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Interferon activation and innate immunity pdf windows 10 free



NK receptor/type I interferon/IL-2 activated Cytolytic function Production of IFN-γ and TNF-α











Onomoto K, Jogi M, Yoo JS, Narita R, Morimoto S, Takemura A, et al. For PLpro from human common cold virus HCoV-NL63 it was shown, although only by over-expression experiments, that it can deubiquitinate Mdm2, the E3 ligase that mediates p53 ubiquitination and subsequent degradation, thereby possibly inhibiting apoptosis and innates mediates p53 ubiquitination and subsequent degradation. immune signaling [124]. These events critically regulate the downstream signaling to ensure a sufficiently strong, but not overly explosive triggering of innate immunopathology. Recently, it has become clear that particular type III IFNs (IL-28/29), or IFN lambdas, which were discovered in [3, 5, 24]). Biotechnol Genet Eng Rev. Some studies have focused on mapping the interactions of respiratory viruses, and their immune evasion proteins, with their host cells to find promising cell-to fin based drug targets [191, 192], and this could be an effective way to developing novel vaccines and antiviral drugs. Effective rhinovirus and CoV antivirals and vaccines have also been lacking, and for these viruses causing common colds, an additional hurdle is the cost-effectiveness of these medicines. Influenza A Virus Protein PA-X Contributes to Viral Growth and Suppression of the Host Antiviral and Immune Responses. Khaperskyy DA, Emara MM, Johnston BP, Anderson P, Hatchette TF, McCormick C. Respiratory syncytial virus nonstructural protein 2 specifically inhibits type I interferon signal transduction. Sheppard P, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, Whitmore TE, et al. The general idea is that immune cells such as macrophages and DCs adapt the choice for the use of their metabolic systems to an immune-activated situation that requires increased amounts of energy. Membranous replication factories induced by plus-strand RNA sensor RIG-I. Since each virus employs multiple different activities to suppress immune responses, and often evolved multifunctional proteins to do so, it remains difficult to acquire a complete picture of the immune evasive arsenal of a virus and how this is balanced with symptoms and disease outcome in different cell types or situations. Internal initiation of translation of eukaryotic mRNA directed by a sequence derived from poliovirus RNA. Cervantes-Ortiz SL, Zamorano Cuervo N, Grandvaux N. Yang X, Hu Z, Fan S, Zhang Q, Zhong Y, Guo D, et al. Covalent linkage of a protein to a defined nucleotide sequence at the 5'-terminus of virion and replicative intermediate RNAs of poliovirus. Since the new insights mentioned above have generally not yet, or only to a limited extent, been investigated in the context of viral evasion, this will not be further elaborated in the subsequent sections for the selected respiratory viruses. Innate Immune Evasion by Respiratory Viruses. Innate Immune Evasion, this will not be further elaborated in the subsequent sections for the selected respiratory viruses. RNA genome, such as the respiratory viruses highlighted in this review, produce several RNA species during viral replication, which are normally absent in uninfected cells. Ultimately, the idea is that once GBPs associate with the viral RO membranes, they cause disruption and/or modification of these structures, resulting in less efficient viral replication [49, 50]. Sulea T, Lindner HA, Purisima EO, Ménard R. 2014 Oct;25(5):577-85. Viral Mimicry to Usurp Ubiquitin and SUMO Host Pathways. This factor is cleaved by both 2A and 3C proteases of rhinovirus to halt type I IFN signal transduction [116]. J Allergy Clin Immunol. 2009 Oct;297(4):L559-67. None of these have, however, reached the market yet [73, 150, 194]. The structure of the 5' terminal cap of the respiratory syncytial virus mRNA. Infect Chemother. 2017 Aug;37(8):331-41. 2014 Dec;194:124-37. Kotenko SV, Gallagher G, Baurin VV, Lewis-Antes A, Shen M, Shah NK, et al. 2014 Sep;345(6204):1250684. 2009 May;5(5):439-49. 2016 Aug;428(17):3467-82. Cytokine Growth Factor Rev. Influenza a virus NS1 protein induced A20 contributes to viral replication by suppressing interferon-induced antiviral response. Human respiratory syncytial virus nucleoprotein and inclusion bodies antagonize the innate immune response. Human respiratory syncytial virus nucleoprotein and inclusion bodies antagonize the innate immune response. inducible GTPases go to their target membranes via the LC3-conjugation system of autophagy. 2017 Jun;8:1117. Sensing of invading pathogens by GBPs: at the crossroads between cell-autonomous and innate immunity. Oudshoorn D, Rijs K, Limpens RW, Groen K, Koster AJ, Snijder EJ, et al. CoV, coronavirus; RSV, respiratory syncytial virus; ROs, replication organelles. Besides the major strategies for innate immune suppression by respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here, and/or members of their families, of which many may be unique to only one or 2 of the respiratory viruses discussed here. here. Host detection and the stealthy phenotype in influenza virus infection. 2013 Dec;144(6):1906-12. Recently, a number of efforts for MERS-CoV vaccines have reached the stage of clinical trials, and having these vaccines of dangerous outbreaks with this lethal virus [193]. A more or less obvious way of exploiting a virus' innate immune evasive functions for the development of new vaccines is to remove one or more of these from the virus using reverse genetic technology. 2018 Apr;9:743. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. 2012 Mar;26(3):1290-300. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. Okamoto M, Tsukamoto H, Kouwaki T, Seya T, Oshiumi H. Evasion of influenza A viruses from innate and adaptive immune responses. Tanaka T, Kamitani W, DeDiego ML, Enjuanes L, Matsuura Y. Yang X, Hu Z, Zhang Q, Fan S, Zhong Y, Guo D, et al. Natural killer T cells, mucosal-associated invariant T cells, and neutrophils, for example, each form a bridge between the innate and adaptive machineries and play very important roles during the clearance of respiratory viruses (reviewed in [1, 6, 10]). It is not clear, however, whether (part of) the viral replication takes place outside the replication organelles in these mutant virus infections, and whether replication organelles do, or do not, protect viral replication from innate immune attack therefore remains elusive after all. Indeed, this virus also inhibits the formation of stress granules, and influenza virus encoded NS1 seems to play a major role in this [104]. In the past decades, details of the molecular mechanism in which NS1 influences host shut-off have been investigated, and it is also clear that these mechanisms can be strain-specific [72, 80]. Like influenza viruses, CoVs such as SARS-CoV and MERS-CoV also use a combination of ways to achieve host shut-off both at the transcriptional and the translational levels. Prof. Khaperskyy DA, Hatchette TF, McCormick C. This suggests that the activity of 4a, and possibly other stress granule-inhibiting MERS-CoV proteins, may differ per cell line, or that cell lines differ in the activity of 4a, and possibly other stress granule formation [102, 103]. Wang D, Fang L, Li P, Sun L, Fan J, Zhang Q, et al. 1977 Mar;74(3):961-5. 2018 Feb;9(3):272. 2015 Jun;89(12):6442-52. This kind of interactions illustrates the arms race between the cellular immune responses and viral evasion, which due to continuous evolution of the 5' Terminus of Viral RNAsApparently, the shielding of viral replication products by ROs is not a watertight system, and to further avoid recognition by the innate immune RNA sensors. 2019 Jan;5(1):1. Deng X, Hackbart M, Mettelman RC, O'Brien A, Mielech AM, Yi G, et al. Deubiquitination, a new function of the severe acute respiratory syndrome coronavirus papain-like protease? 2018 Feb;8(1):3746. Interestingly, this innate immune evasion activity of NS1 is counteracted by cellular protein NF90, which partly prevents the suppression of PKR triggered stress granule formation by NS1 by binding both PKR and NS1 [105]. Weber-Gerlach M, Weber F. Nat Med. All these data suggest that viruses likely evolved escape mechanisms for RNA degradation to be able to set-up a productive infection in this hostile environment, however, the details of several of these mechanisms for the respiratory viruses discussed here are still unknown. Active Suppression, is an effective way to actively suppress all cellular protein expression, is an effective way to actively suppress all cellular innate immune responses against the virus, and simultaneously suppression of Innate Immune Signaling Routes by Respiratory Viruses Host shut-off, that is viruses halting cellular protein expression, is an effective way to actively suppress all cellular protein expression. provide the virus with the full capacity of the cellular translation machinery for their own use. 1993 Sep;268(26):19200-3. Walker EJ, Younessi P, Fulcher AJ, McCuaig R, Thomas BJ, Bardin PG, et al. Immune and inflammatory response in bronchiolitis due to respiratory Syncytial Virus and Rhinovirus infections in infants. 2000 Oct;74(19):8953-65. This also implies that, given the restricted genetic space available to these viruses, the evasive functions must be pivotal for viruses to survive, otherwise they would likely not have evolved. 2017 Feb;502:33-8. Oudshoorn D, van der Hoeven B, Limpens RW, Beugeling C, Snijder EJ, Bárcena M, et al. Interaction of SARS and MERS Coronaviruses with the Antiviral Interferon Response. Davis ME, Gack MU. Investigation of the latter will, therefore, be pivotal for the true understanding of viral ROs and their role in protection from innate immune responses. Attack of the Replication organelles by the Innate Immune SystemBesides the question whether the replication organelles protect from innate immune sensors that recognize viral RNA, it is also largely unclear whether the innate immune system possesses sensors or effectors that target viral replication organelles themselves. 2017 Jul/Aug;30(6):408-20. NS1 interacts with an essential component of the 3' end processing machinery of cellular pre-mRNAs, CPSF30, whereby 3'-end cleavage and polyadenylation of cellular mRNAs is inhibited, thereby contributing to host shut-off. Lee YF, Nomoto A, Detjen BM, Wimmer E. K48 and K63-linked ubiquitin chains are best studied and are generally the cause of degradation or activation of the substrate, respectively. 2015 Apr;11:83-8. Berkhout B. 2016 May;6(1):25454. 2009 Nov;83(22):11581 7. Andreakos E, Salagianni M, Galani IE, Koltsida O. These were shown to have a role in innate immune evasion, although the truncated PAXdeltaC20 seems to single-stranded RNA bearing 5'-phosphates. Naumenko V, Turk M, Jenne CN, Kim SJ. Hsu AC. 2018;51(1):173-85. 