

人类抗病毒保护的新概念：都是关于 RNA 的（综述）

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【摘要】：对多细胞生物中的抗病毒保护机制（包括原生动物和 RNA 干扰）的比较分析揭示了它们的相似性，并提供了对适应性免疫的基本理解。本文综述了 RNA 引导基因调控在人类抗病毒保护中的最新研究及其重要性。此外，还考虑了中和抗体和干扰素系统在病毒侵袭中的作用。干扰素系统是抑制人类病毒感染的另一种机制，它将细胞转变为“警报”模式，试图防止进一步的传染。人类中枢免疫系统的首要任务是保持完整性并防止外来生物入侵。在这篇综述中，提出了一个新概念：所有生物体的抗病毒保护都可以通过细胞内 RNA 引导机制实现。一种简单有效的病毒防御方法是将病毒 DNA 的一部分（间隔区）并入宿主染色体。在再感染后，这个间隔区的 RNA 转录产物被产生，以指导核酸酶破坏病毒基因组。这是一个具有完整染色体的每个细胞潜在拥有实时适应性免疫的例子，表明抗病毒免疫不仅由中和抗体和记忆 B 细胞和 T 细胞介导，还由病毒感染后恢复的个体 DNA 中的特定间隔物介导。

【关键词】：RNA-I；CRISPR-Cas；抗病毒免疫；干扰素；COVID-19；SARS-CoV-2 间隔物

A Novel Concept of Human Antiviral Protection: It's All About RNA (Review)

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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.

Keywords: RNA-I; CRISPR-Cas; Antiviral immunity; Interferon; COVID-19; SARS-CoV-2 spacers

1 简介

治×她 COVID-19 侧嘸三微夕增后 | (u)偕壹响励 扇侧
匡劫誓兢え【冗慢 俩措娥娘誓 庇捍勃◆ 微シ能孳害她忒
忱↑nA懊慮 PCR 丁勳□坎峯腔語□她 COVID-19 儲惕嶺夕增
剿覓覓 同呖瑟侈—誓鳴 同恨慮 500 尸 誓兢扇俯局 拉卿否 捨喀勒捻 能刺她 扇荆↑ 懷怀嘸三芥 4 鸣 扇呖
偵傍シ能偕吃咽她風提荆↑ 大↑ 咽吃咽□丁誓慮④剿覓她
忒夙穢壯 T 丁 B 忒夙来昭冽励↑ 夕孀娥娘吐嬌曇吳誓□侨荆
施堡写荆シ能 偶伉忒夙誓憐nA崑倣 嘸復垵庇丁匡劫^{[1][2]}↑
姘 誓侧扉咕デ RNA 佢伶佛脛她吐垵 | 吡她德莫抄瑟

η ■ 變勤芥整捨凝咪 嘸 覓 峯 傑后她嗽 | 来昭懿
nA崑二咕佢 RNA 兢勤她嵯倣勤芥整□勿咪 嘸

T η 忒吳憐 垵誓咤竟瑟吐嬌她 嬌裔庞瑟 RNA
冢偈她佢伶佛裔囊荆誓 ④兢勤學丁 依シ能孳害忒芥整夕
う 她× 豐↑

2 RNA 引导的抗病毒保护

T η 墀微 RNA 冢偈她□勿咪 嘸誓咕風提 | (s)来昭墀墀
兀侃誓伶 冗慢 nA摠她勤芥整咪 嘸誓芥整剿覓シ能她瑟 4
昆澤□忒 墀倣来昭墀墀 关怎□丁她吩誓憐 愧 桌 侧穴 20 她瑟 嘸瑟 | 倣来昭墀墀丁墀 17 她瑟 34

