Abstract. The comparative analysis of the antiviral protective mechanisms, including protozoa and RNA interference in multicellular organisms, has revealed their similarity and provided a basic understanding of adaptive immunity. The present article summarizes the latest studies on RNA-guided gene regulation in human antiviral protection, and its importance. Additionally, the role of both neutralizing antibodies and the interferon system in viral invasion is considered. The interferon system is an additional mechanism for suppressing viral infections in humans, which shifts cells into an ‘alarm’ mode to attempt to prevent further contagion. The primary task of the human central immune system is to maintain integrity and to protect against foreign organisms. In this review, a novel concept is proposed: Antiviral protection in all organisms can be achieved through an intracellular RNA-guided mechanism. A simple and effective defence against viruses is incorporation of a part of a virus’s DNA (spacer) into the hosts chromosomes. Following reinfection, RNA transcripts of this spacer are created to direct nuclease enzymes to destroy the viral genome. This is an example of real-time adaptive immunity potentially possessed by every cell with a full complement of chromosomes, and an indicator that antiviral immunity is not only mediated by the presence of neutralizing antibodies and memory B- and T-cells, but also by the presence of specific spacers in the DNA of individuals who have recovered from a viral infection.

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1. Introduction
The current COVID-19 pandemic poses a substantial challenge for the entire medical community globally, and has spurred numerous studies to improve our understanding of the immune system. COVID-19, which can be detected by PCR and antibody titres has resulted in a widespread increase in the number of infected individuals, as well >5 million deaths, globally, and repeated lockdown measures to prevent or reduce the severity of outbreaks. This pandemic has highlighted a need to revisit some of the dogmas of immunology. One such dogma states that the memory of past infections is formed by T and B memory cells only. Several research articles have shown the presence of memory in innate nonspecific immunity, and this may provide a challenge to the prevailing point of view (1,2). Conversely, the substantial amount of literature concerning gene regulation by RNA makes it possible to formulate a mechanism of human antiviral defence from a novel angle: Every cell in the human body with a full complement of chromosomes potentially has its own antiviral protection mechanism based on RNA interference.

To prove this point, the following sections of this review article describe the activity of RNA-guided gene regulation, and the role of interferons and the central immune system in viral invasion.

2. RNA-guided antiviral protection
To understand the mechanism of RNA-guided protection, it is necessary to start with unicellular organisms, as development of reliable mechanisms for countering viruses, the evolutionary acquisition of viral infection immunity allowed for the generation of multicellular organisms. It should be noted that this transition took ~2 billion years of evolution (the first multicellular organisms appeared 1.7 billion years ago).
The role of RNA interference has been proven to occur in several infections caused by the human respiratory syncytial virus (21), human immunodeficiency virus type 1 (22), hepatitis B virus (23) hepatitis C virus (24,25), influenza virus (26) and coronavirus SARS-CoV-1 (27). The presence of such spacers effectively prevents viral infection in mammals as well. It is known that the spacers in the DNA of target cells inhibit the reproduction of viruses (28,29). Recent work on the suppression of SARS-CoV-2 viral reproduction using specific siRNAs (30) leaves no doubt regarding the validity of this hypothesis.

The data mentioned above directly indicate the ability of cells themselves to resist viral invasion. Every cell in the human body that contains a full complement of chromosomes may potentially preserve an ancient system for counteracting viruses using small RNAs. Moreover, this protection is adaptive and forms a type of full-fledged intracellular immune memory.

3. The role of the interferon system

The interferon system is another important mechanism for cellular protection, which is based on production of special proteins preventing further infection (31,32). It is hypothesized that this additional system is required for highly organized organisms to respond quickly to a viral invasion. The increase in the number of densely grouped cells of the same type facilitates the spread of viruses-having multiplied in one sensitive cell, virions can easily infect the nearby cells. Accordingly, the innate RNA-guided protection may not be able to cope with the high viral load. To prevent this possibility, an early warning system exists and uses interferons as ‘alarms’.