2006 Jan; 344(2): 328-39. Pizzorno A, Dubois J, Machado D, Cartet G, Traversier A, Julien T, et al. Hale BG, Albrecht RA, García-Sastre A. Cellular Innate Immunity: An Old Game with New Players. Inflammatory damage on respiratory and nervous systems due to hRSV infection. The signal that the ubiquitin chain gives depends on the linkage type(s) of the chain. Ubiquitin in the activation and attenuation of innate antiviral immunity. When this first activation of the type II IFN machinery forms the second line of defense over broader areas of the tissue (reviewed in [24]). Viruses Seen by Our Cells: The Role of Viral RNA Sensors. Sci Signal. 2018 Jul;26(7):598-610. Proc Natl Acad Sci USA. Weber M, Weber F. 2016 Jan;213(1):1-13. 2005 Mar;201(6):937-47. Besides NS1, the influenza nucleoprotein NP and polymerase subunit PA-X help to prevent stress granule formation, due to their RNA protection and host-shut off functions, respectively [103]. For rhinoviruses, nothing is known about their capacity to manipulate stress granule formation, however, for other picornaviruses the 2A and L proteases have recently been shown to interfere by cleaving stress granule factors such as G3BP1 and G3BP2 [106-109]. It has lately become apparent that these proteases often have sidefunctions that support immune evasion by these viruses. Among the viruses and CoVs carry a positive strand RNA genome, and each of the members of these viruses and CoVs carry a positive strand RNA genome, and each of the members of these virus families encode at least 2 proteases. Rhinoviruses use their 2A papain-like protease (PLpro) to effectively disable cap-dependent translation by cleaving eiF4G to induce host-shut off. 2010 Apr;3(118):jc2. p53 down-regulates SARS coronavirus replication and is targeted by the SARS-unique domain and PLpro via E3 ubiquitin ligase RCHY1. Flanegan JB, Petterson RF, Ambros V, Hewlett NJ, Baltimore D. 2015 Apr;202:89-100. Molecular pathology of emerging coronavirus infections. 2018 Aug;7:1299. Leader-Containing Uncapped Viral Transcript Activates RIG-I in Antiviral Stress Granules. 2016 Dec;7(6):7. 2011 Apr;85(8):3758-66. F1000Res. Galani IE, Triantafyllia V, Eleminiadou EE, Koltsida O, Stavropoulos A, Manioudaki M, et al. How this works exactly is unclear to date. Respiratory pathogens are associated with asthma. 2011 Feb;89(2):189-94. Ban J, Lee NR, Lee NJ, Lee JK, Quan FS, Inn KS. Fehr AR, Jankevicius G, Ahel I, Perlman S. Complement Evasion Strategies of Viruses: an Overview. Lindquist ME, Lifland AW, Utley TJ, Santangelo PJ, Crowe JE Jr. Respiratory syncytial virus induces host RNA stress granules to facilitate viral replication. The knowledge we gained about the innate immune evasive activity of viral deubiquitinases like MERS-CoV PLpro also prompted an innovative antiviral option encompassing the screening for high affinity ubiquitin sequence variants that actually block the entire activity of the viral protease and therefore form promising antiviral molecules [196]. Acknowledgements that actually block the entire activity of the viral protease and therefore form promising antiviral molecules [196]. Acknowledgements that actually block the entire activity of the viral protease and therefore form promising antiviral molecules [196]. Jul;195(1):243-7. 2015 Jan;290(5):3172-82. 2013 Dec;100(3):615-35. 2012 Sep;86(17):9527-30. The immune modulation by these alternative PA proteins is thought to be achieved by stimulating host shut-off, another innate immune evasion of host proteins, including those involved in the activation of the innate antiviral state. 2017 Oct;37:17-27. Cheng SC, Quintin J, Cramer RA, Shepardson KM, Saeed S, Kumar V, et al. The battle between influenza and the innate immune response in the human respiratory tract. Bavagnoli L, Cucuzza S, Campanini G, Rovida F, Paolucci S, Baldanti F, et al. Cytoplasmic inclusions of respiratory syncytial virus-infected cells: formation of inclusion bodies in transfected cells that coexpress the nucleoprotein, and the 22K protein. Inhibition of cytoplasmic mRNA stress granule formation by a viral proteinase. Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. 2012 Jul;487(7408):486-90. Modulation of the immune response by Middle East respiratory syndrome coronavirus. Regulation of innate immune functions by guanylate-binding proteins. 2013 Apr;381(9875):1405-16. This direction of course forms an obvious avenue for new research that should be undertaken, since it is likely that viruses also target these newly discovered mechanisms. An important question is how exactly the viral innate immune evasive functions of respiratory viruses influence disease outcome and ultimate immune responses. Trottein F, Paget C. The exacerbation of asthma symptoms upon infection with rhinoviruses have been associated with defective types I and III IFN responses. [185, 186]. Differential processing of nuclear pore complex proteins by rhinovirus 2A proteases from different species and serotypes. Identification of common biological pathways and drug targets across multiple respiratory viruses based on human host gene expression analysis. Front Immunol. J Cell Physiol. 2016 May;8(5):8. Lancet. 2015 Jan;235(2):185-95. Menachery VD, Debbink K, Baric RS. Although the impact of a common cold may not be high, the fact that these infections are extremely widespread in the human population makes controlling these viruses a desirable goal. Generally, the fact that these infections are extremely widespread in the human population makes controlling these viruses a for all viruses discussed in this review, is governed by ubiquitin linked through its lysine at position 63 (forming K63-linked chains). SG formation relies on eIF4GI-G3BP interaction which is targeted by picornavirus stress antagonists. Immunity. Crystal structure of the Middle East respiratory syndrome coronavirus (MERS-CoV) papain-like protease bound to ubiquitin facilitates targeted disruption of deubiquitinating activity to demonstrate its role in innate immune suppression. Wu W, Zhang W, Duggan ES, Booth JL, Zou MH, Metcalf JP. Huge amounts of air and aerosols pass these cells each day, whereby the lung tissue, as well as the rest of the respiratory tract is probably almost constantly exposed to viruses and bacteria present in the inhaled air. 2012 Aug;86(15):8245-58. MxA is a well-known human type I and III interferon-inducible factor that inhibits influenza A virus protein PA-X and its naturally deleted variant show different enzymatic properties in comparison to the viral endonuclease PA. Innate Immunity to Respiratory Infection in Early Life. 2017 Sep;24:60-4. Smith SB, Dampier W, Tozeren A, Brown JR, Magid-Slav M. The central molecule is ubiquitin, a small 76 amino acid protein that can be conjugated with its C-terminus to lysine residues in substrate proteins. Although the exact mechanism of inhibition is stil not clear for several of the viruses inhibited by Mx proteins, Mx GTPase family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx, Culley FJ. Rhinovirus 16 2A Protease family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx proteins Culley FJ. Rhinovirus 16 2A Protease family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx proteins Culley FJ. Rhinovirus 16 2A Protease family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx proteins Culley FJ. Rhinovirus 16 2A Protease family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx proteins Culley FJ. Rhinovirus 16 2A Protease family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx proteins Culley FJ. Rhinovirus 16 2A Protease family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx proteins Culley FJ. Rhinovirus 16 2A Protease family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx proteins Culley FJ. Rhinovirus 16 2A Protease family members bind to intracellular membranes, and in cytosolic +RNA virus infections Mx proteins Culley FJ. Rhinovirus 16 2A Protease family members bind to intracellular membranes family members Affects Nuclear Localization of 3CD during Infection. Immunity to RSV in Early-Life. Three classes of enzymes are needed for the conjugation: activating E1 enzyme, and an E3 ligase. Chan YK, Gack MU. This is different from SARS-CoV nsp1, which inhibits all mRNA translations. Each of these mentioned receptors, or sensors recognize forms of RNA (e.g., 5' triphosphate RNA, double-stranded RNA [dsRNA]) that are produced by (respiratory) RNA viruses during their infection process, and which are distinguishable from the RNA species that are normally present in the cells (such as capped mRNA in the cells (such as capped mRNA)) that are produced by (respiratory) RNA viruses during their infection process, and which are distinguishable from the RNA species that are normally present in the cells (such as capped mRNA). Virus-Host Interaction. Sustained IFN-I Expression during Established Persistent Viral Infection: A "Bad Seed" for Protective Immunity. DEAD-box helicases: the Yin and Yang roles in viral infections. Bruce SR, Atkins CL, Colasurdo GN, Alcorn JL. These activities are thought to influence host immune response signaling for which cytosol-nucleus communication and trafficking is essential. TRIM proteins: another class of viral victims. Also later in life, the innate immune system plays an important role in the lungs these first response against incoming viruses are governed primarily by alveolar and interstitial macrophages, DCs airway epithelial cells, innate lymphocytes, and neutrophils. The innate immune response signaling cascade starts with the recognition of pathogen-associated molecular patterns by pattern recognition receptors (PRRs). 2019 Jan;93(2):93. Aspects of immunological memory, which were thought to be only present in the adaptive immune system, have now clearly been shown to play a role in the innate immune response as well, also that induced by viruses, and was named "trained innate immunity" [9]. To Conquer the Host, Influenza Virus Is Packing It In: Interferon-Antagonistic Strategies beyond NS1. Unterholzner L, Almine JF. Influenza A virus inhibits cytoplasmic stress granule formation. Additionally, it seems that type III IFN does not trigger inflammation as much as type I IFN, and this probably indicates an important unique aspect of the type III IFN does not trigger inflammation between innate and adaptive responses that has been the general view for a long time is probably not accurate. 2019 Jan;11(1):11. McCormick C, Khaperskyy DA. Kindler E, Gil-Cruz C, Spanier J, Li Y, Wilhelm J, Rabouw HH, et al. In this review, the focus will be on the selection of common viruses that invade the lungs: coronaviruses (CoVs), rhinoviruses, respiratory syncytial virus (RSV), and influenza, which all have an RNA genome. A protein covalently linked to poliovirus genome RNA. 2015 Aug;70(8):910-20. Human Respiratory Syncytial Virus: Role of Innate Immunity in Clearance and Disease Progression. Zhu X, Fang L, Wang D, Yang Y, Chen J, Ye X, et al. Yuan P, Bartlam M, Lou Z, Chen S, Zhou J, He X, et al. 2017 Oct;8(4):199-207. 2010 May;84(10):5423-30. Interactions Between NS1 of Influenza A Viruses and Interferon-α/β: Determinants for Vaccine Development. