

Immunity, Volume 38

Supplemental Information

Cytosolic Sensing of Viruses

Delphine Goubau, Safia Deddouche, and Caetano Reis e Sousa

Table S1. List of Viruses Reported to Be Recognized by Mammalian RLRs*

Genome	Virus family	RIG-I	MDA5	LGP2	Virus	References
(-)ssRNA virus	<i>Rhabdoviridae</i> (NS)	✓	✓		Vesicular stomatitis virus (VSV)	Kato, et al., 2005, 2008; Satoh et al., 2010
		✓	✓		Rabies virus (RV)	Faul et al., 2010; Hornung, et al., 2006
	<i>Paramyxoviridae</i> (NS)	✓	✓	✓	Sendai virus (SeV)	Gitlin et al., 2010; Kato et al., 2005; Loo et al., 2008; Satoh et al., 2010; Strähle et al., 2007; Suthar et al., 2012; Yount et al., 2008
		✓	✓		Newcastle disease virus	Kato et al., 2005; Loo et al., 2008; Yoneyama, et al., 2005
		✓	✓		Respiratory syncytial virus (RSV)	Liu et al., 2007; Loo et al., 2008; Yoboua et al., 2010
		✓	✓		Human metapneumovirus	Baños-Lara et al., 2013; Liao et al., 2008
		✓	✓		Measles virus	Plumet et al., 2007; Shingai et al., 2007
		✓			Nipah virus	Habjan et al., 2008
		✓			Human parainfluenza virus type I	Boonyaratanaornkit et al., 2011
	<i>Orthomyxoviridae</i> (S)	✓			Influenza A virus	Kato et al., 2006; Loo et al., 2008
		✓			Influenza B virus	Loo et al., 2008
(+ssRNA virus	<i>Filoviridae</i> (NS)	✓			Zaire Ebola virus	Habjan et al., 2008
	<i>Arenaviridae</i> (S)	✓			Lassa virus	Habjan et al., 2008
		✓			Lymphocytic choriomeningitis virus	Zhou et al., 2010
	<i>Bunyaviridae</i> (S)	✓			La Crosse virus	Verbruggen et al., 2011; Weber et al., 2013
		✓			Rift Valley fever virus	Habjan et al., 2008; Weber et al., 2013
	<i>Flaviviridae</i> (NS)	✓	✓		Hepatitis C virus (HCV)	Saito et al., 2008; Schoggins et al., 2011; Sumpter et al., 2005
		✓	✓		Japanese encephalitis virus (JEV)	Kato et al., 2006; Satoh et al., 2010
		✓	✓	✓	Dengue virus (DENV)	da Conceição et al., 2012; Loo et al., 2008; Suthar et al., 2012
		✓	✓	✓	West Nile virus (WNV)	Fredericksen et al., 2008; Schoggins et al., 2011; Suthar et al., 2012
	<i>Coronoviridae</i> (NS)	✓			Murine hepatitis virus	Roth-Cross et al., 2008; Zust et al., 2011
dsRNA virus	<i>Caliciviridae</i> (NS)	✓			Norovirus	McCartney et al., 2008
	<i>Picornaviridae</i> (NS)	✓	✓		Encephalomyocarditis virus (EMCV)	Feng et al., 2012; Gitlin et al., 2006; Kato et al., 2006; Satoh et al., 2010; Venkataraman et al., 2007
		✓			Theiler's murine encephalomyelitis virus	Jin et al., 2012; Kato et al., 2006; Pichlmair et al., 2009
		✓			Saffoldvirus 3	Feng et al., 2012
		✓			Equine rhinitis A virus	Feng et al., 2012
		✓			Human parechovirus 1	Feng et al., 2012
		✓			Enterovirus 71	Feng et al., 2012
		✓			Coxsackieviruses B3 and A21	Feng et al., 2012; Hünh et al., 2010; Wang et al., 2010
	<i>Togaviridae</i> (NS)	✓			Chikungunya virus	Schoggins et al., 2011
		✓	✓		Venezuelan equine encephalitis virus	Schoggins et al., 2011
DNA virus (via RNA intermediate)		✓	✓		Sindbis virus	Burke et al., 2009; Pichlmair et al., 2009
		✓	✓		Semliki forest virus	Pichlmair et al., 2009; Schulz et al., 2010; Weber et al., 2013
	<i>Reoviridae</i> (S)	✓	✓	✓	Orthoreovirus	Holm et al., 2007; Kato et al., 2008; Loo et al., 2008; Pichlmair et al., 2009; Satoh et al., 2010; Shmulevitz et al., 2010
		✓	✓		Rotavirus	Broquet et al., 2011; Sen et al., 2011
		✓	✓		Bluetongue virus	Chauveau et al., 2012
Other non-viral	<i>Herpesviridae</i>	✓			Epstein-Barr virus (EBV)	Minamitani et al., 2009; Samanta et al., 2006
		✓	✓		Herpes simplex virus -2 (HSV-2)	Melchjorsen et al., 2010; Rasmussen et al., 2009
	<i>Poxviridae</i>	✓	✓		Vaccinia virus (VACV)	Pichlmair et al., 2009; Pollpeter et al., 2011
	<i>Adenoviridae</i>	✓			Adenovirus	Cheng et al., 2007; Minamitani et al., 2009
Other non-viral	Gram(-) bacterium	✓	✓		<i>Legionella pneumophila</i>	Monroe et al., 2009
		✓			<i>Shigella flexneri</i>	Jehl et al., 2012
	Gram(+) bacterium	✓	✓	✓	<i>Listeria monocytogenes</i>	Abdullah et al., 2012; Pollpeter et al., 2011
	Mixed population	✓			Intestinal commensal bacteria	Li et al., 2011