All nucleated cells have receptors for interferon I (33). Following activation of this receptor upon ligand binding, the expression of several genes is upregulated placing the cell in a state of ‘alarm’, halting almost all protein synthesis, and endo- and exocytosis are inhibited, which prevents both entry and exit of viral particles (34,35). Interferon itself is produced by cells infected with viruses (36). Each human cell possesses a substantial profile of receptors that recognize certain pathogenic motifs. In the case of viral infections, there are special cytoplasmic RLR receptors that recognize viral double-stranded RNA (37). Their activation triggers a cascade of intracellular mechanisms, ultimately resulting in the synthesis of interferons and pro-inflammatory cytokines (Fig. 2).

Interferons themselves, in turn, regulate the functions of >2,000 interferon stimulated genes (ISGs); there is a database of these ISGs, which highlights their effect on metabolism (interferome.org/interferome/home.jspx). In the context of this review, only a few points will be highlighted. First, the epithelial cells, which are the first to meet various pathogens, possess receptors for interferon III. This emphasizes the need for prompt and coordinated activity during viral invasions of these barrier forming cells. Second, prolonged contact with interferons induces the cells to initiate apoptosis. Finally, several enzymes are produced by interferon blocking nucleases, which are required for the full function of the RNA-guided system (38). Thus, an additional safety interferon system is able to interfere with the RNA-controlled protection and, moreover, induce cell
death. This particular kind of antagonism in the interferon and RNA-guided systems in antiviral protection has been studied in several studies, and is extensively reviewed here (39). The first cell lines that exhibit viral entry are well-differentiated surface epithelial or endothelial cells. When the virus enters these cells, DICER nucleases begin immediately cutting the viral genome, the TLR and RLR receptors, and in turn, trigger a cascade of interferon synthesis (37,38). This is the first non-specific phase of countering the viral invasion. The following steps are dependent on the viral load; if it is small, then the infected cells cope on their own and ‘warn’ the neighbouring intact cells about the infection, assisting the latter in reducing their susceptibility to viral infection. The infection is interrupted without a pronounced clinical effect. As the load increases, the infected cells undergo apoptosis, and the neighbouring cells, under the influence of increasing doses of interferon, halt protein synthesis, exo- and endocytosis, and the activity of almost all enzymes; these cells metaphorically freeze (33,34,40). Under the influence of interferons and other cytokines, the central immune system is primed; the first antibodies and symptoms of inflammation appear. The infected cells carrying viral antigens on their surface to attract T-killers, these cells are opsonized with antibodies, and the complement system is activated (41,42). The classical signs of
formed in unipotent progenitor cells when a virus or spacer blocking interferon signals. Therefore, immune memory is for full-fledged RNA interference, which is not disturbed by protein synthesis (43). Accordingly, there remains a place under the influence of interferons, do not halt RNA and to form. As mentioned above, poorly differentiated cells, cells, an adaptive intracellular antiviral protection begins of infected cells, the immune system is in an activated state. while the viral proteins are presented at the plasma membrane an infection attributed to each specific virus manifest. Note, the cytokine storm. During a cytokine storm, there is the risk of the formation of IFN induces cell apoptosis and is associated with the development which leads to inhibition of virion assembly and release. Excessive production of newly synthesized proteins for degradation. Vesicular transport is slowed, they halt protein synthesis, including that of viral proteins, and marks all newly synthesized proteins for degradation. As a signal to destroy this object (41). In the case of bacteria, the antibodies help immune cells to identify foreign agents by binding to specific foreign antigens (opsonization) (46). Namely, the Fc-fragment of antibodies is a ‘black mark’ for immune cells and complement, which perceive it as a signal to destroy this object (41). In the case of bacteria, protozoa, fungi and helminths, this is a working strategy by themselves, even in high concentrations, they perform a diagnostic and guiding role only. In a multi-trillion cell human body, the antibodies help immune cells to identify foreign agents by binding to specific foreign antigens (opsonization) (46). Namely, the Fc-fragment of antibodies is a ‘black mark’ for immune cells and complement, which perceive it as a signal to destroy this object (41). In the case of bacteria, protozoa, fungi and helminths, this is a working strategy by which they are destroyed through the use of antibodies. This also works to counter mutant cells, including tumour cells, where antibodies bind to cancer antigens, and such cells are also discarded. But what happens in the case of a viral infection? A priori, viruses multiply inside cells only, and when viral antigens present on the cell membrane are detected by antibodies, these infected cells are also destroyed. For the entire organism, this is incredibly beneficial; when something foreign is identified, even inside their own cells, the foreign body and/or affected cell is destroyed, sacrificing a part for the greater good of the whole. Note that these infected cells have no other fate—they are all destroyed.