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. In this way, the virus may become attenuated and at the same time it may trigger better innate immune responses due to the lack of one or more of its evasive functions. Human Rhinovirus 3C protease cleaves RIPK1, concurrent with caspase 8 activation. Kim SS, Sze L, Liu C, Lam KP. Vaccines (Basel). Molecular Mechanisms of Innate Immune Inhibition by Non-Segmented Negative-Sense RNA Viruses. 2010 Dec;84(23):12274-84. 2017 Nov;511:123-34. Visser LJ, Medina GN, Rabouw HH, de Groot RJ, Langereis MA, de Los Santos T, et al. A thorough understanding of the virus-host interactions during these respiratory infections will most probably be pivotal to ultimately meet these challenges. 2011 Dec;7(12):e1002433. Coronavirus nonstructural protein 1: common and distinct functions in the regulation of host and viral gene expression. Collins PL, Melero JA. Tay H, Wark PA, Bartlett NW. The structure of the shut-off of host-cell protein synthesis. 2017 Aug;240:81-6. PLoS One. Respiratory Syncytial Virus and Cellular Stress Responses: Impact on Replication and Physiopathology. This then positively influences the response upon a subsequent pathogen encounter, just as in the adaptive immune system [26]. J Virol. Drug Dosage: The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. Subcellular Localizations of RIG-I, TRIM25, and MAVS Complexes. The leader proteinase of foot-and-mouth disease virus negatively regulates the type I interferon pathway by acting as a viral deubiquitinase. This state quite efficiently inhibits further spread of the infection, and simultaneously triggers further adaptive responses that in most cases eventually will clear the virus from the infected individual. Strategies of highly pathogenic RNA viruses to block dsRNA detection by RIG-I-like receptors: hide, mask, hit. Glanville N, Johnston SL. J Gen Virol. However, in view of ongoing research, changes in government regulations, and the exceptors: hide, mask, hit. constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any changes in indications and precautions. An indirect way for viruses to manipulate host shut-off mechanisms discussed for the other respiratory viruses above, may be the induction of stress granules. Farrag MA, Almajhdi FN. Cleavage of IPS-1 in cells infected with human rhinovirus. These alternative products of the PA gene from segment 3 of the influenza genome are called PA-X or PAXdeltaC20, which were discovered recently to also have an endonuclease activity. 2015;386:121-47. Viral Evasion Strategies in Type I IFN Signaling - A Summary of Recent Developments. Multifaceted roles of TRIM38 in innate immune and inflammatory responses. Organelle-like membrane compartmentalization of positive-strand RNA virus replication factories. Recently, it also became clear that after respiratory (bacterial) infections this mechanism indeed has a role, and strikingly, signaling from adaptive (CD8+ T cell responses) "back" to innate immune memory to protect from re-infection [27, 28]. Besides these different responses, most of which are IFNmediated, small non-coding (micro, circular, ...) RNAs, RNAi, and IFN-independent antiviral responses can be regarded as part of the innate immune responses can be regarded as part of the innate immune responses can be regarded as part of the innate immune response package as well [29-31]. van de Sandt CE, Kreijtz JH, Rimmelzwaan GF. Yet, in contrast to most other childhood infections as well as other viral and bacterial diseases, prophylactic vaccines or effective antiviral treatments against viral respiratory infections are either still not available, or provide only limited protection. Romero-Brey I, Bartenschlager R. Importantly, virtually all research investigating the role and structure of viral ROs was performed in cell cultures, and little is known about their presence or numbers during infections in animal models or real hosts. This is particularly important when the recommended agent is a new and/or infrequently employed drug. 2010 Jan;5(1):23-41. 2014 Jul;6(7):2826-57. Segmented negative-strand RNA viruses and RIG-I: divide (your genome) and rule. In the respiratory tract, several of the newly identified cell types and mechanisms that integrate aspects from both branches of human immunity are now thought to be very important for the defense against respiratory infections. Mielech AM, Chen Y, Mesecar AD, Baker SC. Similarly, SARS-CoV PLpro can deubiquitinate E3 ligase RCHY1 to stimulate ubiquitination of p53 by this ligase, and thus also potentially inhibit apoptosis [125]. For influenza, several different interactions with the ubiquitin system have been identified that critically influence the outcome of the infection [126]. 2018 Aug;19(8):800-8. Porcine Epidemic Diarrhea Virus 3C-Like Protease Regulates Its Interferon Antagonism by Cleaving NEMO. 2015 Oct;43(19):9405-17. Innate immunity in the lungs. Uridylation by TUT4 and TUT7 marks mRNA for degradation. Ramaswamy M, Shi L, Monick MM, Hunninghake GW, Look DC. Immunology. However, recent data indicated that RIG-I can be active in the nucleus against influenza RNA [51]. J Interferon Cytokine Res. Said EA, Tremblay N, Al-Balushi MS, Al-Jabri AA, Lamarre D. A molecular arms race between host innate antiviral response and emerging human coronaviruses. Huo Y, Shen J, Wu H, Zhang C, Guo L, Yang J, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, Tan CP, Näslund TI, Liljeström P, Weber F, et al. Pichlmair A, Schulz O, esponse also impacts subsequent adaptive responses, and therefore viral innate immune evasion often undermines fully protective immunity. Narayanan K, Ramirez SI Lokugamage KG, Makino S. Disclaimer: The statements, opinions and data contained in this publication are solely those of the individual authors and contributors and the virulence and its capacity. to evade the host's immune responses on the virus' side, together dictate the disease outcome. This review will focus on the evasion of the innate immune system by the array of respiratory viruses as introduced above, to highlight this important aspect of the virus' side, together dictate the disease outcome. This review will focus on the evasion of the innate immune system by the array of respiratory viruses as introduced above, to highlight this important aspect of the virus' side, together dictate the disease outcome. This review will focus on the evasion of the innate immune system by the array of respiratory viruses as introduced above, to highlight this important aspect of the virus' side, together dictate the disease outcome. This review will focus on the evasion of the virus' side, together dictate the disease outcome. This review will focus on the evasion of the virus' side, together dictate the disease outcome. This review will focus on the evasion of the virus' side, together dictate the disease outcome. This review will focus on the evasion of the virus' side, together dictate the disease outcome. This review will focus on the evasion of the virus' side, together dictate the disease outcome. This review will focus on the evasion of the virus' side antiviral strategies against these important viruses. This may well also prevent stress granule formation, however as mentioned, this has not been investigated for rhinoviruses yet. Trends Microbiol. Croft SN, Walker EJ, Ghildyal R. discovered the role of influenza encoded NS1 in host shut-off [81]. Interaction of 2A proteinase of human rhinovirus yet. genetic group A with eIF4E is required for eIF4G cleavage during infection. CoVs encode endonuclease activity in one of their non-structural proteins, and recent reports indicated that this is instrumental to avoid recognition by the MDA5, protein kinase R (PKR), and OAS/RNAse L machineries [65, 66]. Functions of the influenza A virus NS1 protein in antiviral defense. Competitive fitness in coronaviruses is not correlated with size or number of double-membrane vesicles under reduced-temperature growth conditions. EMBO J. Further research is needed to conclude whether these opposite effects indeed benefit the respective infections, or whether either of the results is incorrect. Ghildyal R, Jordan B, Li D, Dagher H, Bardin PG, Gern JE, et al. The viral genome, packaged in nucleocapsid proteins and bearing a panhandle- and 5'-triphosphate structure is recognized by RIG-I, presumably in the cytosol while on its way to the nucleus, or when being incorporated into new virus particles [52-54]. The host immune response in respiratory virus infection: balancing virus clearance and immunopathology. Virology. Wirology. Wirology. Wirology. Nodulation of Both Innate and Adaptive Immunity. Global burden of childhood pneumonia and diarrhoea. Respiratory syncytial virus infection of airway cells: role of microRNAs. Pediatr 13. Additionally, the cell has evolved multiple ways to attack influenza replication, for example, by GBPs that are localized in the nucleus and the cytosol [56]. In summary, the formation of membranous headquarters may be a major strategy for respiratory viruses to avoid innate immune recognition of viral nucleic acid products in the cytosol. Contoli M, Ito K, Padovani A, Poletti D, Marku B, Edwards MR, et al. Representations of viral genomes were adapted from ViralZone: www.expasy.org/viralzone, SIB Swiss Institute of Bioinformatics under the Creative Commons License. Molecular Mechanisms of Foot-and-Mouth Disease Virus Targeting the Host Antiviral Response. NF90 is a novel influenza A virus NS1-interacting protein that antagonizes the inhibitory role of NS1 on PKR phosphorylation. 2016 Feb;31(1):12-23. 2015 Aug;7(9):4854-72. Virus Escape and Manipulation of Cellular Nonsense-Mediated mRNA Decay. IL-28, IL-29 and their class II cytokine receptor IL-28R. 2013 Mar;45(1):11-21. Zhang S, Carriere J, Lin X, Xie N, Feng P. The 2A protease of these viruses is responsible for this, by directly cleaving this factor [88, 89]. Pieter Hiemstra (LUMC, Leiden, The Netherlands) for critically reading the manuscript and for helpful comments and discussions. Disclosure Statement The author declares no conflicts of interest. Funding Sources The author was funded by a primary institutional appointment as associate professor at Leiden University Medical Center, Leiden, The Netherlands. While picornavirus family member foot-and-mouth disease virus leader protease was shown to have deubiquitinating activity [137], neither 2A nor 3C protease from rhinovirus has been implicated in ubiquitin-regulated processes to date, and no other reports hinting at manipulation of the ubiquitin system by rhinoviruses have been published to my knowledge. Conclusions and Discussion The data summarized and discussed above illustrate that innate immune evasion is a major function of respiratory and other RNA viruses (Fig. 1), which probably takes a significant volume of the genetic capacity of these viruses. Recombinant MERS-CoV in which ORF 4 (encoding 4a and 4b proteins) was removed, however, still suppressed stress granule formation [100]. Specific inhibition of type I interferon signal transduction by respiratory syncytial virus. After all, all +RNA viruses produce membranous replication, recognizing and attacking them would provide an efficient way for the innate immune system to inhibit viral infection. Recent insights suggest that stress granules may form a platform for innate immune responses, since the accumulation of (viral) RNA species there provides a pool of substrates for cellular sensors such as RIG-I and MDA5 [92-94]. Netea MG, Joosten LA. 2018 Jan;8:1942. 