*Ticks (✓) indicate that the corresponding RLRs has been implicated in the detection of the corresponding virus. (NS) and (S) refers to "non-segmented" and "segmented" viral genome, respectively.

References

- Baños-Lara, M.D.R., Ghosh, A., and Guerrero-Plata, A. (2013). Critical Role of MDA5 in the Interferon Response Induced by Human Metapneumovirus Infection in Dendritic Cells and In Vivo. *J Virol* 87, 1242–1251.
- Broquet, A.H., Hirata, Y., McAllister, C.S., and Kagnoff, M.F. (2011). RIG-I/MDA5/MAVS are required to signal a protective IFN response in rotavirus-infected intestinal epithelium. *J Immunol* 186, 1618–1626.
- Burke, C.W., Gardner, C.L., Steffan, J.J., Ryman, K.D., and Klimstra, W.B. (2009). Characteristics of alpha/beta interferon induction after infection of murine fibroblasts with wild-type and mutant alphaviruses. *Virology* 395, 121–132.
- Chauveau, E., Doceul, V., Lara, E., Adam, M., Breard, E., Sailleau, C., Viarouge, C., Desprat, A., Meyer, G., Schwartz-Cornil, I., et al. (2012). Sensing and control of Bluetongue virus infection in epithelial cells via RIG-I and MDA5 helicases. *J Virol* 86, 11789–11799.
- Cheng, G., Zhong, J., Chung, J., and Chisari, F.V. (2007). Double-stranded DNA and double-stranded RNA induce a common antiviral signaling pathway in human cells. *Proc Natl Acad Sci USA* 104, 9035–9040.
- da Conceição, T.M., Rust, N.M., Berbel, A.C.E.R., Martins, N.B., do Nascimento Santos, C.A., Da Poian, A.T., and de Arruda, L.B. (2012). Essential role of RIG-I in the activation of endothelial cells by dengue virus. *Virology* 435, 281–292.
- Faul, E.J., Wanjalla, C.N., Suthar, M.S., Gale, M., Wirblich, C., and Schnell, M.J. (2010). Rabies virus infection induces type I interferon production in an IPS-1 dependent manner while dendritic cell activation relies on IFNAR signaling. *PLoS Pathog* 6, e1001016.
- Gitlin, L., Benoit, L., Song, C., Cella, M., Gilfillan, S., Holtzman, M.J., and Colonna, M. (2010). Melanoma differentiation-associated gene 5 (MDA5) is involved in the innate immune response to Paramyxoviridae infection in vivo. *PLoS Pathog* 6, e1000734.
- Holm, G.H., Zurney, J., Tumilasci, V., Leveille, S., Danthi, P., Hiscott, J., Sherry, B., and Dermody, T.S. (2007). Retinoic acid-inducible gene-I and interferon-beta promoter stimulator-1 augment proapoptotic responses following mammalian reovirus infection via interferon regulatory factor-3. *J Biol Chem* 282, 21953–21961.
- Hühn, M.H., McCartney, S.A., Lind, K., Svedin, E., Colonna, M., and Flodström-Tullberg, M. (2010). Melanoma differentiation-associated protein-5 (MDA-5) limits early viral replication but is not essential for the induction of type 1 interferons after Coxsackievirus infection. *Virology* 401, 42–48.
- Jehl, S.P., Nogueira, C.V., Zhang, X., and Starnbach, M.N. (2012). IFNy Inhibits the Cytosolic Replication of *Shigella flexneri* via the Cytoplasmic RNA Sensor RIG-I. *PLoS Pathog* 8, e1002809.
- Jin, Y.-H., Kim, S.J., So, E.Y., Meng, L., Colonna, M., and Kim, B.S. (2012). Melanoma Differentiation-Associated Gene 5 Is Critical for Protection against Theiler's Virus-Induced Demyelinating Disease. *J Virol* 86, 1531–1543.