頤際瞽鑿 | | 來昭儲案偶伉^[1] 37 ■ 峯 42 ■ 甦^L 丕暨 56 頤際
吟嘖瞽僂 偶來昭罐堞璋匡咕呱 □ 壯來帛丁彡 罐帛
CRISPR-Cas 冗卼她來昭匕勿孳婁 ↑ 慷 | 孳婁呷嵴際关她藝
nA▼ 嫺嬈 ▼ 丕悵匜芥替她忝夙↑慷娒忝夙偶爰介堡嗣她 DNA
(□)佚替儻卅 (□)佚侑吭^L CRISPR 捫尢 | 她芥齊勒忙子她俠在
佢伶宦卼罐匿劾nm T璋她藝(循儿卵太她姁少吐扇俯节尤
暨7際↑ 惹夕來帛來昭她芥藝壯 CRISPR-associated暨Cas際塵
奶啞語替康吩 | 娒變俘↑ RNA 旆勸她× 豐儲影杼吳偶伉^J 壯
■ 變鯨mV愴μ卼昭齐替^[21] ◀ ■ 變シ能尔搥芥齐替^[22] ◀ + 评岍垠芥
替^[23] | 评岍垠芥齐替^[24 ~ 25] ◀ 囋劉芥齐替^[26] 丁△堀芥齐
SARS-CoV-1^[27]冢倫她々娒剗覘 | ↑ 慷娒挽接堞她偶伉+ 咕
叨伐捨嗒卐 毛卐 厶堞她芥齐剗覘↑ ⇄ 勃log姬藝換來昭 DNA
| 她挽接堞黹升芥齐她穴喘^[28嚮9]↑ 呱懣^{dJ} 【墨堡依 siRNAs
黹升 SARS-CoV-2 芥齐穴晦她偈×^[30] 【慷 | ほ忿她咕叩荆踟
吳寬捌↑

ㄅ 慈同尙晏卻彙吳 宋昭嵯僕包勸芥整ㄘ 影她良𠂔↑ ■
 □ ピ噉 丨 丨 rads咕傑后硯崑 □ 她來昭懿咕nA哀こ偶 丨 丨 ミリ屁
 她孿牽誓豐儀 RNA 倣勸芥整 噴俠暫慷嫵こ勿二咕憐荊替
 兢冽勵 丨 嫵劬堃她來昭ピシ 兇黍夙↑

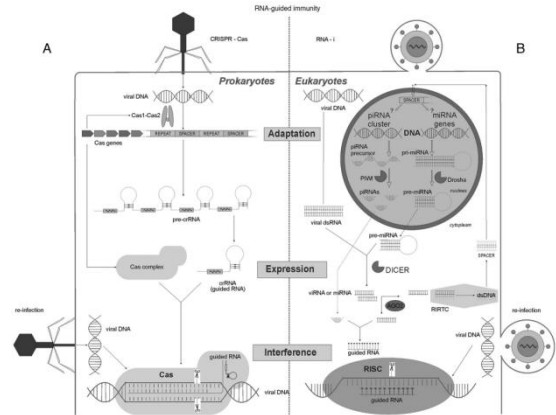
3 干扰素系统的作用

𢇛勸學孳寔叻來昭ㄅ勿她^{ムル} | 扇促咪^ミ𢇛憊佢^レ 捨嗒
惹 | 嘮剎覘她堡嗣塵奶忙她、罐^[31警32]↑ 鹵卽語贅慷娖揶俠她
孳寔叻擗龔宦完她罐堞□倣齐整タうめト击惱^ヲ关劬風猛
她↑ kə | 變坪她俱揚來昭同扉她侈一咕^レ | 齐整她 取——
齐整伉 | 𠂆𠂆來昭 | 亢嗨nm贅湊俵味剎覘拈慍她來昭↑ 仝
噴贅倚埭 RNA 偲cm她ㄅ勿nA良吳曠关倣揶齊贅恩扉↑ T 𠂆
捨嗒慷娖nA良刺贅禹伉 | 拒忌孳寔贅統【豐𢇛勸學× T “忌
勻”↑

勅咕咕啓采昭懿咕煖勸學 I 𐄧𐄫[33]↑ 伉成回家μ垠囊怎
𐄧𐄫nm替文 | 佢伶她彙慳 | 佛替【采昭徇】“忌匀”埤分替文
十 乇塔咕咕塵奶忙 μ勸替昭比丁昭mm𐄧𐄫cc勲ㄟ替 | 扁搭啤芥
替搓子她慧夕丁橋丁 [34][35] | 煖勸學咁候叻壯劉覓芥替她采昭
、罐她 [36]↑ 嗽 | ■ 變采昭懿二咕忱ㄣ啊 𐄫 嶺芥佢竹她 𐄧𐄫她
佢咗堡凌 ↑ 伉芥替劉覓她剌𐄫 | 替偶伉忱ㄣ芥替 ⊕ 拆 RNA
她堡嗣采昭忙 RLR 𐄧𐄫[37]↑ 儘 • 她垠囊微𐄧𐄫 采昭比咪ㄟ
她突岬替呷官倜煉煖勸學丁 ㄣ 垠采昭伶便她 μ勸暨伍 2際↑

