Encyclopedia of AIDS
DOI 10.1007/978-1-4614-9610-6_77-1

DDX3, Cofactors, and RNA Export

Venkat R. K. Yedavalli*
Molecular Virology Section, Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

Definition

RNA helicases are enzymes that bind to RNA, hydrolyze ATP in an RNA-binding-dependent manner, and separate two annealed RNA duplex strands. Based on sequencing data, there are approximately 85 deduced RNA helicases in the human genome. They have been postulated to have many different functions inside cells. DDX3 is a DEAD (Asp-Glu-Ala-Asp) box RNA helicase protein. There are two forms of the protein. DDX3X is encoded on the X chromosome at position Xp11.3-p11.23 while DDX3Y is located at Yq11. The X-encoded protein and the Y-encoded protein are 91 % identical. The DDX3 helicase has attributed roles in pre-mRNA splicing, RNA export, and translation of mRNAs, among other functions.

Organization of DDX3 Protein

There are five superfamilies of helicases, SF1–5 (Kwong et al. 2005). DDX3 is a member of the SF2 family of helicases. Helicases are operationally defined by whether they can bind single- or double-stranded nucleic acids, unwind RNA or DNA, or both, in either 5′ to 3′ or 3′ to 5′ directions. They generally, albeit not invariably, contain certain conserved signature motifs (Kwong et al. 2005). The two major superfamilies of helicases, SF1 and SF2, share at least seven conserved protein motifs. These include domains that specify for nucleic acid binding, ATP hydrolysis, and core helicase activity. The conserved motifs in DDX3 and the demonstration of its RNA unwinding activity have been previously outlined (Yedavalli et al. 2004).

Pleiotropic Functions Attributed to DDX3

Several different functions have been attributed to DDX3. For example, it has been reported that DDX3 has a cell proliferative function through enhancing the translation of cyclin E1 (Lai et al. 2010) and that DDX3 can influence the progression of some cancers through increasing the expressing of the SNAIL transcription factor (Sun et al. 2011). On the other hand, DDX3 has also been reported to act as a tumor suppressor through its transcriptional upregulation of p21waf1/cip1 (Chao et al. 2006), and in settings of environmental insult, DDX3 was reported to inhibit eIF4e (eukaryotic initiation factor 4E), leading to a repression of translation accompanied by an increase in stress granule formation (Shih et al. 2012). DDX3's inhibitory effect on eIF4e-mediated translation appears to correlate with its described tumor-suppressing function, but interestingly, these activities apparently do not require intact ATPase or helicase functions (Shih et al. 2008). DDX3 also has been reported to play roles in neuronal RNA granules and RNA transport (Kanai et al. 2004), in

*Email: vyedavalli@mail.nih.gov

DOI 10.1007/978-1-4614-9610-6_77-1

spliceosomes and RNA splicing (Zhou et al. 2002), in innate antiviral immunity to virus infections (Schroder 2011), as well as in interactions with HCV (Ariumi et al. 2007; Angus et al. 2010) and HIV (Yedavalli et al. 2004; Chen et al. 2012).

Interactions of DDX3 with HIV

Several viruses encode RNA helicases. Herpes virus UL5 and UL9, alphavirus nsP2, rubella virus p70, SARS coronavirus nsp13, hepatitis E virus ORF1, and flavivirus NS3 are some examples of virus-encoded helicases (Jeang and Yedavalli 2006). HIV-1 does not encode an RNA helicase, but there is growing evidence that it interacts with several RNA helicases for replication (Chen et al. 2012). First, cDNA microarray analyses have found that the expression of RNA helicases DHX9, DDX11, DDX18, DDX21, and DDX24 are changed in human cells by HIV-1 infection (Krishnan and Zeichner 2004). Second, a recent mass spectrometric proteomic study found that HIV-1 Gag complexes with DHX9, DDX18, DDX21, DDX24, HIV-1 Vpr interact with DDX20, and Env gp120 binds DDX6 (Jager et al. 2012). In a separate study, Rev, in the presence of RNA, was reported to bind DDX1, DDX3, DDX5, DHX9, DDX17, DDX24, DHX36, and DDX47 (Naji et al. 2012); and DDX24 and DHX30 were described to be involved in Rev-influenced packaging of HIV-1 RNA (Ma et al. 2008; Zhou et al. 2008a).