- Liao, S., Bao, X., Liu, T., Lai, S., Li, K., Garofalo, R.P., and Casola, A. (2008). Role of retinoic acid inducible gene-I in human metapneumovirus-induced cellular signalling. *J Gen Virol* 89, 1978–1986.
- Liu, P., Jamaluddin, M., Li, K., Garofalo, R.P., Casola, A., and Brasier, A.R. (2007). Retinoic acid-inducible gene I mediates early antiviral response and Toll-like receptor 3 expression in respiratory syncytial virus-infected airway epithelial cells. *J Virol* 81, 1401–1411.
- Minamitani, T., Iwakiri, D., and Takada, K. (2011). Adenovirus virus-associated RNAs induce type I interferon expression through a RIG-I-mediated pathway. *J Virol* 85, 4035–4040.
- Plumet, S., Herschke, F., Bourhis, J.-M., Valentin, H., Longhi, S., and Gerlier, D. (2007). Cytosolic 5'-Triphosphate Ended Viral Leader Transcript of Measles Virus as Activator of the RIG I-Mediated Interferon Response. *PLoS ONE* 2, 279.
- Pollpeter, D., Komuro, A., Barber, G.N., and Horvath, C.M. (2011). Impaired cellular responses to cytosolic DNA or infection with *Listeria monocytogenes* and vaccinia virus in the absence of the murine LGP2 protein. *PLoS ONE* 6, e18842.
- Rasmussen, S.B., Jensen, S.B., Nielsen, C., Quartin, E., Kato, H., Chen, Z.J., Silverman, R.H., Akira, S., and Paludan, S.R. (2009). Herpes simplex virus infection is sensed by both Toll-like receptors and retinoic acid-inducible gene- like receptors, which synergize to induce type I interferon production. *J Gen Virol* 90, 74–78.
- Saito, T., Owen, D.M., Jiang, F., Marcotrigiano, J., and Gale, M.J. (2008). Innate immunity induced by composition-dependent RIG-I recognition of hepatitis C virus RNA. *Nature* 454, 523–527.
- Samanta, M., Iwakiri, D., Kanda, T., Imaizumi, T., and Takada, K. (2006). EB virus-encoded RNAs are recognized by RIG-I and activate signaling to induce type I IFN. *Embo J* 25, 4207–4214.
- Satoh, T., Kato, H., Kumagai, Y., Yoneyama, M., Sato, S., Matsushita, K., Tsujimura, T., Fujita, T., Akira, S., and Takeuchi, O. (2010). LGP2 is a positive regulator of RIG-I- and MDA5-mediated antiviral responses. *Proc Natl Acad Sci USA* 107, 1512–1517.
- Schulz, O., Pichlmair, A., Rehwinkel, J., Rogers, N.C., Scheuner, D., Kato, H., Takeuchi, O., Akira, S., Kaufman, R.J., and Reis e Sousa, C. (2010). Protein kinase R contributes to immunity against specific viruses by regulating interferon mRNA integrity. *Cell Host Microbe* 7, 354–361.
- Sen, A., Pruijssers, A.J., and Dermody, T.S. (2011). The early interferon response to rotavirus is regulated by PKR and depends on MAVS/IPS-1, RIG-I, MDA-5, and IRF3. *J Virol* 85, 3717–3732.
- Shingai, M., Ebihara, T., Begum, N.A., Kato, A., Honma, T., Matsumoto, K., Saito, H., Ogura, H., Matsumoto, M., and Seya, T. (2007). Differential type I IFN-inducing abilities of wild-type versus vaccine strains of measles virus. *J Immunol* 179, 6123–6133.
- Shmulevitz, M., Pan, L.-Z., Garant, K., Pan, D., and Lee, P.W.K. (2010). Oncogenic Ras promotes reovirus spread by suppressing IFN-beta production through negative regulation of RIG-I signaling. *Cancer Res* 70, 4912–4921.