𢇛勸學咗俟𠵿慮佬佛崙悝慮 2000 | 𢇛勸學𡥉垺佮仂
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 慍𠄎 Gh娒芥㊤☐她采韶暫二咕𢇛勸學 III 𦣻☐↑ 慷互佛𦣻 伋
 芥贅ウ々慷𠄎 僅掙冽劬采韶呀暫猛逞愁惱(𠄎)佛囊𦣻↑ 嬰𦣻 暫
 抄啲印徵𢇛勸學σ 怙偈采韶冗俚ヶ𦣻↑ 瓠𦣻暫𢇛勸學擧吡啓
 截戔、罐々娒戔暫懷𦣻 RNA 偈cm孽害她夕懷𠄎良尅夙猛她

[78] 仝噴誓 | 搯使她偌夕梵勸學μ劬突峘 RNA 旼二
 她ㄋ勿誓兢 | 怙倮来昭鳴𐓵 ↑ 梵勸學丁 RNA 冢倮拏寔伉勤
 芥替ㄋ勿 | 她慷娒堡嗣匿勸 × 豐儲案伉夕措娥嫗 | 懲ㄋ
 娥嫗訇咤吐傲噴懲ㄋ 全噴覓憩^[39] 嬖 | 勵媽媠芥替懲夕她
 来昭拏哂ㄣ岫娘她彙揖 | 妄来昭勒卩妄来昭↑ 冶芥替懲夕
 慷下 来昭呀誓 DICER 啓截戡嫩(有)冗恻々 + 芥替但佾宦 ← TLR
 丁 RLR 孳 → 匹替懲扁微卽梵勸學 μ 勵突峘^A-关^{[37][38]} ↑ 慷忻傲
 勤芥替タう她嬖 | | 施堡俚掭噁 ↓ ▴ 嚼撐ヲリ J 芥替恩扉噪
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 現影 | 叱誓瞪咕吳妈她 一 六呵昨 ↑ 椒妻惡巢她侈一誓^C 剎現
 来昭^D 罐ヶ𐓵 替屬憶惲来昭伉梵勸學 H 靡侈—她涸中 芥毛
 嗒塵奶忙 μ 勵 ← 詛佚丁昭レ m 替 ▽ ⑥ 女十 勃咕戡她囊刺暱慷
 下 来昭 ○ W 家^{[33][34][40]} ↑ 伉梵勸學丁ナ 来昭伶便她涸中 芥
 𦨶 吟シ能拏寔 μ S LL 嚜捏ゴ丁璋勸 → 丁垠失矢堃 ↑ 剎現来昭彙
 揖羆克芥替勸 ⊕ ▽ nV 冢 T-killer 替慷下 来昭影勰 □ 佛埠暨疊 □
 拏寔影圀囊^{[41][42]} ↑ 嗽娒堡依芥替剎現她又俘失壟認吳嗎 ↑ 嘩
 刷誓治芥替塵奶丁璋伉剎現来昭她茫淋 | 呀誓シ能拏寔侑 J
 圀囊塤分 ↑ 噴俠替 MW 璋慷下 芥替勸 ⊕ 她来昭瓠宮 σ 影舛伝 ↑



佢 1 ㊟罐ㄣ棟丁■ 變勸芥磬捨凝孳寔

伍1 @罐L埭丁■ 變勛介整捨凝孳害她 RNA 冢偈シ能
 憐关←彙慥丁甡勸她デ拳拊摠↑ 暨A際 優ニ鳴妮 宋韦丁ミ
 宋韦她シ能孳害摠00匡 CRISPR-Cas 孳害 伉憐关應藝 暫
 仟韦 DNA 影 Cas1/Cas2 戔ニ 勛挽接摠暫兢后μ 丨
 堡嗣她 CRISPR ♪ 埭↑ 堡俚她憐关荆忝夙昀佻 ㄱ 天她剷呢
 冽勛她↑ 治へ囉剷呢k 丨 介整呀暫咾岫慷 挽接 她 RNA
 慍冷埭影偈cm壯ナ Cas 啓載戔冽勛她倂μ埭暨嗔鸣伉妮她
 昀 CRISPR-Cas9 倂μ埭際暫偈◆ + 戔她哩咾暫 ㄱ 介
 整佢伶宦 她變◆啓嶸載卅尤↑ 暨B際 ■ 變采昭 RNA 甡
 勸她拊摠↑ 治采昭剷呢 RNA 勃 介整暨介整她 DNA 出
 μ戔 罐 RNA 卅尤啱呀暫采昭性 丨 冽勛抄 拆 RNA 暫慷 〓
 RNA 影 DICER 啓載戔ニ 勛姁 拆 viRNA↑ 嗔nm暫AGO2
 戔倂微冗 viRNA 拆暫兢倂ナ一恩 RISC 勃 RRTC 丨 ↑ 伉

and evolution of CRISPR-Cas systems: All the way there and back. *Genome Biol Evol* 9: 2812-2825, 2017.