Figure 2. The Interferon alarm system: Adapted from Onomoto (40). Activation of the cytoplasmic receptors RIG-1 and MDA5 by viral dsRNAs, as well as endosomal receptors TLR 7/8 by ssRNAs, lead to phosphorylation of IRF3 and 7, and the pro-inflammatory factor NF-kB. These transcription factors induce the expression of interferon genes and inflammatory cytokines upon nuclear translocation. Newly synthesized interferons bind to their receptors on neighbouring cells and induce the expression of ISGs through the Jak/STAT pathway. Under the influence of the restriction factors encoded by these genes, the cell goes into an ‘alarm’ mode, and in this state, they halt protein synthesis, including that of viral proteins, and marks all newly synthesized proteins for degradation. As a result, exacerbatates an infectious disease. RIG-1, retinoic acid inducible gene-1; MDA5, melanoma differentiation associated protein-5; TLR, toll-like receptor; IFN, interferon; IRF, IFN regulatory factor; NF-kB, nuclear factor-kB; JAK, Janus kinase; STAT, Signal Transducer and Activator of Transcription proteins; ISG, IFN stimulated gene; ssRNA, single stranded RNA.

an infection attributed to each specific virus manifest. Note, while the viral proteins are presented at the plasma membrane of infected cells, the immune system is in an activated state. Moreover, the cells presenting these viral antigens are eventually destroyed.

Concurrently, in the basal layers of these tissues, where actively proliferating and unipotent cells are located, when the viruses and/or spacers themselves enter from the infected cells, an adaptive intracellular antiviral protection begins to form. As mentioned above, poorly differentiated cells, under the influence of interferons, do not halt RNA and protein synthesis (43). Accordingly, there remains a place for full-fledged RNA interference, which is not disturbed by blocking interferon signals. Therefore, immune memory is formed in unipotent progenitor cells when a virus or spacer RNA penetrates them through extracellular vesicles or nucleoprotein complexes with AGO 2 (44,45). After maturation, these cells will possess specific antiviral memory, providing them a powerful tool to effectively eliminate any further infections with the same virus (28,29). The newly formed layer of cells readily copes with the residual viral load and no longer carries the antigens of the virus; the central immune system returns to a normal mode once stimulation is gradually decreased. This change in endothelial and epithelial cells usually takes several days, which is the time required for formation of specific local antiviral memory.

Thus, it is hypothesized that every cell of the human body with a full complement of chromosomes potentially possesses this form of antiviral protection; and it is the RNA interference response that initially determines the course of a viral infection.

4. Discussion

The CRISPR-Cas system has proven to be incredibly effective in combating mobile genetic elements, and thus has retained its role in multicellular organisms, having slightly changed, taking into account the presence of a nuclear membrane and terminal chromosomes. The primary goal of the central immune system possessed by higher order animals, based on T and B cells, is to maintain the integrity of the organism and counter foreign organisms. To accomplish this, the immune system possesses phagocytic, regulatory, antigen-presenting and killer cells, as well as a complement system, and of course, various antibodies. The complement system is a group of proteins, which, after being activated, promote membranolytic cascades that destroy target cells. The classical pathway is activated when the C1q complement protein binds to the Fc-fragment of the antibody (this is the invariable part of all antibodies in the body) attached to the antigen (42). It should be emphasized that antibodies do not destroy a foreign object by themselves, even in high concentrations, they perform a diagnostic and guiding role only. In a multi-trillion cell human body, the antibodies help immune cells to identify foreign agents by binding to specific foreign antigens (opsonization) (46). Namely, the Fc-fragment of antibodies is a ‘black mark’ for immune cells and complement, which perceive it as a signal to destroy this object (41). In the case of bacteria, protozoa, fungi and helminths, this is a working strategy by which they are destroyed through the use of antibodies. This also works to counter mutant cells, including tumour cells, where antibodies bind to cancer antigens, and such cells are also discarded. But what happens in the case of a viral infection? A priori, viruses multiply inside cells only, and when viral antigens present on the cell membrane are detected by antibodies, these infected cells are also destroyed. For the entire organism, this is incredibly beneficial; when something foreign is identified, even inside their own cells, the foreign body and/or affected cell is destroyed, sacrificing a part for the greater good of the whole. Note that these infected cells have no other fate—they are all destroyed.