Strähle, L., Marq, J.-B., Brini, A., Hausmann, S., Kolakofsky, D., and Garcin, D. (2007). Activation of the beta interferon promoter by unnatural Sendai virus infection requires RIG-I and is inhibited by viral C proteins. *J Virol* 81, 12227–12237.

Sumpter, R., Loo, Y.-M., Foy, E., Li, K., Yoneyama, M., Fujita, T., Lemon, S.M., and Gale, M. (2005). Regulating intracellular antiviral defense and permissiveness to hepatitis C virus RNA replication through a cellular RNA helicase, RIG-I. *J Virol* 79, 2689–2699.

Venkataraman, T., Valdes, M., Elsby, R., Kakuta, S., Caceres, G., Saijo, S., Iwakura, Y., and Barber, G.N. (2007). Loss of DExD/H box RNA helicase LGP2 manifests disparate antiviral responses. *J Immunol* 178, 6444–6455.

Verbruggen, P., Ruf, M., Blakqori, G., Överby, A.K., Heidemann, M., Eick, D., and Weber, F. (2011). Interferon antagonist NSs of La Crosse virus triggers a DNA damage response-like degradation of transcribing RNA polymerase II. *J Biol Chem* 286, 3681–3692.

Wang, J.P., Cerny, A., Asher, D.R., Kurt-Jones, E.A., Bronson, R.T., and Finberg, R.W. (2010). MDA5 and MAVS mediate type I interferon responses to coxsackie B virus. *J Virol* 84, 254–260.

Yoboua, F., Martel, A., Duval, A., Mukawera, E., and Grandvaux, N. (2010). Respiratory syncytial virus-mediated NF-kappa B p65 phosphorylation at serine 536 is dependent on RIG-I, TRAF6, and IKK beta. *J Virol* 84, 7267–7277.

Yount, J.S., Gitlin, L., Moran, T.M., and López, C.B. (2008). MDA5 participates in the detection of paramyxovirus infection and is essential for the early activation of dendritic cells in response to Sendai Virus defective interfering particles. *J Immunol* 180, 4910–4918.

Zhou, S., Cerny, A.M., Zacharia, A., Fitzgerald, K.A., Kurt-Jones, E.A., and Finberg, R.W. (2010). Induction and inhibition of type I interferon responses by distinct components of lymphocytic choriomeningitis virus. *J Virol* 84, 9452–9462.