The role of DDX3 in HIV-1 biology was first broached by Yedavalli et al. (2004). They reported that DDX3 is a nucleocytoplasmic shuttling protein that binds CRM1 (see ▶ CRM1), a nuclear export factor, and also that DDX3 is involved in the egress from the nucleus of Rev/RRE-dependent unspliced and partially spliced HIV-1 RNAs (see ▶ HIV-1 Rev Expression and Functions) (Yedavalli et al. 2004). Another RNA helicase, DDX1, was found to also provide a similar nuclear-to-cytoplasmic transport of HIV-1 RNAs (Fang et al. 2004). However, among all the RNA helicases postulated to be important for HIV-1, in three recent siRNA-based genome-wide screens for HIV-1 dependency factors, DDX3 was the only RNA helicase found in all three studies to be required for HIV-1 propagation in human cells (Brass et al. 2008; Konig et al. 2008; Zhou et al. 2008b). In addition to DDX3's role in HIV-1 RNA transport, there is emerging evidence that DDX3 can also contribute to the translation of viral RNAs (Liu et al. 2011; Lee et al. 2008). More investigation is needed to parse the mechanistic distinctions between DDX3 activity needed for RNA transport versus RNA translation.

Conclusion

Extant data suggest that the DDX3 RNA helicase plays roles in cell proliferation, tumor progression, and virus infection of human cells. Above, the contributions of DDX3 to several pathological processes are outlined, arguing that this helicase could be an important drug target. It is thus encouraging that progress has been made in the development of small molecule compounds that target DDX3 (see ▶ Cellular Cofactors of HIV as Drug Targets) (Yedavalli et al. 2008; Maga et al. 2011; Radi et al. 2012). Going forward, these candidates should help investigators to further dissect the mechanism(s) and function(s) of DDX3.

DOI 10.1007/978-1-4614-9610-6_77-1

References

Angus AG, Dalrymple D, Boulant S, et al. Requirement of cellular DDX3 for hepatitis C virus replication is unrelated to its interaction with the viral core protein. J Gen Virol. 2010;91(Pt 1):122–32.

Ariumi Y, Kuroki M, Abe K, et al. DDX3 DEAD-box RNA helicase is required for hepatitis C virus RNA replication. J Virol. 2007;81(24):13922–6.

Brass AL, Dykxhoorn DM, Benita Y, et al. Identification of host proteins required for HIV infection through a functional genomic screen. Science. 2008;319(5865):921–6.

Chao CH, Chen CM, Cheng PL, Shih JW, Tsou AP, Lee YH. DDX3, a DEAD box RNA helicase with tumor growth-suppressive property and transcriptional regulation activity of the p21waf1/cip1 promoter, is a candidate tumor suppressor. Cancer Res. 2006;66(13):6579–88.

Chen CY, Liu X, Boris-Lawrie K, Sharma A, Jeang KT. Cellular RNA helicases and HIV-1: insights from genome-wide, proteomic, and molecular studies. Virus Res. 2012;201302:357–65.

Fang J, Kubota S, Yang B, et al. A DEAD box protein facilitates HIV-1 replication as a cellular co-factor of Rev. Virology. 2004;330(2):471–80.

Jager S, Cimermancic P, Gulbahce N, et al. Global landscape of HIV-human protein complexes. Nature. 2012;481(7381):365–70.

Jeang KT, Yedavalli V. Role of RNA helicases in HIV-1 replication. Nucleic Acids Res. 2006;34(15):4198–205.

Kanai Y, Dohmae N, Hirokawa N. Kinesin transports RNA: isolation and characterization of an RNA-transporting granule. Neuron. 2004;43(4):513–25.

Konig R, Zhou Y, Elleder D, et al. Global analysis of host-pathogen interactions that regulate early-stage HIV-1 replication. Cell. 2008;135(1):49–60.

