observed during normal cell culture conditions [49]. This would suggest that DDX3 is an arbitrary regulator of NF-κB pathway whose activity depends on the cellular conditions.

DDX3 is the main component promoting the assembly of cytoplasmic granules, such as processing bodies (P-bodies) and stress granules [50,130]. P-bodies are constitutively present in cells, where they carry out mRNA degradation. On the other hand, stress granules are assembled during cellular stress conditions to store mRNA and ribonucleoproteins, and to stall translation initiation. Both of these structures participate in cellular response against viruses and restriction of viral replication [51,133]. Importantly, the fact that RLRs can also be recruited to and activated in stress granules further strengthens and interconnects the multiple roles of DDX3 in innate immunity [134].

Considering the importance of DDX3 in a number of innate immune mechanisms, it is not surprising that viruses have evolved strategies to evade host defenses by preventing DDX3 from participating in innate immunity. A number of viruses have been reported to interfere with formation of cytoplasmic granules and exploit DDX3 as a host factor for replication. This is seen in cases of hepatitis C virus, HIV-1, norovirus, West Nile virus, and Japanese encephalitis virus [55]. For example, during HCV infection the binding of HCV core protein to DDX3 disrupts the interaction between DDX3 and MAVS [56], decreases the expression of DDX3 and redistributes DDX3 to lipid droplets (the cytoplasmic sites of HCV replication) [57]. Since DDX3 is important for the maintenance of lipid homeostasis, such decrease in expression levels and sequestration of DDX3 does not only aid in the viral evasion of the host immunity, but also results in retention of lipids in cells and subsequent steatosis [54]. Similarly, HIV-1 interrupts MAVS signaling as viral feedback to the initial sensing of HIV-1 RNA by DDX3 [58]. At the same time, HIV-1 utilizes the CRM1/DDX3 complex in nucleus for the Rev-dependent nuclear export of viral RNAs, or DDX3 itself to promote the translation of the HIV-1 unspliced mRNA [59].

DHX9

DHX 9, also known as RNA helicase A or Nuclear DNA Helicase II, is a DNA/RNA helicase from the DEAH-box helicase family involved in regulation of transcription [135−137] and translation [138,139], DNA replication [140], embryonic stem cell differentiation [141], as well as genome repair and maintenance [142−144]. In addition, DHX9 is also present in several immune pathways.

Along with DHX36, DHX9 has been demonstrated to serve as a microbial DNA sensor in the cytosol of plasmacytoid dendritic cells [88]. DHX9 specifically binds class B CpG motifs via its DUF (domain of unknown function) domain. Its DUF and helicase C domains then interact with the TIR (Toll/interleukin-1 receptor) domain of MyD88 (myeloid differentiation primary response gene 88, the adapter protein commonly associated with the Toll-like receptors) [88]. Upon receiving the signal from DHX9, MyD88 induces downstream signaling cascade to activate NF-κB subunit 50, ultimately resulting in the production of IL-6, TNF and, partly, IFN-α [88]. DHX9 is also an important sensor of viral dsRNA in myeloid dendritic cells, and has been found to sense both long and short poly I:C, as well as reovirus and influenza A virus [89]. DHX9 binds dsRNA via dsRBD (dsRNA-binding domain) domains and transduces the signal to MAVS, thereby triggering IRF3 and NF-κB-dependent expression of response genes [89]. Furthermore, DHX9 has been discovered to sense short dsRNA and activate the formation of NLRP9b (NOD-like receptor family, pyrin domain containing 9B) inflammasome as a response to rotavirus infection in intestinal epithelial cells [90]. Inflammasomes, such as NLRP9b inflammasome, are cytosolic protein complexes in the innate immune cells (such as myeloid cells and epithelial cells) capable of initiating caspase-1-mediated IL-1β and IL-18 maturation and/or gasdermin-induced pyroptosis in response to pathogens, cellular stress, and other danger signals [90,145].

Interestingly, a structural analysis of the DHX9 dsRBD domains in complex with dsRNA elucidated the mechanisms underlying dsRNA binding by DHX9, and provided evidence on how the sensing of the small interfering RNA by DHX9 plays a role in the assembly of RISC (RNA-induced silencing complex) [146]. Given that RNA interference is also an element of the mammalian antiviral immune response [91], the assembly or RISC may be another way for DHX9 to counter virus infection.