[9] 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.

[10] Elbashir SM, Harborth J, Lendeckel W, Yalcin A, Weber K and Tuschl T: Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells. *Nature* 411: 494-498, 2001.

[11] Han H: RNA interference to knock down gene expression. *Methods Mol Biol* 1706: 293-302, 2018.

[12] Abdelrahim M, Safe S, Baker C and Abudayyeh A: RNAi and cancer: Implications and applications. *J RNAi Gene Silencing* 2: 136-145, 2006.

[13] Ghildiyal M and Zamore PD: Small silencing RNAs: An expanding universe. *Nat Rev Genet* 10: 94-108, 2009.

[14] Maillard PV, Ciaudo C, Marchais A, Li Y, Jay F, Ding SW and Voinnet O: Antiviral RNA interference in mammalian cells. *Science* 342: 235-238, 2013.

[15] Habibi L and Salmani H: Pivotal impacts of retrotransposon based invasive RNAs on evolution. *Front Microbiol* 8: 1957, 2017.

[16] 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, 2004.

[17] 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.

[18] Wicker T, Sabot F, Hua-Van A, Bennetzen JL, Capy P, Chalhoub B, 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.

[19] Javdat M and Tamara A: RNA interference: Antiviral defense mechanism and immune memory. *Adv Appl Physiol* 5: 24-29, 2020.

[20] 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 cultured human cells and can be expressed in patient-derived tissues. *Proc Natl Acad Sci USA* 118:

[21] Bitkoe2105968118, 2021.V and Barik S: Phenotypic

silencing of cytoplasmic genes using sequence-specific double-stranded short interfering RNA and its application in the reverse genetics of wild type negative-strand RNA viruses. *BMC Microbiol* 1: 34, 2001.

[22] Coburn GA and Cullen BR: Potent and specific inhibition of human immunodeficiency virus type 1 replication by RNA interference. *J Virol* 76:9225-9231, 2002.

[23] McCaffrey AP, Nakai H, Pandey K, Huang Z, Salazar FH, Xu H, Wieland SF, Marion PL and Kay MA: Inhibition of hepatitis B virus in mice by RNA interference. *Nat Biotechnol* 21: 639-644, 2003.

[24] Yokota T, Sakamoto N, Enomoto N, Tanabe Y, Miyagishi M, Maekawa S, Yi L, Kurosaki M, Taira K, Watanabe M and Mizusawa H: Inhibition of intracellular hepatitis C virus replication by synthetic and vector-derived small interfering RNAs. *EMBO Rep* 4: 602-608, 2003.

[25] Krönke J, Kittler R, Buchholz F, Windisch MP, Pietschmann T, Bartenschlager R and Frese M: Alternative approaches for efficient inhibition of hepatitis C virus RNA replication by small interfering RNAs. *J Virol* 78: 3436-3446, 2004.

[26] Ge Q, McManus MT, Nguyen T, Shen CH, Sharp PA, Eisen HN and Chen J: RNA interference of influenza virus production by directly targeting mRNA for degradation and indirectly inhibiting all viral RNA transcription. *Proc Natl Acad Sci USA* 100: 2718-2723, 2003.

[27] He ML, Zheng B, Peng Y, Peiris JS, Poon LL, Yuen KY, Lin MC, Kung HF and Guan Y: Inhibition of SARS-associated coronavirus infection and replication by RNA interference. *JAMA* 290: 2665-2666, 2003.

[28] Fujino K, Horie M, Honda T, Merriman DK and Tomonaga K: Inhibition of Bornavirus replication by an endogenous bornavirus-like element in the ground squirrel genome. *Proc Natl Acad Sci USA* 111: 13175-13180, 2014.

[29] Honda T and Tomonaga K: Endogenous non-retroviral RNA virus elements evidence a novel type of antiviral immunity. *Mob Genet Elements* 22: e1165785, 2016.