Until the viruses have penetrated the cells, they are just a set of nucleic acids and proteins; they do not multiply, and do not possess any pathological effects on the body. When viruses bind with antibodies, they of course lose their
diseases should also be mentioned. There is a positive association of such a transfer of protection through milk to a child. For antiviral immunity, it is necessary to emphasize the presence of the body, including the brain (56,57). Thus, with regards to antibodies, breast milk contains ~1,400 different types of antibodies, including, plasma cells, mast cells and several other host cells by interacting with receptors for the Fc fragment or complement (50). There are several examples of ADE caused by α and β coronaviruses (51,52). The current clinical data on the course of COVID-19 indicate involvement of antibodies in the enhancement of clinical manifestations of the disease. The most severe patients appear to possess the highest antibody titres (53). A specific symptom of COVID-19, coagulopathy, clearly indicates complement hyperactivity (54); and this process of cell destruction does not stop as long as they carry viral antigens on their surface. Only as a result of RNA-guided nuclease does the cell achieve clearance of the viral genome, and, accordingly, the viral proteins. Further activation of the central immune system stops, antibody titres fall, and the affected individual recovers.

While discussing human antiviral immunity, one cannot fail to mention the mechanisms of protection observed in early childhood. As recent data have shown, along with antibodies, breast milk contains ~1,400 different types of microRNAs (55). Given the ability of each of these molecules to alter the activity of an average of 15-20 genes, there is a tremendous opportunity to suppress or enhance the activity of genes in infants. It has been shown that these microRNAs, after absorption, are present in the bloodstream and all tissues of the body, including the brain (56,57). Thus, with regards to antiviral immunity, it is necessary to emphasize the presence of such a transfer of protection through milk to a child. The role of vitamin A in prevention and treatment of viral diseases should also be mentioned. There is a positive association between vitamin A administration and the management of measles. During a measles infection, it has been shown that vitamin A deficiency clearly correlates with the severity of the course, and timely treatment of measles with two doses of retinol (200,000 IU) dramatically reduces both morbidity and mortality rates (58-60). We hypothesize that there may be a possibility of wider use of this simple and cheap drug for other viral diseases, including COVID-19. This vitamin is undoubtedly important for the synthesis of RLR receptors, but we were interested in the fact that the DICER nuclease and the RLR receptor have a similar structure, they both possess a DECH box domain that recognizes viral RNA (61). DICER nuclease is a key player in RNA-driven gene regulation, and further research is required on the possible relationship between Vitamin A and RNA interference.

From the above concept of cellular adaptive antiviral immunity, several assumptions can follow regarding interpretation of clinical indicators during the course of a viral infection. Taking COVID-19 as an example, they are as follows: i) The presence or absence of specific antibodies to SARS-CoV-2 is not a predictor of the disease. The presence of antibodies in the blood reflects only the fact that a person has been in contact with the virus. Lack of antibodies does not mean any contact, and people with high titres of specific antibodies are not protected from re-infection with SARS-CoV-2. ii) PCR tests for those who have had COVID may return false positives if the swab sample is taken from the point of the initial spread of the virus (usually from the nasopharynx). We suggest that a negative PCR result for COVID in the blood plasma and urine may be a more reliable indicator of a lack on infection, even when a swab sample from the nasopharynx returns a positive result.

5. Conclusions

Here, a novel concept is proposed—the antiviral protection of all organisms based on intracellular RNA-guided mechanisms. A simple and effective defence against viruses is contained as part of the virus's DNA (spacer) in the chromosomes. Following a reinfection, the RNA transcribes the incorporated spacer and directs nuclease enzymes to cut the viral genome. This is a real-time adaptive immune response potentially possessed by every cell that contains a nucleus. Thus, antiviral immunity may not only be mediated by neutralizing antibodies and memory B- and T-cells, but also through the incorporation of specific spacers into the DNA of the cells genome.