DHX9 is a known target of immune evasion and exploitation by several viruses. For example, the ATPase-dependent helicase activity of DHX9 is required for HIV-1 RNA translation [92]. DHX9 can also bind to the primer binding site segment of the 5′ untranslated region (UTR) in the genomic HIV-1 RNA during the virion assembly, which increases the overall infectivity of HIV-1 [92,93]. The myxoma virus (rabbit-targeting member of the *Poxviridae* family) protein M029 recruits DHX9 to promote viral infection in myeloid cells [94]. Additionally, the influenza B virus NS1 protein interacts with DHX9, but the interaction hasn't been functionally characterized yet [95].

Lastly, DHX9 is an autoantigen associated with the early stages of systemic lupus erythematosus and possibly with primary Sjögren's syndrome [147,148]. In accord with high female-to-male incidence ratios in these two diseases, the expression of DHX9 has also been found to be higher in females than in males [148]. Considering the fact that the autoimmune diseases are thought to be caused by microbial infection, the time context of DHX9 autogenicity and its importance in cytosolic DNA/RNA sensing, it is possible that the function of DHX9 in innate immunity is closely related to the onset of lupus and primary Sjögren's syndrome. Further research would be required to verify this assumption.

DHX15

DHX15 is a DEAH-box helicase ubiquitously expressed in human organs and tissues [149]. Within a cell, DHX15 is distributed across nucleus, nucleolus, cytosol, and mitochondria, with different functions in each location [97,150]. Nuclear DHX15 is important for early stages pre-mRNA splicing (in nuclear speckles) [151,152], during which it is regulated by a number of proteins, such as RBM5 (RNA-binding motif protein 5) [99] and TFIP11 (tuftelin-interacting protein 11) [153]. RBM5 is an alternative splicing regulator of apoptosis-related genes, thus implying that DHX15 regulates apoptosis through splicing of these genes [99]. In nucleolus, DHX15 participates in ribosome biogenesis, forming a complex with NKRF (NF-κB-repressing factor) and exonuclease XRN2 [100]. Apart from these functions, DHX15 located in cytosol and on mitochondrial membrane plays a role in in antiviral innate immune response and signaling [96−98]. Most interestingly, these roles are independent of ATPase activity and are characteristically cell type-specific, with distinct roles reported in HeLa cells, embryonic kidney cell lines (HEK 293 and HEK 293T), myeloid dendritic cells and intestinal epithelial cells. During poly I:C stimulation or encephalomyocarditis virus (EMCV) and Sendai virus infection in HeLa and HEK 293 cells, DHX15 forms complex with MAVS and interacts with TRAF6 to stimulate proinflammatory cytokine response and caspase-3-mediated apoptosis through NF-κB and JNK/p38 MAPK (mitogen-activated protein kinase) pathways [97]. DHX15 was found to weakly bind dsRNA and was not required for IRF3 activation, but was necessary for the optimal cytokine expression (including IFN-β) [97]. Likewise, DHX15 triggers the aggregation of MAVS in myeloid dendritic cells in the presence of viral dsRNA [96]. However, not only was DHX15 observed to be critical for the activation of IRF3, NF-κB, and MAPK, but it also specifically bound poly I:C (size 1.5−8 kb) or Sendai virus and reovirus dsRNA in tandem with DHX9, thus acting as a direct sensor of viral dsRNA [96]. In the intestinal epithelial cells, DHX15 exhibits yet another mode of action: it associates with the NLRP6 (nucleotide-binding oligomerization domain-like receptor 6) to sense long viral dsRNA and transduce the signal to MAVS, eventually inducing the expression of both type I and type III IFNs by activation of the transcription factors IRF3 and IRF7 [98]. In contrast to these cells, DHX15 is dispensable for the expression of IFN-β as an immune response to viral infection in HEK 293T cells [96]. These differences suggest existence of interaction between DHX15 and cell/tissue type-specific proteins which modulate the activity of DHX15 and MAVS signaling pathway. Moreover, the fact that the nucleolar DHX15 interacts with NKRF points out to the possibility that this DEAH-box helicase may participate in NF-κB signaling on two different levels [100,154,155]. Further research is needed to gain better understanding of the activities of DHX15.

As of May 2017, DHX15 is the only DEAH-box helicase whose crystal structure has been revealed in a nearly-complete form, lacking only the N-terminal extension domain [156]. DHX15 is divided into six structural domains, namely the N-terminal extension, the RecA1 and RecA2 domains, the winged-helix domain, the ratchet domain and the oligonucleotide /oligosaccharide-binding (OB)-fold domain. Among them, the OB-fold domain is important for interaction with the G-patch proteins, such as NKRF [100,156].