2016 Jul;38(4):471-82. Indeed, the viruses that have a +RNA genome, which replicate exclusively in the cytosol such as the CoVs and rhinoviruses that invade the lungs, generally modify intracellular membranes elaborately to form headquarters of viral RNA replication, also called "replication, also called "replication, also called "replication, also called "replication, also called "replication factories," "double membrane vesicles" (DMVs; CoVs), "double membrane vesicles" (DMVs; DeDiego ML. 2012;7(8):e43031. Biochem Biophys Res Commun. Potent and selective inhibition of pathogenic viruses by engineered ubiquitin variants. Biering SB, Choi J, Halstrom RA, Brown HM, Beatty WL, Lee S, et al. A more recent report in which CoVs and their cap-structures were studied indicated that the latter viruses make sure to add 2'-C methylation to their cap-structures using a dedicated viral enzyme called nsp16. 2018 Jan;8(1):1569. 2018 Feb;14(2):e1006901. In mice, encephalomyocarditis virus and murine norovirus, which are both +RNA viruses, are suppressed by interferon (-gamma)-induced GBPs [45]. Severe acute respiratory syndrome coronavirus protein nsp1 is a novel eukaryotic translation inhibitor that represses multiple steps of translation initiation. 2011 Apr;413(1):103-10. Interestingly though, PA-X was shown to cleave dsRNA quite efficiently [70], which may not be very relevant for host shut-off, as the cell does not really produce dsRNA. This turned out to be important to avoid recognition by the MDA5 sensor and subsequent triggering of innate immune responses [63, 64]. Besides using viral endoribonucleases PA-X and derivatives to attack cellular mRNAs, as has been briefly discussed for influenza viruses above, the viral polymerase complex and the viral "immune evasion" NS1 each also contribute importantly to host shut-off during influenza infection. 2017 Aug;7:367. 2015 Jul;50(7):727-32. Te Velthuis AJ, Long JC, Bauer DL, Fan RL, Yen HL, Sharps J, et al. 2015 Nov;89(21):10970-81. The fact that respiratory infections are one of the leading causes of mortality in children under 5 years of age [18, 19] suggests that the interactions of the (innate) immune responses in the infant respiratory tract with incoming pathogens is indeed a delicate one, and the balance between severe illness and overcoming an infection may be relatively easily tipping towards the dangerous side. One of the differences is that MERS-CoV encoded nsp1 distinguishes between cellular mRNAs produced in the nucleus, and viral mRNAs in the cytosol, and the translation of the latter is not inhibited by MERS-CoV nsp1. Wang BX, Fish EN. 2009 Apr;458(7240):909-13. That the innate immune response plays an important role in defense against respiratory infections in early life may be further illustrated by the fact that severe RSV infections in children are linked with polymorphisms in genes encoding innate immune factors (reviewed in [14, 20]). In the case of CoV, the viral N protein plays a role in counteracting this latter effect [79], presumably by packaging the viral RNAs, thereby protecting them from degradation. Wada M, Lokugamage KG, Nakagawa K, Narayanan K, Makino S. 2012;7(3):e33174. Ubiquitination in the antiviral immune response. Curr Opin Virol. Coronavirus non-structural protein 16: evasion, attenuation, and possible treatments. Wong LY, Lui PY, Jin DY. 2017;46:875-90.e6. Since influenza replicates in the nucleus (see also below), the idea is that MxA attacks influenza while its products are in the cytosol. Sun Y, López CB. Hayashi T, MacDonald LA, Takimoto T. Antivir Ther. In the last decade, it has become clear that many viruses manipulate stress granule formation, for example, RSV, as was also mentioned above. 2015 Oct;6(10):712-21. Contoli M, Message SD, Laza-Stanca V, Edwards MR, Wark PA, Bartlett NW, et al. RSV and CoVs provide their mRNAs with cap structures themselves, using enzymatic functions in their polymerase complexes. Cell Mol Immunol. Early endonuclease-mediated evasion of RNA sensing ensures efficient coronavirus replication. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Dagenais-Lussier X, Loucif H, Murira A, Laulhé X, Stäger S, Lamarre A, et al. Widespread 3'-end uridylation in eukaryotic RNA viruses. 2018 Apr;34(1):3-32. Barik S. Petersen JF, Cherney MM, Liebig HD, Skern T, Kuechler E, James MN. Interplay between Cellular Metabolism and Cytokine Responses during Viral Infection. Mechanisms of innate immune evasion in re-emerging RNA viruses. 2013 Aug;8(8):e71316. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. 2017 May;114(21):E4251-60. 2011 Feb;12(2):137-43. 2012 Jul;337(6091):199-204. 2012 Dec;86(24):13598-608. Influenza non-structural protein NS1, for which many different innate immune evasion strategies have been described, binds and sequesters viral RNA to protect it from being sensed by RIG-I, and this also protects from the activation of PKR and OAS/RNAse L-mediated viral RNAs as well, besides the 5' ends, as it was shown that Tut4 and Tut7, 2 cellular terminal uridylyltransferases can add one or 2 uridines to the 3' ends of polyadenylated influenza mRNAs, as well as RNAs of several other viruses, to target these RNAs for degradation by cellular machineries [75-77]. Chest. Rhinovirus 3C protease can localize in the nucleus and alter active and passive nucleocytoplasmic transport. 2019 Mar;156(3):217-27. Also, the negativestranded RSV genome and its replication enzymes are found associated with cytosolic occluded structures, in that case named inclusion bodies [38, 39]. 2015 Jun;12:1-6. Rabouw HH, Langereis MA, Knaap RC, Dalebout TJ, Canton J, Sola I, et al. 2018 Nov;3(11):1234-42. Besides contributing to the problem of limited immunological protection, viral innate immune evasion may also contribute to often reported immune over-reactions, including cytokine storms, damaging inflammation, and other severe complications [181-184]. Given that these viruses are generally difficult to control due to factors of viral immune modulation, the more knowledge we gain on the link between virus infection and (innate) immune responses in the host, the higher the chance that we may be able to develop successful and cost-effective remedies. 2015 Jul;25(7):771-84. It is therefore not a surprise that a lot of viruses have evolved ways to manipulate the ubiquitin system and ubiquitin-like molecules such as ISG15, which they do in very diverse ways [121]. After the discovery of a structural resemblance between SARS-CoV expressed PLpro and the cellular deubiquitinating activity and could potentially deconjugate cellular (or viral) substrates to disrupt ubiquitin-mediated signaling, as well as deconjugate ISG15 off its substrates [123]. A later report by Nakagawa et al. For influenza the situation is slightly different, since this virus elicits protective immunity [172]; however, its genetic drift and shift causes new strains that are not, or inefficiently, recognized by existing influenza immunity which generally means that individuals will experience multiple influenza infections in the course of their lives. The accumulation of untranslated mRNAs and stalled translation and pre-initiation complexes trigger the formation of stress granules. Curr Opin Microbiol. 2018 Aug;9(1):3199. Gack MU, Albrecht RA, Urano T, Inn KS, Huang IC, Carnero E, et al. Canedo-Marroquín G, Acevedo-Acevedo O, Rey-Jurado E, Saavedra JM, Lay MK, Bueno SM, et al. A subsequent report showed that PKR activation is required for the induction [98]. The respiratory viruses discussed here use quite diverse methods to achieve this kind of protection from recognition, concomitantly making sure their mRNAs can be properly recognized by the translation machinery of the cell, which they "chose" to utilize. The rhinoviruses are members of the picornavirus family, and these use a specialized, virally encoded cap-mimicking peptide, called VPg, and attach this to the viral RNA 5' end to protect it from recognizion by the translation machinery of the cell, which they "chose" to utilize. The rhinoviruses are members of the picornavirus family, and these use a specialized, virally encoded cap-mimicking peptide, called VPg, and attach this to the viral RNA 5' end to protect it from recognized by the translation machinery of the cell, which they "chose" to utilize. The rhinoviruses are members of the picornavirus family, and these use a specialized, virally encoded cap-mimicking peptide, called VPg, and attach this to the viral RNA 5' end to protect it from recognized by the translation machinery of the cell, which they "chose" to utilize. The rhinoviruses are members of the picornavirus family, and these use a specialized, virally encoded cap-mimicking peptide, called VPg, and attach this to the viral RNA 5' end to protect it from recognized by the translation machinery of the cell, which they "chose" to utilize. The rhinoviruses are members of the picornavirus family. innate RNA sensors [57, 58]. Lambert L, Culley FJ. For example, dsRNA and RNA with a 5'-triphosphate are commonly produced by RNA trunce the host cells do not normally copy RNA from RNA templates, these intermediate RNA species are recognized by the innate immune sensors discussed above as foreign, resulting in antiviral effector activation. Enter at your own risk: how enteroviruses navigate the dangerous world of pattern recognition receptor signaling. Annu Rev Microbiol. A report by Al-Mulla and co-workers showed that in CoV mutants that produced only half the number of ROs during infection or in which the structures were smaller, replication as well as fitness of these viruses was in fact unaffected or even higher than for wt viruses. Viral immunol. 2014 Sep;35(9):420-8. 2011 Dec;162(1-2):80-99. RIG-I and TLR3 are both required for maximum interferon induction by influenza virus in human lung alveolar epithelial cells. Rhinovirus 3C proteases can inhibit apoptotic cell death and activation of antiviral protein complexes by cleaving cellular substrates to benefit the infection. [101] however showed that the ORF4 MERS-CoV mutant virus did induce stress granules in another cell line (Hela/CD26), and also a virus mutant in which 4a alone was removed was not able to suppress SG formation in these cells. Recent work indicated that interaction of rhinovirus A encoded 2A protease with elF4E, another subunit of the cellular translation initiation complex, is required for the cleavage of elF4G during infection [90]. Finally, for RSV little is known about possible host shut-off mechanisms. Expression of a selection of specific hydrophobic viral proteins of RSV [41], and 2B, 2C and 3A proteins of enterovirus (polio; [42]). Indeed, CoV nsp1 with its host-shut-off activities (see above) is a likely candidate viral protein that could play a role. For RNA viruses in the lungs, the Toll-like receptors (TLRs) 3, 7 and 8, which are present in virtually any cell type including those of the lung, have been shown to be relevant for respiratory infections, as will be elaborated below. Le Pen J, Jiang H, Di Domenico T, Kneuss E, Kosałka J, Leung C, et al. 2007 Nov;2(5):295–305. Protein 4a binds viral dsRNA, which is essential for its antagonistic function in PKR activation and stress granule formation, suggesting that 4a prevents recognition of viral RNA by PKR. Vaccine. García J, García-Barreno B, Vivo A, Melero JA. Okamoto M, Kouwaki T, Fukushima Y, Oshiumi H. Respiratory syncytial virus infection alters surfactant protein A expression in human pulmonary epithelial cells by reducing translation efficiency. Grainge CL, Davies DE. Challenges in developing a cross-serotype rhinovirus vaccine. Cell Discov. 