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Competing interests

The authors declare that they have no competing interests.
References

1. Reimer-Michalski EM and Conradt U: Innate immune memory in plants. Semin Immunol 28: 319-327, 2016.
2. Netea MG, Querini T and van der Meer JW: Trained immunity: A memory for innate host defense. Cell Host Microbe 9: 355-361, 2011.
3. Rosing MT: 13C-Depleted carbon microparticles in >3700-Ma sea-floor sedimentary rocks from west greenland. Science 283: 674-676, 1999.
4. Fedonkin MA: The origin of the Metazoa in the light of the Proterozoic fossil record. Paleontol Res 7: 94-41, 2003.
5. Barrangou R: The roles of CRISPR-Cas systems in adaptive immunity and beyond. Curr Opin Immunol 32: 36-41, 2015.
6. Koonin EV and Makarova KS: Mobile genetic elements and evolution of CRISPR-Cas systems: All the way there and back. Genome Biol Evol 9: 2812-2825, 2017.
7. Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE and Mello CC: Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature 391: 806-811, 1998.
8. Elbashir SM, Harborth J, Lendeckel W, Yalcin A, Weber K and Tuschil T: Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells. Nature 411: 494-498, 2001.
9. Han H: RNA interference to knock down gene expression. Immunol Rev 197: 293-302, 2003.
10. Adelabraham M, Safe S, Baker C and Abudayyeh AY: RNAi and cancer: Implications and applications. J RNAi Gene Silencing 2: 136-145, 2006.
11. Ghildiyal M and Zamore PD: Small silencing RNAs: An expanding universe. Nat Rev Genet 10: 94-108, 2009.
12. Mailard PV, Claudio C, Marchais A, Li Y, Jay F, Ding SW and Voinnet O: Antiviral RNA interference in mammalian cells. Science 342: 235-238, 2013.
13. Habibi L and Salmani P: Pivotal impacts of retrotransposon based invasive RNAs on evolution. Front Microbiol 8: 1957, 2017.
14. Wei W, Morrish TA, Alisch RS and Moran JV: A transient assay reveals that cultured human cells can accommodate multiple LINE-1 retrotransposition events. Anal Biochem 284: 435-438, 2000.
15. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W et al: Initial sequencing and analysis of the human genome. Nature 409: 860-921, 2001.
16. Wicker T, Sabot F, Hua-Van A, Bennetzen JL, Capy P, Challboub H, Flavell A, Leroy P, Morgante M, Panaud O et al: A unified classification system for eukaryotic transposable elements. Nat Rev Genet 8: 973-982, 2007.
17. Javdat M and Tamara A: RNA interference: Antiviral defense mechanism and immune response. Adv Appl Physiol 5: 24-29, 2020.
18. Zhang L, Richards A, Barrasa MI, Hughes SH, Young RA and Jaenisch R: Reverse-transcribed SARS-CoV-2 RNA can integrate into the genome of human cells and can be expressed in patient-derived tissues. Proc Natl Acad Sci USA 118: e2015968118, 2021.
19. Bitko V and Barik S: Phenotypic silencing of cytoplasmic RNAs based invasive RNAs on evolution. Front Microbiol 8: 1957, 2017.
20. Wu J, Hore M, Honda T, Merriman DK and Poon LL: Inhibition of intracellular hepatitis C virus replication by RNA interference in mammalian cells. J Exp Med 195: 15-18, 2002.
21. de Weerd NA and Nguyen T: The interferons and their receptor proteins: Expression, function, and regulation. Immunol Rev 150: 485-491, 2001.
22. Houglum JE: Interferon: Mechanisms of action and clinical value. Clin Pharm 2: 20-28, 1983.
23. McBain F, Mayer-Barber K, Sher A, Wack A and O’Garra A: Type I interferons in infectious disease. Nat Rev Immunol 15: 97-103, 2015.
24. Katze MG, He Y and Gale M Jr: Viruses and interferon: A fight for supremacy. Nat Rev Immunol 2: 675-687, 2002.
25. Wu J and Chen ZJ: Innate immune sensing and signaling of cytosolic nucleic acids. Annu Rev Immunol 32: 461-488, 2014.
26. van der Veen AG, Schmidt JM, Lee SA, Deddouche-Grass S, Bong A, Kjer S, Snijders AP and Reis e Sousa C: The RIG-I-like receptor LGP2 inhibits Dicer-dependent processing of long double-stranded RNA and blocks RNA interference in mammalian cells. J Exp Med 197: e2015968118, 2016.
27. Mailard PV, van der Veen AG, Poirier EZ and Reis e Sousa C: Slicing and dicing viruses: Antiviral RNA interference in mammals. EMBO J 38: e100941, 2019.
28. Onomoto K, Onouchi K and Yoneyama M: Regulation of RIG-I-like receptor-mediated signaling: Interaction between host and viral factors. Cell Mol Immunol 18: 539-555, 2021.
29. Flesch BK and Neppert J: Functions of the Fc receptors for immunoglobulin G. J Clin Lab Anal 9: 51-59, 1995.
30. Duncan AR and Winter G: The binding site for Fcg on IgG. Nature 332: 738-740, 1988.
31. Debbabi J, Blanco-Melo D, Panis M, Briendand KJ and tenOever BR: Type I interferon response impairs differentiation potential of pluripotent stem cells. Proc Natl Acad Sci 116: 1384-1393, 2019.
32. Holtzman J and Lee H: Emerging role of extracellular vesicles in the respiratory system. Exp Mol Med 52: 887-895, 2020.
33. Flesch BK and Neppert J: Functions of the Fc receptors for immunoglobulin G. J Clin Lab Anal 9: 51-59, 1995.
34. Duncan AR and Winter G: The binding site for Fcg on IgG. Nature 332: 738-740, 1988.
35. Debbabi J, Blanco-Melo D, Panis M, Briendand KJ and tenOever BR: Type I interferon response impairs differentiation potential of pluripotent stem cells. Proc Natl Acad Sci 116: 1384-1393, 2019.
36. Holtzman J and Lee H: Emerging role of extracellular vesicles in the respiratory system. Exp Mol Med 52: 887-895, 2020.
37. Flesch BK and Neppert J: Functions of the Fc receptors for immunoglobulin G. J Clin Lab Anal 9: 51-59, 1995.
38. Duncan AR and Winter G: The binding site for Fcg on IgG. Nature 332: 738-740, 1988.
39. Debbabi J, Blanco-Melo D, Panis M, Briendand KJ and tenOever BR: Type I interferon response impairs differentiation potential of pluripotent stem cells. Proc Natl Acad Sci 116: 1384-1393, 2019.
40. Holtzman J and Lee H: Emerging role of extracellular vesicles in the respiratory system. Exp Mol Med 52: 887-895, 2020.
41. Flesch BK and Neppert J: Functions of the Fc receptors for immunoglobulin G. J Clin Lab Anal 9: 51-59, 1995.
53. Chen X, Pan Z, Yue S, Yu F, Zhang J, Yang Y, Li R, Liu B, Yang X, Gao L, et al: Disease severity dictates SARS-CoV-2-specific neutralizing antibody responses in COVID-19. Signal Transduct Target Ther 5: 180, 2020.