Krishnan V, Zeichner SL. Alterations in the expression of DEAD-box and other RNA binding proteins during HIV-1 replication. Retrovirology. 2004;1:42.

Kwong AD, Rao BG, Jeang KT. Viral and cellular RNA helicases as antiviral targets. Nat Rev Drug Discov. 2005;4(10):845–53.

Lai MC, Chang WC, Shieh SY, Tarn WY. DDX3 regulates cell growth through translational control of cyclin E1. Mol Cell Biol. 2010;30(22):5444–53.

Lee CS, Dias AP, Jedrychowski M, Patel AH, Hsu JL, Reed R. Human DDX3 functions in translation and interacts with the translation initiation factor eIF3. Nucleic Acids Res. 2008;36(14):4708–18.

Liu J, Henao-Mejia J, Liu H, Zhao Y, He JJ. Translational regulation of HIV-1 replication by HIV-1 Rev cellular cofactors Sam68, eIF5A, hRIP, and DDX3. J Neuroimmune Pharmacol. 2011;6(2):308–21.

Ma J, Rong L, Zhou Y, et al. The requirement of the DEAD-box protein DDX24 for the packaging of human immunodeficiency virus type 1 RNA. Virology. 2008;375(1):253–64.

Maga G, Falchi F, Radi M, et al. Toward the discovery of novel anti-HIV drugs. Second-generation inhibitors of the cellular ATPase DDX3 with improved anti-HIV activity: synthesis, structure-activity relationship analysis, cytotoxicity studies, and target validation. Chem Med Chem. 2011;6(8):1371–89.

Naji S, Ambrus G, Cimermancic P, et al. Host cell interactome of HIV-1 Rev includes RNA helicases involved in multiple facets of virus production. Mol Cell Proteomics. 2012;11(4):M111.

Radi M, Falchi F, Garbelli A, et al. Discovery of the first small molecule inhibitor of human DDX3 specifically designed to target the RNA binding site: towards the next generation HIV-1 inhibitors. Bioorg Med Chem Lett. 2012;22(5):2094–8.

DOI 10.1007/978-1-4614-9610-6_77-1

Schroder M. Viruses and the human DEAD-box helicase DDX3: inhibition or exploitation? Biochem Soc Trans. 2011;39(2):679–83.

Shih JW, Tsai TY, Chao CH, Wu Lee YH. Candidate tumor suppressor DDX3 RNA helicase specifically represses cap-dependent translation by acting as an eIF4E inhibitory protein. Oncogene. 2008;27(5):700–14.

Shih JW, Wang WT, Tsai TY, Kuo CY, Li HK, Wu Lee YH. Critical roles of RNA helicase DDX3 and its interactions with eIF4E/PABP1 in stress granule assembly and stress response. Biochem J. 2012;441(1):119–29.

Sun M, Song L, Zhou T, Gillespie GY, Jope RS. The role of DDX3 in regulating Snail. Biochim Biophys Acta. 2011;1813(3):438–47.

Yedavalli VS, Neuveut C, Chi YH, Kleiman L, Jeang KT. Requirement of DDX3 DEAD box RNA helicase for HIV-1 Rev-RRE export function. Cell. 2004;119(3):381–92.

Yedavalli VS, Zhang N, Cai H, et al. Ring expanded nucleoside analogues inhibit RNA helicase and intracellular human immunodeficiency virus type 1 replication. J Med Chem. 2008;51(16):5043–51.

Zhou Z, Licklider LJ, Gygi SP, Reed R. Comprehensive proteomic analysis of the human spliceosome. Nature. 2002;419(6903):182–5.

Zhou Y, Ma J, Bushan RB, et al. The packaging of human immunodeficiency virus type 1 RNA is restricted by overexpression of an RNA helicase DHX30. Virology. 2008a;372(1):97–106.

Zhou H, Xu M, Huang Q, et al. Genome-scale RNAi screen for host factors required for HIV replication. Cell Host Microbe. 2008b;4(5):495–504.