The putative RNA binding pocket is located between the two RecA domains and the C-terminal domain (containing the winged-helix domain, the ratchet domain and the OB-fold domain) [156]. Based on the mechanism by which Prp43 (the fungal orthologue of DHX15) binds ssRNA, the

authors suggest that binding of ATP and RNA triggers a structural rearrangement in the RNA binding pocket to form an RNA-accommodating groove [156]. However, DHX15 senses viral RNA in an ATPase-independent manner, indicating existence of other factors that cause the structural rearrangement of the RNA binding pocket.

Similarly to DDX41, DHX15 has also been implied in the pathogenesis of acute myeloid leukemia (AML) [157]. The mutation of the highly conserved arginine significant for RNA binding (R222G) is related to AML, and the overexpression of DHX15 in the AML patients indicates poor cytogenic prognosis and overall survival [156,157]. Of note, overexpressed DHX15 in AML acts through activation of NF-κB pathway just as during the viral infection, but it decreases the levels of caspase-3 and PARP, thereby promoting cell survival [157]. Considering that during the viral response DHX15 also activates apoptotic MAPK signaling, it is possible that DHX15 can activate NF-κB pathway independently of MAVS, or that the transformed myeloid cells in AML use aberrant MAVS signaling.

DDX21

DDX21, also known as nucleolar RNA helicase II, is an ATP-independent helicase associated with many nuclear and nucleolar events, such as ribosomal RNA biogenesis [158] or unwinding of R-loops [159] and RNA guanine quadruplexes [160]. DDX21 also interacts with mitotic regulator PP1 [161] and oncoprotein DEK [162]. Additionally, upregulated DDX21 has been found to promote tumorigenesis in breast cancer by phosphorylating c-Jun, a component of AP-1 transcription factor involved in cell survival pathways [163].

With respect to innate immune pathways, DDX21 occurs as a component of a constitutive, IFN-, TL3-, and RLR-independent viral RNA-sensing cytosolic complex in dendritic cells and macrophages, wherein DDX21 serves as a bridge between DDX1 and DHX36 by binding the two helicases through its PRK domain [37,60]. Following DDX1-mediated RNA sensing, DDX21 and DHX36 transduce the signal to the adaptor TRIF, which sensitizes NF-κB and IRF3 pathways [37]. Presumably as a part of the same complex, DDX21 also triggers the expression of a DAMP protein S100A9, which induces production of proinflammatory cytokines and apoptosis [60]. DDX21-mediated expression of S100A9 is unfavorable during influenza A virus infection, but may be effective against some bacterial infections [60].

DDX21 has been shown to interact with a number of RNA viruses. The DDX1-DDX21-DHX36 complex senses both short and long poly I:C, reovirus and influenza A virus [37]. DDX21 can also act individually to obstruct the replication of influenza A virus through inhibition of the viral RNA polymerase, but this effect is countered in later stages of the infection by the viral NS1 protein, an inhibitor of host antiviral response [61]. Whether DDX21 can similarly impact the replication of other influenza viruses is still unknown. Furthermore, DDX21 translocates from nucleus to inhibit dengue virus replication in the early stages of the infection [64], participates in cellular defense against Hantaan virus [164] and regulates translation of polycistronic mRNA of Borna disease [62]. However, DDX21 also plays a role in HIV-1 pathogenesis by promoting Rev oligomerization on the Rev-responsive element, thus aiding the export of viral transcripts to cytosol [63].

Collectively, DDX21 appears to uptake a number of distinct roles. Some of these roles influence cells in opposite ways, such as the promotion of cell survival via c-Jun phosphorylation and promotion of apoptosis by triggering expression of S100A9, or ribosomal RNA biogenesis and

suppression of ribosomal RNA transcription through formation of rings that encircle RNA polymerase I complexes [165]. We also speculate that, to a certain extent, these activities may be concomitant. For instance, sensing of viral RNA by the DDX1-DDX21-DHX36 complex may stimulate the formation of DDX21 rings containing RNA polymerase I, which would be favorable as a defensive mechanism to attenuate viral replication. Nevertheless, the full scope and determinants of DDX21 activity are still unknown. A notion on the regulation of DDX21 might have been given by a study that identified two micro RNAs (miR-744 and miR-1196) as factors that control DDX21 expression in a NF-κB and Toll-like receptor 4-dependent manner during ischemia-reperfusion injury in skeletal muscles [166]. Further research is required to elucidate the means by which these two mRNAs, as well as other unidentified factors, influence activities of DDX21.