1988 Aug;62(8):2636-43. The interplay between central metabolism and innate immune responses. Curr Top Microbiol Immunol. J Biochem. Agrawal P, Nawadkar R, Ojha H, Kumar J, Sahu A. Paludan SR. p53 degradation by a coronavirus papain-like protease suppresses type I interferon signaling. 2015 Mar;17(3):309-19. 2017 Sep;8:1232. Suhy DA, Giddings TH Jr, Kirkegaard K. 2018 Jan;149:58-74. 2014 Dec;25(6):707-13. Biogenesis and architecture of arterivirus replication organelles. To facilitate comparison between the respiratory viruses described here, known and arguably important innate immune evasion strategies are listed, and for each strategy it is discussed how each virus group exploits its own mechanism. 2018 Nov;175(6):1634-1650.e17. Weber M, Sediri H, Felgenhauer U, Binzen I, Bänfer S, Jacob R, et al. 2005 Apr;79(7):4550-1. In these structures, cellular mRNAs are accumulated upon induction of cellular stress responses that lead to inhibition of cellular translation. Type III Interferons in Viral Infection and Antiviral Immunity. Translation inhibition and stress granules in the antiviral immune response. Species-specific antagonism of host ISGylation by the influenza B virus NS1 protein. Krug RM. Th2 cytokines impair innate immune responses to rhinovirus in respiratory epithelial cells. 2006 Sep;12(9):1023–6. This state can inhibit the development of a productive infection with each of these invading viruses, thereby preventing or at least mitigating illness, before adaptive immunity kicks in to completely clear these viruses from the lungs. Importantly, as a countermeasure against these elaborate defense mechanisms, invading respiratory viruses evolve activities that either circumvent or suppress the innate immune responses to create a window of opportunity for efficient virus replication, thereby often causing disease. Natural killer cell specificity towards disrupting cellular mRNA translation is achieved [86]. 2019 Mar;234(3):2143-51. Munir M. Cell. Coronavirus virulence genes with main focus on SARS-CoV envelope gene. Schindewolf C, Menachery VD. Lei X, Xiao X, Wang J. Zinzula L, Tramontano E. I therefore apologize to any authors who miss discussion of their interesting work in this review. Our recent research revealed that the type I IFN signaling cascade, which is utterly relevant for defense against +RNA viruses, indeed includes effectors that influence the integrity of ROs induced by equine arterivirus and a distant relative of the CoVs [44]. Dias A, Bouvier D, Crépin T, McCarthy AA, Hart DJ, Baudin F, et al. In the later stages of RSV infection in epithelial cells, stress granules are formed, and if expression of G3BP, a factor that is essential for stress granules formation, is knocked-down, replication of RSV is inhibited, suggesting a beneficial role for stress granules are formed. be shown for encephalomyocarditis virus, suggesting that at least several +RNA virus induced ROs can be targeted by the innate immunity, such as trained innate immunity, such as trained innate immune responses and cellular metabolic changes, as discussed in the first part of this review, due to their recent discovery have not yet been studied extensively in the context of possible viral evasion strategies. Walker E, Jensen L, Croft S, Wei K, Fulcher AJ, Jans DA, et al. 2018 Dec;10(12):10. 2009 Jul;83(14):7349-52. Virol Sin. 2015 Dec;90(4):2090-101. However, the mechanistic details of NS2's action has not become completely clear yet, although it has been claimed that NS2 somehow stimulates (K48-linked) ubiquitination of mutations in NS2. There has been a recent debate as to whether these chains are actually conjugated to RIG-I or other factors within the cascade or whether they are free ubiquitin chains that provide a scaffold for activating the aggregation of RIG-I and MAVS, which in turn enables downstream signaling [128]. Am J Respir Cell Mol Biol. Plant EP, Ilyushina NA, Sheikh F, Donnelly RP, Ye Z. Additionally, rhinovirus 2A protease cleaves nuclear pore proteins Nup62 and Nup98, while 3C protease seems to cleave Nup153 [111, 112]. Since the polymerase complex takes care of cap-snatching, it will leave considerable amounts of cellular mRNAs without a cap, and this in fact triggers the degradation of these molecules by cellular mRNAs available for translation. Feng Q, Langereis MA, van Kuppeveld FJ. All these structures, while divers in morphology and contents, seem to concentrate the viral replication machinery, intermediates and products inside membrane-bound vesicles or invaginations, seemingly unreachable for the innate immune sensors of the cytosol. 2018 Apr;2018:9480497. Pathol. Mini viral RNAs act as innate immune agonists during influenza virus infection, and the lingering threat of larger outbreaks is felt as long as the virus replicates in humans, WHO has been recommending the development of specific vaccines for both viruses. This latter feature is of importance to the set of cellular innate immune sensors that recognize these viruses when they enter the cells of the respiratory tract, and the subsequent downstream signaling cascades that are triggered as a result. Lifland AW, Jung J, Alonas E, Zurla C, Crowe JE Jr, Santangelo PJ. To be able to set up a productive infection in the cell, these viruses therefore need to circumvent and/or suppress these intracellular innate antiviral responses. Nucleic Acids Res. The cap-snatching endonuclease of influenza virus polymerase resides in the PA subunit. Praefcke GJ. 2017 Nov;8(6):8. 2016 Jun;90(14):6453-63. Critical role of an antiviral stress granule of an antive of an antiviral stress granule of an antiv containing RIG-I and PKR in viral detection and innate immunity. The main, or 3C-like, protease of CoVs may have side-functions in cleaving innate immune factors as it was shown for 2 porcine CoVs. Manipulation of Ubiquitin and ISG15 Regulated Innate Immune Responses the ubiquitin system is essential for the correct functioning of virtually all important cellular processes. 2010;64(1):241-56. About a decade ago, influenza virus NS1 was shown to bind E3 ligase TRIM25, thereby interfering with K63-linked ubiquitination of RIG-I, and therefore uniquely inhibiting innate immune signaling in the type-I IFN pathway [127]. 1977 Jan;74(1):59-63. Cytokine. 1988 Jul;334(6180):320-5. Induction and Subversion of Human Protective Immunity: Contrasting Influenza and Respiratory Syncytial Virus. Innate immune evasion obviously links to the innate immune responses that are known to be elicited by respiratory and other (RNA) viruses, and while this will be elaborated to a limited extent below, they have also been reviewed comprehensively in recent reviews by others [2-17]. Importance and Composition of Innate Immune Responses against Respiratory Virus InfectionsArguably, the innate immune system is more important in early life, when the adaptive functions are still underdeveloped [14]. Both methylations are part of the canonical cap-structures on cellular mRNAs, but why this is necessary was actually unknown. 2015 May;479-480:52-65. One example is the virus-encoded macrodomain. In antiviral innate immune signaling, ubiquitin is an important regulating factor, and ISG15, and interferon-induced ubiquitin-like molecule, is also an important factor in antiviral innate immunity. Nevertheless, in-depth knowledge of this virus-host interaction creates important avenues for novel antiviral strategies, some of which have already been mentioned in the text above, and some more examples will be discussed in the next section 2013;372:3-38. Lokugamage KG, Narayanan K, Nakagawa K, Terasaki K, Ramirez SI, Tseng CT, et al. Adding a cap-structure or a mimic of this structure to the 5'-end is an effective way, since in this way the cell's own mRNAs are protected from recognition by the innate immune sensors. It is interesting to note that very little is known about the details of interaction of viral replication organelles with the innate immune system. Harris KG, Coyne CB. Trained immunity: A program of innate immune system [43]. Regulation of RIG-I Activation by K63-Linked Polyubiquitination. Kelly B, O'Neill LA. Some recent reports (reviewed in [45-47]) suggest that intracellular membrane modifications such as viral ROs can be recognized and targeted by guanylate-binding proteins (GBPs), a family of dynamin-related large GTPases, of which MxA is a member. 2012 Sep;4(9):1438-76. Terminal uridylyltransferases target RNA viruses as part of the innate immune system. 2014 Dec;194:191-9. 2017 Jan;7:662. Their results indicated that there is no strict correlation between the number of replication organelles and the replication rate of these viruses. 2016 Jan;8(1):8. These domains have been identified in CoVs (and several other nonrespiratory +RNA viruses) and have been shown to counteract IFN signaling with a yet unknown mechanism [138]. 2016 Nov;7:498. Züst R, Cervantes-Barragan L, Habjan M, Maier R, Neuman BW, Ziebuhr J, et al. Nicholls JM. The publisher and the editor(s) disclaim responsibility for any injury to persons or property resulting from any ideas, methods, instructions or products referred to in the content or advertisements. Li T, Li X, Zhu W, Wang H, Mei L, Wu S, et al. [91] suggested that RSV specifically targets mRNA encoding surfactant protein A, an innate immune factor with an important role in the epithelial tissue of the lung, which directly binds to virus particles to cause their destruction by host defense mechanisms. Finally, influenza NS1 was shown to mediate the upregulation of RIG-I [131].RSV also manipulates ubiquitin-mediated signaling, mainly directed by its non-structural proteins NS1 and NS2. Rhinovirus 3C ptosis and triggers caspase-independent cell death. 2014 Sep;5:466. It recently became clear that rhinovirus 2A protease activity also plays a role in targeting rhinovirus 3C protein to the nucleus [113, 114], however, it is not clear what 3C protease is doing there exactly [114, 115]. As discussed in the became clear that rhinovirus 2A protease activity also plays a role in targeting rhinovirus 3C protein to the nucleus [113, 114], however, it is not clear what 3C protease is doing there exactly [114, 115]. As discussed in the bec presses ap ning of this review the type I IFN antiviral pathway is very relevant for RNA virus infections, and an essential adaptor that enables downstream signaling in this pathway is IPS-1 (also called MAVS). Protein Cell. If an activity was allocated to a virus, but the location on the genome is not known, the colored sphere was placed beside the name of the virus. Neutrophils in viral infection. A two-pronged strategy to suppress host protein synthesis by SARS coronavirus Nsp1 protein. 