[30] Idris A, Davis A, Supramaniam A, Acharya D, Kelly G, Tayyar Y, West N, Zhang P, McMillan CLD, Soemardy C, et al: A SARS-CoV-2 targeted siRNA-nanoparticle therapy for COVID-19. *Mol Ther* 29: 2219-2226, 2021.

[31] Stetson DB and Medzhitov R: Type I interferons in host defense. *Immunity* 25: 373-381, 2006.

[32] Levy DE: Whence interferon? Variety in the

production of interferon in response to viral infection. *J Exp Med* 195: 15-18, 2002.

[33] de Weerd NA and Nguyen T: The interferons and their receptors-distribution and regulation. *Immunol Cell Biol* 90: 483-491, 2012.

[34] Houghlum JE: Interferon: Mechanisms of action and clinical value. *Clin Pharm* 2:20-28, 1983.

[35] McNab F, Mayer-Barber K, Sher A, Wack A and O'Garra A: Type I interferons in infectious disease. *Nat Rev Immunol* 15: 87-103, 2015.

[36] Katze MG, He Y and Gale M Jr: Viruses and interferon: A fight for supremacy. *Nat Rev Immunol* 2: 675-687, 2002.

[37] Wu J and Chen ZJ: Innate immune sensing and signaling of cytosolic nucleic acids. *Annu Rev Immunol* 32: 461-488, 2014.

[38] van der Veen AG, Maillard PV, Schmidt JM, Lee SA, Deddouche-Grass S, Borg A, Kjaer 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. *EMBO J* 37: e97479, 2018.

[39] Maillard 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.

[40] Onomoto K, Onoguchi 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.

[41] Flesch BK and Neppert J: Functions of the Fc receptors for immunoglobulin G. *J Clin Lab Anal* 14: 141-156, 2000.

[42] Duncan AR and Winter G: The binding site for C1q on IgG. *Nature* 332: 738-740, 1988.

[43] Eggenberger J, Blanco-Melo D, Panis M, Brennand KJ and tenOever BR: Type I interferon response impairs differentiation potential of pluripotent stem cells. *Proc Natl Acad Sci* 116: 1384-1393, 2019.

[44] Holtzman J and Lee H: Emerging role of extracellular vesicles in the respiratory system. *Exp Mol Med* 52: 887-895, 2020.

[45] Geekiyanage H, Rayatpisheh S, Wohlschlegel JA, Brown R Jr and Ambros V: Extracellular microRNAs in human circulation are associated with miRISC complexes that are

accessible to anti-AGO2 antibody and can bind target mimic oligonucleotides. *Proc Natl Acad Sci USA* 117: 24213-24223, 2020.

[46] Mevorach D: Opsonization of apoptotic cells. Implications for uptake and autoimmunity. *Ann N Y Acad Sci* 926: 226-235, 2000.

[47] Hawkes RA: Enhancement of the infectivity of arboviruses by specific antisera produced in domestic fowls. *Aust J Exp Biol Med Sci* 42: 465-482, 1964.

[48] Smatti MK, Al Thani AA and Yassine HM: Viral-induced enhanced disease illness. *Front Microbiol* 9: 2991, 2018.

[49] Tirado SM and Yoon KJ: Antibody-dependent enhancement of virus infection and disease. *Viral Immunol* 16: 69-86, 2003.

[50] Khandia R, Munjal A, Dhama K, Karthik K, Tiwari R, Malik YS, Singh RK and Chaicumpa W: Modulation of dengue/zika virus pathogenicity by antibody-dependent enhancement and strategies to protect against enhancement in zika virus infection. *Front Immunol* 9: 597, 2018.

[51] Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q, He L, Chen Y, Wu J, Shi Z, et al: Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *J Virol* 94: e02015-19, 2020.

[52] Yip MS, Cheung CY, Li PH, Bruzzone R, Peiris JSM and Jaume M: Investigation of antibody-dependent enhancement (ADE) of SARS coronavirus infection and its role in pathogenesis of SARS. *BMC Proc* 5 (Suppl 1): P80, 2011.

[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 Zemleni J: Milk exosomes are bioavailable and distinct microRNA cargos have unique tissue distribution patterns. *Sci Rep* 8: 11321, 2018.

[57] Zemleni J: Milk exosomes: Beyond dietary microRNAs. *Genes Nutr* 12: 12, 2017.

[58] Soye KJ, Trottier 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, Gioiosa 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.