DDX24

DDX24 is an IFN-inducible and STAT1-dependent negative regulator of innate immune signaling in cytosol and nucleus [65]. A study from 2013 by Ma et al. observed that DDX24 exhibits negative regulatory effects on two distinct levels in RLR-MAVS-mediated signaling pathway [65]. In the upstream signaling transduction, DDX24 competes with RIG-I and MDA5 for binding their respective RNA ligands, whereas in the downstream signaling transduction it interferes with formation of complexes comprising FADD/RIP1, the two coregulators significant for the activation of IRF7 [65]. Nonetheless, the regulatory activities of DDX24 are not limited to RLR-MAVS pathway. p300, a histone acetyltransferase that stabilizes the tumor suppressor protein p53, interacts with N-terminal, Q motif and motif I of DDX24. This interaction results in the suppression of p300-mediated p53 acetylation not only during cell homeostasis, but also upon DNA damage stress [66]. Given the well-established roles of p53 in tumor suppression, apoptosis and cellular senescence, and that more and more studies associate p53 with amplified expression of IFN-stimulated genes during antiviral immune response [67,68], it is safe to assume that the knowledge on the regulatory activities of DDX24 represents only the very tip of the iceberg. One of the uninvestigated activities of DDX24, among others, is potential restriction of HIV-1 RNA transcription through p300. This is possible due to the fact that HIV-1 transactivator of transcription (Tat) recruits p300 to stimulate the transcription initiation [167]. On the whole, the importance and polyvalence of this helicase is further supported by the fact that polyubiquitinated DDX24 is required for early steps of pre-rRNA processing, and that knockout of DDX24 causes embryonic lethality in mice [65,168].

DDX60

DDX60 was demonstrated by the Oshiumi's group to be an interferon-stimulated cytoplasmic helicase with roles both in RLR-dependent and independent antiviral innate immune response [80,81]. Acting as a cell-type-specific activator of RIG-I and MDA5 in macrophages, splenic CD11c$^+$ cells and fibroblasts, DDX60 binds viral RNA and possibly DNA via its helicase domain [80]. Afterwards, DDX60 recruits RIG-I or MDA5 with the help of the ATP-binding site located in its DEAD domain [80]. RIG-I and MDA5 further transmit the signal to MAVS adaptor, ultimately leading to the production of type I IFNs and IFN-inducible genes. Alternatively, DDX60 participates in viral RNA degradation pathway, where it functions as a component of RNA exosome complex [81]. Such mode of action is preferred in hepatocytes against hepatitis B and C viruses

[81,169]. The activity of DDX60 in both pathways is negatively regulated by epidermal growth factor (EGF) receptor [81]. EGF receptor phosphorylates Tyr793 and Tyr796 of DDX60 either in response to EGF (which instead activates Toll-like receptor 3), or by virus-mediated activation of EGF receptor for the evasion of the innate immunity [81−83].

DDX60 appears to be ligand-specific with respect to RNA and DNA sensing. Studies led by Oshiumi report that DDX60 is mainly involved in sensing of poly I:C and ssRNA viruses, such as vesicular stomatitis virus, poliovirus, Sendai virus or hepatitis C virus [80,81]. In addition, DDX60 can sense herpes simplex virus 1 and hepatitis B virus, which respectively belong to dsDNA and dsDNA-RT viruses [80,81]. On the other hand, DDX60 cannot detect a 63-nucleotide 5′ triphosphated ssRNA, indicating that this helicase is unable to recognize viral RNA that undergoes 5′ triphosphate capping [81]. Further studies have also found that Hantaan virus (HNTV) inhibits the transcription of DDX60, but the long noncoding RNA NEAT1 can interfere with these inhibitory effects and thereby deploy DDX60 to counter the HNTV infection [84]. Moreover, the expression of DDX60 is altered during human papillomavirus (HPV) infection in HaCaT cells. HPV-6 infection cause elevated DDX60 levels, whereas HPV-11 and HPV-45 have the opposite effect [170]. Interestingly, upregulated DDX60 has also been discovered in dermatomyositis and advanced oral squamous cell carcinoma, where it may participate in pathogenesis by stimulating secretion of type I IFNs [171,172]. However, no correlation between DDX60 expression and HPV (a common cause of oral squamous cell carcinoma) was found [172].