2014 Jul;10(7):e1004217. 2017 Apr;14(4):331-8. Viral evasion of intracellular DNA and RNA sensing. The impact of respiratory virus infections on the health of children and adults can be very significant. The appearance of advertisements or/and product references in the publication is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality or safety. Yao Y, Jeyanathan M, Haddadi S, Barra NG, Vaseghi-Shanjani M, Damjanovic D, et al. Influenza Virus: A Master Tactician in Innate Immune Evasion and Novel Therapeutic Interventions. Adv Virus Res. These viruses indeed do not need a cap structure for translation of their RNAs, since they use cap-independent internal ribosomal entry site-mediated translation [59, 60]. 2016 Oct;12(10):e1005982. 2018 Aug;9:1750. Porcine deltacoronavirus nsp5 inhibits interferon-β production through the cleavage of NEMO. This could yield effective modified live virus vaccines that are attenuated by design, and for influenza there has been many attempts at constructing vaccine viruses lacking (parts of) NS1 or containing mutated NS1. The triggering of PKR, a viral RNA sensor, for example, causes phosphorylation of the eiF2alpha translation factor, which halts cellular translation thereby also affecting viral translation. Int J Mol Sci. Onomoto K, Yoneyama M, Fung G, Kato H, Fujita T. 2017 Jan;91(2):91. Nat Rev Immunol. Ma-Lauer Y, Carbajo-Lozoya J, Hein MY, Müller MA, Deng W, Lei J, et al. 2018 Nov;175(6):1463-5. Zhang W, Bailey-Elkin BA, Knaap RC, Khare B, Dalebout TJ, Johnson GG, et al. Viruses. 2014 May;5(3):e01174-14. Lipidated LC3 associates with viral ROs, and while this does not depend on IFN-gamma induction it is clearly stimulated by it. Semin Immunopathol. Cell Death Dis. 1998 Jun;1(7):991-1000. Mx GTPases: dynamin-like antiviral machines of innate immunity. Lötzerich M, Roulin PS, Boucke K, Witte R, Georgiev O, Greber UF. Goraya MU, Wang S, Munir M, Chen JL. Earlier reports suggested that NS2 of RSV can direct proteasomal degradation of signal transducer and activator of transcription 2 (STAT2) in lung epithelial cells [133, 134]. Stress Granule-Inducing Eukaryotic Translation Initiation Factor 4A Inhibitors Block Influenza A Virus Replication. Kamitani W, Huang C, Narayanan K, Lokugamage KG, Makino S. Quite recently it was shown that RSV NS1 targets TRIM25 to suppress RIG-I ubiquitination, very similar to influenza's NS1's strategy [132]. 2014 Dec;95(Pt 12):2594-611. 1993 Mar;74(Pt 3):485-90. A common strategy for host RNA degradation by divergent viruses. Front Cell Infect Microbiol. Viral Macrodomains: Unique Mediators of Viral Replication and Pathogenesis. Many, if not all, viruses, including the respiratory viruses listed above, suppress innate immune responses to gain a window of opportunity for efficient virus replication and setting-up of the infection. Particular virus espinatory viruses listed above, suppress innate immune responses to gain a window of opportunity for efficient virus espinatory viruses. but the information discussed will not be complete. 2014 Dec;159(6):1365-76. 2005;2(5):403-11. Additionally, many influenza strains express shorter forms of this protein encoded by the same gene, overlapping with PA at the N-terminal region, but with an alternative or truncated C-terminal region, added through a ribosomal frame shift or by natural truncation, respectively [69]. Marc D. 2018 Nov;10(11):10. Proc Am Thorac Soc. During all these signal transduction pathways, regulation of activation and inhibition of signal transduction in the cascades is governed in a strict manner by phosphorylation events as well as ubiquitination of different linkage types (K48, K63, K27, etc.) on numerous factors in the pathways (reviewed in [21]). Picornavirus 2A protease regulates stress granule formation to facilitate viral translation. Lim J, Ha M, Chang H, Kwon SC, Simanshu DK, Patel DJ, et al. J Immunol Res. Yuan L, Chen Z, Song S, Wang S, Tian C, Xing G, et al. Natural Killer T Cells and Mucosal-Associated Invariant T Cells in Lung Infections, van der Hoeven B, Oudshoorn D, Koster AJ, Snijder EJ, Kikkert M, Bárcena M. Role of deficient type III interferon-lambda production in asthma exacerbations. Rhinovirus 3C protease facilitates specific nucleoporin cleavage and mislocalisation of nuclear proteins in infected host cells. 2015 Mar;23(3):154-63. However, suppressed antiviral innate immune response during virus-induced asthma exacerbations is likely also influenced by the innate immune evasive functions of respiratory viruses, as these activities contribute to more severe pathogenicity and slower virus clearance, likely stimulating asthmatic manifestations [182, 189]. Nat Rev Microbiol. 2003 Jan;4(1):63-8. Curr Opin Immunol. Nsp3 of coronaviruses: structures and functions of a large multi-domain protein. Respiratory syncytial virus: still crazy after all these years. The general idea about the mechanism governing this is that epigenetic changes on innate immune factor genes in specialized immune cells such as macrophages are made after the activation of the innate immune response. Ramaswamy M, Shi L, Varga SM, Barik S, Behlke MA, Look DC. Indeed, these sensors have been shown to be recruited to stress granules, supporting this view [94-96]. Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickam V, et al. 2017;9(2):111-25. Collins PL, Fearns R, Graham BS. Advances in our understanding of critical viral and host factors. 2014 Dec;289(50):34667-82. The same counts for the rhinoviruses. Besides the replication organelles, the viral 5' end RNA capping/protection mechanisms, and the viral endonucleases, other ways of shielding RNA from innate immune sensors or protecting it from degradation are exploited by respiratory viruses. Newton AH, Cardani A, Braciale TJ. Bohmwald K, Espinoza JA, Becerra D, Rivera K, Lay MK, Bueno SM, et al. The latter 2 systems recognize and destroy foreign RNA in the cytosol independently of the RIG-I-like sensors to remove microbial products. Expert Rev Respir Med. A recent report showed that binding of eiF4GI translation factor to stress granule-inducing protein G3BP1 is essential for antiviral stress granule formation, and this interaction is disrupted by the 2A or L proteases of picornaviruses [110]. Understanding (innate) immune evasion by respiratory viruses could, therefore, shed light on the possibilities for the prevention and cure of asthmatic complications associated with respiratory infections. Closing Remarks: Use of Knowledge on Viral Innate Immune Evasion Strategies for Development of Novel Vaccines and AntiviralsFor particularly RSV and influenza, efforts to develop effective and long-lasting vaccines and antivirals have been relatively unsuccessful for decades [179, 190]. These mutations when introduced into the virus prevent STAT2 from being degraded during infection, providing possibilities for novel vaccines [135]. Although it was reported that RSV infection in cell culture and in patients causes induction of ISG15 and that ISG15 conjugation to proteins has an antiviral effects or not. For rhinoviruses, it is unclear how it interacts with the cell's ubiquitin system. The evolution and diversity of the nonsense mediated mRNA decay pathway. RNAi-mediated antiviral immunity in mammals. Though it may be counter-intuitive for an RNA at certain locations or in certain stages of the infection to avoid the triggering of the RNA sensing and virus-destroying machineries. Influenza also encodes one or more endoribonucleases, the primary one in the PA protein, which is part of the viral polymerase complex together with the PB-1 and PB-2 subunits. The first line of defense at the entire length of the tract from the nasopharynx to the alveolar membrane is formed by the innate immune system [1, 2]. How myeloid cells contribute to the pathogenesis of prominent emerging zoonotic diseases. 2011 Oct;85(20):10874-83. 2015 Mar;115:21-38. Jang SK, Kräusslich HG, Nicklin MJ, Duke GM, Palmenberg AC, Wimmer E. Ubiquitin in Influenza virus NS1 protein mutations at position 171 impact innate interferon responses by respiratory epithelial cells. Rudnicka A, Yamauchi Y. Nat Immunol. Meier-Stephenson V, Mrozowich T, Pham M, Patel TR. 2004 Oct;85(Pt 10):2969-79. Ribose 2'-O-methylation provides a molecular signature for the distinction of self and non-self mRNA dependent on the RNA sensor Mda5. Drahos J, Racaniello VR. The PA endonuclease is responsible for cleaving the host mRNAs for cap-snatching during transcription of the influenza RNA [67, 68], another mechanism of innate immunity and stress granule responses. mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity. 2016;96:219-43. It is still not clear which cellular and viral factors are deconjugated by PLpro during infection, but mutant MERS-CoV in which the deubiquitinating/de-ISG15ylating function of PLpro was removed clearly showed increased type I IFN innate immune responses (Knaap et al., unpublished results), indicating that PLpro's DUB activity has an important role in the suppression of innate immunity during infection. In our own group, we have been exploring the removal of viral deubiquitination activity from the viral PLpro of MERS-CoV and are in the process of analyzing the effect on disease outcome and immune responses in a mouse model (195) and unpublished results). Viral Replication Complexes Are Targeted by LC3-Guided Interferon-Inducible GTPases. 2016 Oct;8(10):8. However, it is not yet clear which type I IFN-inducible factors are responsible. Whelan JN, Tran KC, van Rossum DB, Teng MN. Fleming SB. Interestingly, RSV RNAs have cap-structures that contain a 7-methyl guanosine; however, these caps are devoid of 2'-O-methylation [62]. This indeed suggests that PA-X, besides having a role in the degradation of cellular mRNAs, may also degrade viral RNA to prevent recognition by innate immune sensors and activation of innate immune sensors and activation of innate immune sensors and activation of cellular mRNAs, may also degrade viral RNA to prevent recognition by innate immune sensors and activation of innate immune sensors and activation of innate immune sensors and activation of cellular mRNAs, may also degrade viral RNA to prevent recognition by innate immune sensors and activation of innate immune sensors and has not been identified in the RSV genome, so this virus may use alternative innate immune evasion strategies, as discussed elsewhere in this review. Cell Physiol Biochem. Liu Y, Olagnier D, Lin R. Undoubtedly, yet other evasive activities are additionally still to be identified. Nat Microbiol. Human Respiratory Syncytial Virus NS 1 Targets TRIM25 to Suppress RIG-I Ubiquitination and Subsequent RIG-I-Mediated Antiviral Signaling. Lokugamage KG, Narayanan K, Huang C, Makino S. Wells AI, Coyne CB. Aumayr M, Schrempf A, Üzülmez Ö, Olek KM, Skern T. 2017 Jan;35(3):481-8. Influenza a virus host shutoff disables antiviral stress-induced translation arrest. Interferon-λ Mediates Nonredundant Front-Line Antiviral Protection against Influenza Virus Infection without Compromising Host Fitness. 