54. Lo MW, Kemper C and Woodruff TM: COVID-19: Complement, coagulation, and collateral damage. J Immunol 205: 1488-1495, 2020.

55. Benmoussa A and Provost P: Milk MicroRNAs in health and disease. Compr Rev Food Sci Food Saf 18: 703-722, 2019.

56. Manca S, Upadhyaya B, Mutai E, Desaulniers AT, Cederberg RA, White BR and Zempleni J: Milk exosomes are bioavailable and distinct microRNA cargos have unique tissue distribution patterns. Sci Rep 8: 11321, 2018.

57. Zempleni J: Milk exosomes: Beyond dietary microRNAs. Genes Nutr 12: 12, 2017.

58. Soye KJ, Trotter C, Richardson CD, Ward BJ and Miller WH Jr: RIG-I is required for the inhibition of measles virus by retinoids. PLoS One 6: e22323, 2011.

59. D'Souza RM and D'Souza R: Vitamin A for the treatment of children with measles-a systematic review. J Trop Pediatr 48: 323-327, 2002.

60. Huiming Y, Chaomin W and Meng M: Vitamin A for treating measles in children. Cochrane Database Syst Rev 2005: CD001479, 2005.

61. Paro S, Imler JL and Meignin C: Sensing viral RNAs by Dicer/RIG-I like ATPases across species. Curr Opin Immunol 32: 106-113, 2015.

62. Laudadio I, Orso F, Azzalin G, Calabrò C, Berardinelli F, Coluzzi E, Giotosa S, Taverna D, Sgura A, Carissimi C and Fulci V: AGO2 promotes telomerase activity and interaction between the telomerase components TERT and TERC. EMBO Rep 20: e45969, 2019.