Not all studies support the reported roles of DDX60 in antiviral immunity. In a study similar to those from the Oshiumi's group, Goubau et al. failed to identify the function of DDX60 in sensing viruses or other pathogens, could not confirm that DDX60 binds RLRs, and found DDX60 to be dispensable for the production of type I IFNs [173]. Further research is needed to explain the reasons behind these ambiguous results.

DDX60L

DDX60L neighbors DDX60 on chromosome IV, and its amino acid sequence is ∼70% homologous to DDX60 [71]. However, our knowledge on functions of DDX60L in innate immunity is still scarce. A study from 2015 describes DDX60L as an innate immune effector of type I, type II, and type III IFN response that acts independently of DDX60 against hepatitis C virus (HCV) in liver cells [71]. The expression of DDX60L is induced soon after the acute HCV infection, during which it represses the viral RNA replication in a manner independent of IRES-mediated translation or RNA stability, and enhances RIG-I-dependent IRF3 activation [71]. DDX60L is likely to be highly specific in its antiviral functions, as it was unable to inhibit replication of hepatitis A virus, regardless of its similarity to HCV [71]. In addition, it is noteworthy to mention that DDX60L is also upregulated in IFN-β-treated EpsteinBarr-transformed B cells derived from multiple sclerosis patients [174].

DDX46

DDX46 is the only nuclear DEAD/DEAH-box helicase proven to negatively regulate the antiviral innate immune response [69]. Viral infection induces the acetylation of DDX46 at Lys470, which facilitates the interaction between the DEAD domain of DDX46 and ALKBH5, a demethylase that

erases the N^6-methyladenosine (m^6A) modification responsible for the export of mRNA transcripts to cytoplasm and their subsequent translation [69]. The negative regulation of antiviral innate immune response performed by DDX46 specifically targets mRNA transcripts containing CCGGUU motif and m^6A modification, such as *Mavs*, *Traf3* and *Traf6* mRNA [69]. As a consequence, these antiviral mRNA transcripts remain in nucleus, which impedes the production of type I IFNs.

With regard to its role in pathogenesis of diseases, the upregulated expression of DDX46 found in esophageal squamous cell carcinoma (ESCC) was shown to promote cell growth and survival [175]. Conversely, knockdown of DDX46 substantially reduced phosphorylation of Akt and IκBα, inhibited cell growth and induced apoptosis by suppressing NF-κB signaling [175]. Although the knockdown of DDX46 in macrophages had a different effect on NF-κB signaling during antiviral immune response (i.e. enhanced activation of NF-κB and increased production of proinflammatory cytokines and IFN- β), we speculate that overexpression of DDX46 might benefit ESCC cell growth and survival by increasing the nuclear retention of mRNA transcripts involved in tumor inhibition and apoptosis.

DHX33

DHX33 is a DEAH-box helicase important for 47S rRNA synthesis, mRNA translation initiation and cell cycle control on the transcriptional level [176−178]. Moreover, DHX33 is the first identified sensor of viral dsRNA and bacterial RNA capable of activating the NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome [85]. In order to activate NLRP3 inflammasome, DHX33 first binds microbial RNA with its helicase C domain [85]. TRIM33 then induces the K63-linked polyubiquitination of DHX33 at lysine 218 [86]. This event is crucial for the interaction between DHX33 and NLRP3, leading to subsequent activation of the inflammasome, caspase-1 cleavage, and processing of pro-IL-1β and pro-IL-18 [85,86].

In addition to the activation of the NLRP3 inflammasome, DHX33 also acts as a viral dsRNA sensor participating in MAVS-mediated innate immune response in myeloid dendritic cells [87]. DHX33 was shown to sense poly I:C and reovirus in a RLR-independent manner, after which it interacted with the C-terminal domain of MAVS via its helicase C domain, ultimately leading to the activation of MAPK, NF-κB and IRF3 [87].