2006 Nov;314(5801):997-1001. 2009 Apr;458(7240):914-8. 2012 Apr;26(4):1629-39. Infectious Agents as Stimuli of Trained Innate Immunity. Allergy. Gasteiger G, D'Osualdo A, Schubert DA, Weber A, Bruscia EM, Hartl D. Trained Immunity and Local Innate Immune Memory in the Lung. They bind to a distinct heterodimeric receptor consisting of IFNLR1 and IL10RB (as opposed to type I IFN that binds to IFNAR1/2), but seem to trigger downstream signaling that is very similar to the type I IFN that binds to IFNAR1/2). I IFNs. However, whereas type I IFNs are made by many different cell types, IFN lambdas are primarily expressed by epithelial cells and DCs. Recent literature suggests that despite the clear similarities between the types I and III IFN signaling pathways, the type III IFN machinery seems especially equipped to protect epithelial surfaces from pathogenic attacks, and forms the primary local defense upon invasion of low doses of viruses and bacteria. It may well be that, besides their strong genetic variation, the innate immune evasive activities of the mentioned respiratory viruses play a role in this lack of eliciting protective immunity [180], and to possibly improve our options for effective antiviral strategies, it seems pivotal to further investigate this. Middle East Respiratory Syndrome Vaccine Candidates: cautious Optimism. © 2019 The Author(s) Published by S. Lamphear BJ, Yan R, Yang F, Waters D, Liebig HD, Klump H, et al. The recognition by RIG-I is the major trigger to the production of type I IFN during influenza infection, while also TLR3 plays a role [55]. RSV, for example, seems to induce stress granules and this benefits its replication, as will be discussed in the next section. Manipulation of Stress Granule FormationStress granules are structures in which, upon stress responses such as resulting from virus infections, the cell concentrates mRNAs that are produced but can no longer be translated. 2017 Oct;17(10):647-60. 2013 Sep;63(3):230-6. Detailed knowledge on the mechanisms whereby these viruses deal with and modify the immune responses they encounter is therefore pivotal to genuinely advance this field. Nuclear-resident RIG-I senses viral replication inducing antiviral immunity. A segment of the 5' nontranslated region of encephalomyocarditis virus RNA directs internal entry of ribosomes during in vitro translation. Marjolein KikkertDepartment of Infectious Diseases LU-CID, Albinusdreef 2NL-2333 ZA Leiden (The Netherlands)E-Mail m.kikkert@lumc.nl First-Page Preview Received: March 21, 2019Accepted: August 07, 2019Published online: October 14, 2019 Issue release date: January - February Number of Figures: 1 Numb NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND). In lung tissue, antiviral defenses may be further compromised by other mechanisms that impair these defenses such as Th2 cytokines IL-4 and IL-13 [187], and possibly high affinity IgE receptor expression and crosslinking [188]. Bailey-Elkin BA, Knaap RC, Johnson GG, Dalebout TJ, Ninaber DK, van Kasteren PB, et al. Oshiumi H, Matsumoto M, Seya T. 2017 Dec;9(12):9. 2007;12(4 Pt B):651-8. Báez-Santos YM, St John SE, Mesecar AD. Induction and suppression of innate antiviral responses by picornaviruses. Supramaniam A, Lui H, Bellette BM, Rudd PA, Herrero LJ. 2014 Apr;5(2):e01107-13. STAT2 and STAT1 are transcription factors in the second round of innate immune signaling after binding of IFN to its receptor on the original, or surrounding cells. Lloyd JP. van der Hoek L. 2019 Apr;294(16):6430-38. 2016 Feb;12(2):e1005444. 2014 Dec;194:184-90. 2012 Oct;86(20):11128-37. 2018 Sep;10(10):10. While the protective function of such organelles in the context of innate immune sensing is assumed by many researchers, hardly any reports present investigation, let alone proof, of this concept. Santos JC, Broz P. RSV apparently does not need this 2'-O-methylation on its caps, and this may be explained by the observation that this virus is able to sequester MDA5 (and innate immune adapter MAVS) into its inclusion bodies (the RSV replication headquarters as discussed above) using association with its N protein, to avoid MDA5-dependent recognition of viral RNA species and subsequent innate immune response [38]. Viral Endoribonuclease ActivityYet another activity provides additional means of avoiding recognition, and that is viral endoribonuclease activity. The stress granule protein G3BP1 binds viral dsRNA and RIG-I to enhance IFN-β response. 2016 Jun;10(6):629-41. References Martin TR, Frevert CW. Several other reports also show how RSV counteracts the formation of stress granules [99], suggesting a negative effect of stress granule formation. The consequences for the host's immune response are that it is often incomplete, delayed or diminished, or displays overly strong induction (after the delay) that may cause tissue damage. Am J Physiol Lung Cell Mol Physiol. Camouflage and interception: how pathogens evade detection by intracellular nucleic acid sensors. White JP, Cardenas AM, Marissen WE, Lloyd RE. 2017 Dec;10(1):10. A new splice variant of the human guanylate-binding protein 3 mediates anti-influenza viruses steal mRNA cap-structures from host mRNAs in the nucleus during transcription in a process called "cap-snatching," in

which the viral nucleoprotein plays a major role [61]. Quo vadis? Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Further research is needed to confirm such a hypothesis. Interestingly, while CoVs, rhinoviruses, and RSV replicate in the cytosol of respiratory epithelial cells and shield their replicating RNAs as discussed above, influenza virus apparently takes another route, and as the only known exception to the rule this RNA virus replicates in the nucleus. Nat Struct Mol Biol. 2009 Nov;16(11):1134-40. 2017 Jun;7:252. Middle East Respiratory Syndrome Coronavirus nsp1 Inhibits Host Gene Expression by Selectively Targeting mRNAs Transcribed in the Nucleus while Sparing mRNAs of Cytoplasmic Origin. González-Sanz R, Mata M, Bermejo-Martín J, Álvarez A, Cortijo J, Melero JA, et al. Amineva SP, Aminev AG, Palmenberg AC, Gern JE. Nsp1, the most 5'-terminal subunit of the replicate polyprotein of these viruses, was shown to cause host shut-off by binding to cellular factors of the translation machinery thereby preventing translation of host mRNAs. SARS-CoV nsp1 binds the 40S subunit of ribosomes to halt translation [82-85], however, for the MERS-CoV encoded nsp1 the mechanism of halting translation of cellular mRNA seems a bit different [86]. Several reports indicate that GBPs other than the Mx proteins act against human +RNA viruses such as hepatitis C virus, classical swine fever virus, and dengue virus, which are all members of the flavivirus family, possibly by attacking their ROs. In pigs, GBPs inhibit porcine reproductive and respiratory syndrome virus (an arterivirus, distantly related to the CoVs). FEBS Lett. Influenza virus NS1 protein interacts with the cellular 30 kDa subunit of CPSF and inhibits 3'end formation of cellular pre-mRNAs. Mol Cell. The general symptoms of these virus infections, these infections, these should be relatively cheap. 2017 Feb;13(2):e1006195. Rodríguez Pulido M, Sáiz M. Front Microbiol. J Innate Immun. 2010 Feb;140(3):397-408. Ascough S, Paterson S, Chiu C. Viral Immunol. 2016 Aug;113(35):E5192-201. Heaton SM, Borg NA, Dixit VM. Many of these additional evasive activities have been comprehensively reviewed recently by others [13, 17, 72, 74, 99, 108, 123, 139-177]. Evasion of natural killer cells by influenza virus. Rusek P, Wala M, Druszczyńska M, Fol M. The functions of PLpro of CoVs in manipulating the ubiquitin regulation of the innate immune system will be discussed later. Usage and distribution for commercial purposes as well as any distribution in the innate immune signaling cascade. For murine norovirus, it has now become clear that GBPs are indeed targeted to viral ROs and that this depends on part of the autophagy machinery, namely the LC3 conjugation system [49]. Whether PA-X also degrades viral dsRNA species to prevent recognition by cytosolic RNA sensors is not entirely clear, but mutant viruses in which this PA-X protein was expressed in significantly lower amounts elicited higher levels of innate immune response; for example, IFN-beta production was much higher in these infections [71]. Nidovirus papain-like proteases: multifunctional enzymes with protease, deubiquitinating and deISGylating activities. 2018 Oct;104(4):729-35. Furthermore, and similar to what some of the CoV PLpro's may do (see above in this section), Influenza NS1 was recently shown to destabilize Mdm2 E3 ligase which somehow benefits the IAV infection. Induction of innate immunity and its perturbation by influenza viruses. Mechanistically, this effect on viral replication could link to the viral RNA species and intermediates becoming exposed upon disruption of RO membranes by GBPs to the cytosolic innate immune RNA sensors such as RIG-I and MDA5, which subsequently triggers antiviral innate and adaptive immune responses to suppress further replication. Zhou JH, Wang YN, Chang QY, Ma P, Hu Y, Cao X. Sánchez-Aparicio MT, Ayllón J, Leo-Macias A, Wolff T, García-Sastre A. Some studies on SARS-CoV and MERS-CoV infections in patients suggest that the delayed innate immune evasion, contributes to an exacerbated response [144]. Identification of Respiratory Syncytial Virus Nonstructural Protein 2 Residues Essential for Exploitation of the Host Ubiquitin System and Inhibition of Innate Immune Responses. Slaine PD, Kleer M, Smith NK, Khaperskyy DA, McCormick C. Sci Rep. 2018 Mar;371(3):505-16. Finally, perspectives for use of the reviewed knowledge for the development of novel antiviral strategies will be sketched. FASEB J. 2016 Jan-Feb; 29(1):11-26. Versteeg GA, Hale BG, van Boheemen S, Wolff T, Lenschow DJ, García-Sastre A. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Rossi GA, Silvestri M, Colin AA. 2017 Nov;8:1570. Guo H, Kumar P, Malarkannan S. 2015 Oct; 36:14-21. 1999 Oct; 18(20):5463-75. MBio. Yet, the young infant is probably exposed to as many incoming pathogens as older children and adults are, so the innate immune system plays a very important role in the protection from respiratory infection in young children. Host and Viral Modulation of RIG-I-Mediated Antiviral Immunity. Modulation of Innate Immune Responses by the Influenza A NS1 and PA-X Proteins. In this way, the innate immune system senses foreign material that is possibly pathogenic, and this triggers downstream signaling to ultimately induce transcription factors in the nucleus which in turn stimulate expression of types I and III interferons (IFNs) and other proinflammatory cytokines. 2018 Mar;9:323. In this review, innate immune responses relevant for respiratory viruses with an RNA genome will briefly be summarized, and viral innate immune evasion based on shielding viral RNA species away from cellular innate immune sensors will be discussed from different angles. 