FUTURE PERSPECTIVES

As demonstrated in this chapter and summarized in Fig. 9.1, DEAD/DEAH-box helicases have indisputably confirmed their participation in the human innate immunity. What's more, they have shown a remarkable range of functions in the innate immune pathways (Table 9.1), particularly in the STING- and MAVS-mediated signaling. In innate immunity, DEAD/DEAH-box helicases have been found to act as sensors or cosensors of microbial nucleic acids (e.g., DDX17, DDX41, DDX60, DHX9, DHX15, DHX29, DHX33, and DDX1-DDX21-DHX36), adapter proteins mediating downstream signaling (e.g., DDX3), negative regulators of the signaling pathways or gene expression (e.g., DDX6, DDX24, DDX25, and DDX46), and components of processing bodies and stress granules (e.g., DDX3 and DDX6). Indeed, the fact that viruses either hijack DEAD/DEAH-box proteins or exploit them as host factors of viral replication only underscores the significance of
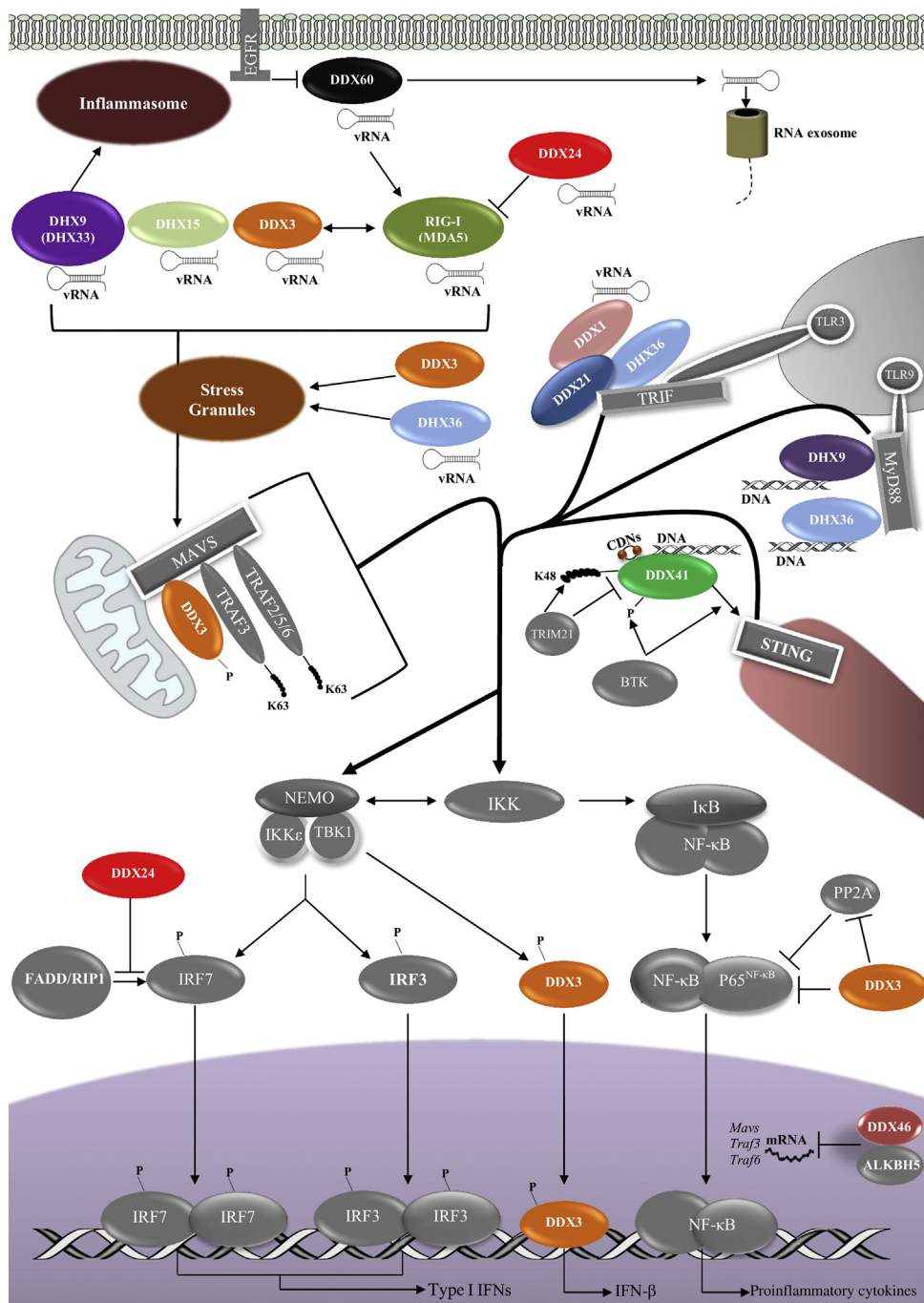
Roles of DEAD/DEAH box helicases in innate immune signaling pathways. Note that the signaling pathways have been simplified to place the focus on DEAD/DEAH-box proteins and their immediate interaction with other proteins. For that reason, many signaling proteins were omitted and some differences between different pathways were not considered. MyD88 signaling utilizes a very distinctive pathway that is not shown in the figure. Instead, MyD88 was connected to other pathways because it also results in activation of IRF7 and NF-κB.

these helicases in innate immunity. However, many questions remain to be answered with regard to the roles of DEAD/DEAH-box helicases of helicases in the innate immunity. Some of these questions are addressed below:

DO ALL DEAD/DEAH-BOX HELICASES PARTICIPATE IN INNATE IMMUNITY?

Originally associated only with RNA metabolism, an increasing number of DEAD/DEAH-box helicases is being found to exhibit multifunctionality in pathways unrelated to RNA metabolism, such as innate immune signaling. Therefore, it is likely that new DEAD/DEAH-box helicases will be identified as effectors of innate immunity. To this end, our knowledge combined with phylogenetic and structural comparison of would be of great use in identification of new DEAD/DEAH-box helicases in innate immunity. However, when comparing, it should be noted that closely related DEAD/DEAH-box helicases might exhibit different functions, such as in cases of DDX60 and DDX60L [71]. Cell type-specific innate immune responses, different stimuli and conditions should also be taken into account. Moreover, future studies should consider that many DEAD/DEAH-box helicases are constitutively expressed in cells, and that their levels may not increase during innate immune response (author's observation based on the literature). This would mean that the functions of some DEAD/DEAH-box helicases in innate immunity may not be easily detected.

WHY DO SO MANY DEAD/DEAH-BOX HELICASES ACT AS SENSORS OF MICROBIAL DNA/RNA?

As demonstrated in this chapter, a large number of DEAD/DEAH-box helicases serve as sensors of microbial DNA and RNA. We propose several explanations for this phenomenon:

I. *Tissue and cell type specificity.* DEAD/DEAH-box helicases serve as sensors in different types of cells. For example, the viral dsRNA cosensors DDX60 and DHX29 have a similar mode of action [80,120]. Upon sensing of viral RNA, both helicases activate RLRs, thus triggering downstream RLR-MAVS signaling. However, the importance of DDX60 as a cosensor is limited to macrophages, splenic $CD11c^+$ cells and fibroblasts, whereas DHX29 is known to specifically act in human airway epithelial cells and fibroblasts [80,120]. The possible reason for this might be that DEAD/DEAH-box helicases are known to have (slightly) different functions in different cells. DHX15 is an interesting example, as it exhibits at least three cell type-dependent roles in antiviral immunity [96−98].

II. *Complementarity.* DEAD/DEAH-box helicases may act as nucleic acid sensors in the same type of cells, but possess specificity for different ligands or signal through different pathways, thus achieving complementarity through specialization in their sensing of microbial nucleic acids and downstream signaling. This is the case with DDX1-DDX21-DHX36, DHX9, DHX15 and RLRs, which sense distinct (but overlapping) viral dsRNA and utilize different signaling pathways in dendritic cells [20,37,89,96]. Complementarity might be useful due to the fact that the organism counters viral hijacking by the virtue of adding complexity to its PRR arsenal. In other words, while one viral nucleic acid sensor and its signaling pathway can be targeted by all viruses, a set of sensors with different signaling pathways could be more beneficial for the host defenses.

III. *Redundancy.* DEAD/DEAH-box helicases may act as nucleic acid sensors or cosensors in the same type of cells and bind the same type of ligands. For example, both DHX9 and DHX33 sense reovirus in myeloid dendritic cells [87,89]. Similarly to the complementarity, redundancy could also be useful for countering the viral hijacking, as virus may possess specificity to inhibit only one of the two sensors. Moreover, redundancy can be used to enhance the innate immune response.

IV. *Prevention of aberrant/exuberant activation of innate immune signaling.* The viral RNA-sensing RLRs and DNA-sensing cGAS are interferon-stimulated genes [79,179], and are expressed in relatively small concentrations in the absence of infection. We hypothesize that these sensors may have a strong affinity for their respective ligands and produce a robust immune response against them. However, if the strong ligand binding is paired with relatively low ligand specificity, such kind of cytosolic nucleic acid sensors may be detrimental for cells in the absence of infection, resulting in a strong, unwanted immune response against self [180]. To prevent that from happening, constitutively expressed DEAD/DEAH-box helicase sensors, such as DDX41 [72], DHX9 [89] and DHX33 [87], may mediate the first wave of innate immune signaling and interferon production during infections, only later to be replaced by the interferon-stimulated RLRs and cGAS.