2018 Oct;32:9-14. Up till today, it therefore remains unclear what the role of stress granules during RSV infection is exactly. CoVs also manipulate the host's immune responses, thereby breaking through pre-existing natural or vaccine inflicted immunity. 2018 Oct;39(10):848-58. Virus Res. Nordmann A, Wixler L, Boergeling Y, Wixler V, Ludwig S. 2015 Jan;385(9966):430-40. Int J Med Microbiol. Innate Antiviral Defenses Independent of Inducible IFNa/B Production. Middle East Respiratory Coronavirus Accessory Protein 4a Inhibits PKR-Mediated Antiviral Stress Responses. Haller O, Staeheli P, Schwemmle M, Kochs G. Interaction of the innate immune system with positive-strand RNA virus replication organelles. 2018 Sep;10(9):10. Wang D, Fang L, Shi Y, Zhang H, Gao L, Peng G, et al. Nature. 2016 Sep;90(19):8389-94. Cell Res. RNA sensors like the RIG-Ilike sensors or TLRs were thought to be absent there, and therefore replication inside the nucleus may have been an alternative solution to avoid innate immune recognition of viral RNA virus infection. 2018 Oct;115(43):E10157-66. Cell Host Microbe. RIG-I detects viral genomic RNA during negative-strand RNA virus infection. Nakagawa K, Narayanan K, Wada M, Makino S. Oh SW, Onomoto K, Wakimoto M, Onoguchi K, Ishidate F, Fujiwara T, et al. In collaboration with the group of Frank van Kuppeveld, our lab showed that MERS-CoV encoded 4a protein (translated from ORF4 in the virus) impedes dsRNA-mediated PKR activation, thereby preventing stress granule formation [100]. Jagger BW, Wise HM, Kash JC, Walters KA, Wills NM, Xiao YL, et al. Feng W, Sun X, Shi N, Zhang M, Guan Z, Duan M. 2016 Aug;590(16):2797-810. ISG15 Is Upregulated in Respiratory Syncytial Virus Infection and Reduces Virus Growth through Protein ISGylation. Mapping the cleavage site in protein synthesis initiation factor eIF-4 gamma of the 2A proteases from human Coxsackievirus and rhinovirus. A myriad of different cells, innate lymphoid cells, and dendritic cells (DCs) have a major role in this first defense, while in these and other cells of the respiratory tract the sensing, and several subsequent specific molecular intra- and intercellular signaling cascades ensure the establishment of the so- called antiviral state in the lungs. Overview of respiratory viruses and major immune evasive activities as discussed in this review. Cheng SC, Joosten LA, Netea MG. Whether the cell can in turn recognize and attack these structures is still relatively unknown. along with viral countermeasures against these attacks. Viral Inhibition of the IFN-Induced JAK/STAT Signalling Pathway: Development of Live Attenuated Vaccines by Mutation of Viral-Encoded IFN-Antagonists. Influenza B virus-encoded NS1 additionally inhibits ISG15 antiviral activity by binding the N-terminus of human ISG15 (and not mouse ISG15) [129]. Given these data, it may be likely that rhinoviruses also affect stress granule formation using their proteases, which is further supported by data described in the next paragraph, but this needs to be investigated. Respiratory Virus Proteases, which is further supported by data described in the next paragraph, but this needs to be investigated. Respiratory Virus Proteases, which is further supported by data described in the next paragraph, but this needs to be investigated. Respiratory Virus Proteases, which is further supported by data described in the next paragraph, but this needs to be investigated. Respiratory Virus Proteases, which is further supported by data described in the next paragraph. proteases, which they generally use to cleave their viral polyproteins into functional subunits during the viral life cycle. A report by Bruce et al. Additionally, the interactions of viral polyproteins into functional subunits during to end to be added a subunity of the viral life cycle. the authors, this is because Mdm2 seems to have a p53-independent antiviral function which is then alleviated [130]. 2016 Nov;90(24):11032-42. Influenza virus non-structural protein NS1: interferon antagonism and beyond. Subsequently, viral enzymatic activities that suppress innate immune responses will be discussed, including activities causing host shut-off and manipulation of stress granule formation. Interplay between coronavirus, a cytoplasmic RNA virus, and nonsense-mediated immune evasion and viral manipulation of the ubiquitin system will be addressed. Science. Wimmer P, Schreiner S. 2012 Aug;130(2):489-95. Al-Mulla HM, Turrell L, Smith NM, Payne L, Baliji S, Züst R, et al. Small GTPases. Shokri S, Mong W, Glaunsinger BA. Remodeling the endoplasmic reticulum by poliovirus infection and by individual viral proteins: an autophagy-like origin for virus-induced vesicles. Menachery VD, Eisfeld AJ, Schäfer A, Josset L, Sims AC, Proll S, et al. Severe acute respiratory syndrome coronavirus nsp1 facilitates efficient propagation in cells through a specific translational shutoff of host mRNA. Dash P, Thomas PG. Huang C, Lokugamage KG, Rozovics JM, Narayanan K, Semler BL, Makino S Rehwinkel J, Tan CP, Goubau D, Schulz O, Pichlmair A, Bier K, et al. 2018 Sep;25(9):778-86. Given the widespread prevalence, a general lack of natural sterilizing immunity, and/or high morbidity and lethality rates of diseases caused by influenza, respiratory syncytial virus, coronaviruses, and rhinoviruses, this difficult situation is a genuine societal challenge. This resembles "the Warburg effect", as described in tumor cells, and after pathogen sensing innate immune response thus triggers changes in the cell's metabolism for the new situation [34]. Levene RE, Gaglia MM. 2017 Jul;22(1):74-85.e7. Additionally a recent report indicated that cytosolic coronaviral mRNAs are targeted by the cellular nonsense-mediated decay pathway, a pathway that detects aberrant translation termination features such as premature termination codons in mRNA, resulting in the degradation of these mRNAs [78]. Scutigliani EM, Kikkert M. Additional ubiquitins can be added to the first via one of 7 lysines in ubiquitin itself, yielding poly-ubiquitin chains. Influenza virus adaptation PB2-627K modulates nucleocapsid inhibition by the pathogen sensor RIG-I. Rhinovirus 3C protease precursors 3CD and 3CD' localize to the nuclei of infected cells. An elaborate machinery is therefore present at this large surface to defend this tissue against invading pathogens, including mechanical barriers such as a mucus layer. They are absent in influenza virus, rhinoviruses, and RSV, and therefore has not been discussed in this review. 2016 Sep;37(9):588-96. An emerging hot topic is also the interplay of innate immune response with cellular metabolism, so-called immunometabolism, which likely is quite relevant for respiratory viral infections [4, 32, 33]. Future Microbiol. Ma DY, Suthar MS. Additionally, the nsp1 protein of both viruses causes host mRNA degradation, however, not through intrinsic endoribonuclease activity of nsp1 itself but by activating the cellular mRNA degradation machinery and its exonuclease Xrn1 [82, 83, 86, 87]. Rhinoviruses, like poliovirus and other enteroviruses, cleave translation initiation factor elF4G to shut down cap-dependent translation of viral mRNAs since these viruses depend on internal ribosomal entry site-mediated translation (see above). Gralinski LE, Baric RS. An obvious primary strategy would be to shield away the replication intermediates with their dangerous, recognizable features, from the innate immune sensors roaming the cytosol. Crystal structure of an avian influenza polymerase PA(N) reveals an endonuclease active site. Interferon-\lambdas: Front-Line Guardians of Immunity and Homeostasis in the Respiratory Tract. Karger AG, Basel The epithelium of the lungs is the largest surface in the human body that is in contact with our environment. Liu G, Lu Y, Thulasi Raman SN, Xu F, Wu Q, Li Z, et al. 2012 Jan;151(1):5-11. Inhibition of Stress Granule Formation by Middle East Respiratory Syndrome Coronavirus 4a Accessory Protein Facilitates Viral Translation Leading to Efficient Virus Replication. Balistreri G, Bognanni C, Mühlemann O. Vandini S, Calamelli E, Faldella G, Lanari M. Lei J, Kusov Y, Hilgenfeld R. Kindler E, Thiel V, Weber F. The cost-effectiveness balance is also a factor for the CoVs causing severe infections, that is, SARS-CoV and MERS-CoV, since infections with these viruses are either not being reported any more (SARS-CoV), or are quite localized and relatively scarce (MERS-CoV). J Leukoc Biol. Schulz KS, Mossman KL. Type III Interferons in Antiviral Defenses at Barrier Surfaces. This is, however, in contrast to what was mentioned for NL63 CoV, where PLpro seems to stabilize Mdm2 to also benefit infection [124]. Human coronaviruses: what do they cause? 2016 Jun;14(6):360-73. Netea MG, Joosten LA, Latz E, Mills KH, Natoli G, Stunnenberg HG, et al. Antiviral Innate Immune Response Interferes with the Formation of Replication-Associated Membrane Structures Induced by a Positive-Strand RNA Virus. 2016 Jul; 220:70-90. Cell Tissue Res. The location in the viral genomes where immune evasive activities are encoded are indicated with colored spheres. This is not surprising given the role of NS1 in host-shut-off as well as in protecting the viral RNA from recognition by RNA sensors in the cell (see above), thereby preventing the activation of PKR and concomitant eiF2alpha phosphorylation and stress granule formation. De Vlugt C, Sikora D, Pelchat M. 2017 Jan;9(1):9. Pathogenic influenza viruses and coronaviruses and coron JA, Castaño-Rodriguez C, Fernandez-Delgado R, et al. It is noticeable that many of the viruses discussed here do not elicit a long-lasting immune protection, and RSV can re-infect individuals sometime after earlier infection, again causing symptoms (reviewed in [178, 179]), which is in sharp contrast to several other childhood-associated viral infections, where lifelong protection is achieved after generally experiencing only one episode of disease. Watters K, Palmenberg AC. SARS coronavirus nsp1 protein induces template-dependent endonucleolytic cleavage of mRNAs: viral mRNAs are resistant to nsp1-induced RNA cleavage. Influenza A virus NS1 targets the ubiquitin ligase TRIM25 to evade recognition by the host viral RNA sensor RIG-I. During RSV infection, surfactant protein A mRNA translation efficiency seems inhibited, however, the mechanism for this effect has not been elucidated to date. A second round of autocrine signaling subsequently ensures that infected, and the surrounding uninfected cells, express a myriad of interferon stimulated genes (ISGs) that establish a so-called antiviral state. Recognition of Viral RNA by Pattern Recognition of Viral RNA by Pattern Recognition of dsRNA sensors and limits apoptosis in macrophages. 2016 Jan:90(7):3428-38. Expression and Cleavage of Middle East Respiratory Syndrome Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated w Mainou BA, Dermody TS, Crowe JE Jr. Activation of protein kinase R is required for induction of stress granules by respiratory syncytial virus but dispensable for viral replication. 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