HOW IS THE ACTIVITY OF DEAD/DEAH-BOX HELICASES REGULATED IN INNATE IMMUNITY? DO OTHER, UNKNOWN PROTEINS INTERACT WITH DEAD/DEAH-BOX HELICASES IN THE CONTEXT OF INNATE IMMUNITY, AND WHAT ARE THOSE PROTEINS?

Since most of the DEAD/DEAH-box helicases in innate immunity have only been discovered in the latest decade, their regulators and interacting partners are still mostly unknown. Finding those proteins would aid us in gaining a better insight into the pathways in which DEAD/DEAH-box helicases are known to participate. This is particularly intriguing for DDX3 [48,49] and DDX21 [60,158,163,165], as both helicases have shown to achieve two opposite effects through their regulatory activities, which possibly depends on the actual cellular conditions.

HOW BROAD IS THE IMPACT OF DEAD/DEAH-BOX HELICASES' ACTIVITY IN INNATE IMMUNITY ON OTHER CELLULAR PATHWAYS AND PROCESSES?

DEAD/DEAH-box helicases are involved in a number of different cellular pathways. Even in the innate immunity, these helicases participate in different pathways, such as STING-, MAVS-, TRIF-, and MyD88-mediated innate immune signaling, inflammasome activation and assembly of cytoplasmic granules. Interestingly, several DEAD/DEAH-box helicases are already known or are thought to play roles in multiple immune pathways. For example, DDX3 is involved in both RLR-MAVS signaling [44−47] and formation of cytoplasmic granules [50,51]; DDX24 is a negative regulator of both RLR-MAVS signaling [65] and tumor suppressor p53 signaling [66], which has recently also been implied in innate immunity [67,68]; DDX25 is a suppressor of NF-κB and IRF3/IRF7 signaling [119], meaning that it is a common negative regulator of all innate immune signaling pathways that converge on these transcription factors; DDX41 senses cytosolic DNA, CDNs

and, possibly, retroviral reverse transcripts [72−74], and thus may contribute to the already-observed crosstalk between STING and RLR-MAVS signaling pathways [181]. DHX9 is an DNA [88] and RNA sensor [89], as well as a factor in assembly of RISC and RNA interference [90], another potential aspect of antiviral response. Such pathway interconnectivity would be essential for more efficient and concerted innate immune response.

Apart from innate immunity, DEAD/DEAH-box helicases participate in many other cellular events, ranging from RNA metabolism to cell-cycle regulation and transcriptional coregulation. With this in mind, we speculate that the activity of DEAD/DEAH-box helicases in innate immunity might cause concomitant effects on the other side of their functional spectrum, as proposed with DDX21 in this chapter. It would be very interesting to identify the broader connection between these distinct pathways, as well as means of their mutual regulation.

ARE DEAD/DEAH-BOX HELICASES INVOLVED (IN THE CONTEXT OF INNATE IMMUNITY) IN PATHOGENESIS OR BODILY DEFENSES AGAINST TUMORS AND INFLAMMATORY DISEASES, SUCH AS AUTOIMMUNE DISEASES?

Innate immunity has well-established roles in immune surveillance and cancer immunoediting [182,183]. STING signaling pathway, type I IFNs and proinflammatory cytokines are implicated in a number of tumors, where they exhibit both pro- and anticancer functions [126,184,185]. Moreover, cancers are often associated with chronic inflammation and inflammasomes [186,187]. Although this makes the involvement of DEAD/DEAH-box helicases in cancer highly possible, the innate immunity-related roles of DEAD/DEAH-box helicases in cancer restriction and pathogenesis have not been investigated yet. However, a large number of DEAD/DEAH-box helicases have been implied in cancer [188,189].

Poor regulation of innate immune signaling, including STING and MAVS pathways, is known to cause inflammatory diseases and autoimmune diseases [119,190]. Interestingly, indications of involvement of DEAD/DEAH-box helicases in autoimmune diseases have already been reported, albeit scarcely [147,148]. Nonetheless, none of those studies focused on mechanisms through which DEAD/DEAH-box helicases participate in inflammation and autoimmune diseases in the context of innate immunity.

ACKNOWLEDGMENTS

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