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MINI REVIEW

Microbiology and Immunology

Molecular signatures in cetacean morbillivirus and host species proteomes: Unveiling the evolutionary dynamics of an enigmatic pathogen?

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Abstract

Cetacean morbillivirus (CeMV) infects marine mammals often causing a fatal respiratory and neurological disease. Recently, CeMV has expanded its geographic and host species range, with cases being reported worldwide among dolphins, whales, seals, and other aquatic mammalian species, and therefore has emerged as the most threatening nonanthropogenic factor affecting marine mammal's health and conservation. Extensive research efforts have aimed to understand CeMV epidemiology and ecology, however, the molecular mechanisms underlying its transmission and pathogenesis are still poorly understood. In particular, the field suffers from a knowledge gap on the structural and functional properties of CeMV proteins and their host interactors. Nevertheless, the body of scientific literature produced in recent years has inaugurated new investigational trends, driving future directions in CeMV molecular research. In this mini-review, the most recent literature has been summarized in the context of such research trends, and categorized into four priority research topics, such as (1) the interaction between CeMV glycoprotein and its host cell receptors across several species; (2) the CeMV molecular determinants responsible for different disease phenotype; (3) the host molecular determinants responsible for differential susceptibility to CeMV infection; (4) the CeMV molecular determinants responsible for difference virulence among circulating CeMV strains. Arguably, these are the most urgent topics that need to be investigated and that most promisingly will help to shed light on the details of CeMV evolutionary dynamics in the immediate future.

KEYWORDS

cetacean morbillivirus, cetaceans, host–pathogen interaction, morbilliviruses, viral pathogenesis

INTRODUCTION

Cetacean morbillivirus (CeMV) is a nonsegmented, single stranded, negative-sense RNA virus regarded as the nonanthropogenic agent that most dramatically impacts cetacean health and conservation worldwide.[1] The tendency of CeMV to cross interspecies barriers was documented in recent years, showing a progressive widening of the host range and geographical distribution.[2–5] In fact, as outbreaks caused by CeMV in cetaceans from both hemispheres show, the five, hitherto recognized viral strains (termed as CeMV-1 to -5) display a high propensity for multi-host transmission and

Abbreviations: BOFDI, brain-only form of dolphin morbillivirus infection; CADM1, cell adhesion molecule 1; CADM2, cell adhesion molecule 2; CD150, cluster of differentiation 150; CDV, canine distemper virus; CeMV, cetacean morbillivirus; ExNTR, extreme N-terminal region; F, fusion; H, hemagglutinin; Ig-V, immunoglobulin-like variable; M, matrix; MeV, measles virus; Mx1, myxovirus 1; Mx2, myxovirus 2; NC, nucleocapsid; NF-kB, nuclear factor kappa B; NOD1, nucleotide-binding oligomerization domain-containing protein 1; NOD2, nucleotide-binding oligomerization domain-containing protein 2; ODE, old-dog encephalitis; P, phosphoprotein; PDV, phocine distemper virus; PVRL-4, poliovirus receptor-like 4; RNP, ribonucleoprotein; SLAM, signaling lymphocytic activation molecule; SNPs, single nucleotide polymorphisms; SSPE, subacute sclerosing panencephalitis; TREM1, triggering receptor expressed on myeloid cells 1; TRIM14, tripartite motif 14.

trans-oceanic spread.[6,7] CeMV infections were reported also in mammals other than cetaceans, including species with mixed aquatic-terrestrial ecology such as the common seal (*Phoca vitulina*),[8] the Eurasian otter (*Lutra lutra*),[9] and the endangered Mediterranean monk seal (*Monachus monachus*).[10] The CeMV host range expansion mirrors the pattern observed for canine distemper virus (CDV) and phocine distemper virus (PDV), two other morbilliviruses infecting aquatic mammals that caused outbreaks among Lake Bajkal seals (*Pusa siberica*), Caspian seals (*Pusa caspica*), and North Sea common seals.[1] Given the uniqueness of cetacean and pinniped ecological niches, factors such as population density, migration, reproduction, and social interactions play key roles in keeping the virus circulating among individuals and in favoring its transmission between species. Nonetheless, molecular signatures in the CeMV and its host proteomes may be crucial in determining viral transmissibility, infectivity, virulence, and pathogenesis, as well as in modulating the dynamics of CeMV evolution within a single one and between different host species. However, despite the significant progress made towards an understanding of CeMV molecular ecology and epidemiology, there is still a knowledge gap to be filled in regard to the mechanisms through which the CeMV cellular cycle takes place. In addition, several features of CeMV pathogenesis remain largely unknown.[11] Therefore, in light of recent findings and without any claim of exhaustiveness, the present mini-review takes stock of four key themes and related outstanding questions on CeMV molecular biology, towards which research efforts should be prioritized.

PRIORITY 1: MOLECULAR BASIS FOR CeMV TRANSMISSION ACROSS MULTIPLE MAMMALIAN SPECIES

One major investigative direction concerns the ability of CeMV to transmit across a wide range of species. Among the eight proteins encoded by the morbillivirus genome, hemagglutinin (H) is the one responsible for the virus binding to membrane receptors, thereby enabling its entry into host cells.[12] The signaling lymphocytic activation molecule (SLAM; also known as cluster of differentiation 150, CD150) and the poliovirus receptor-like 4 (PVRL-4; commonly known as nectin-4) are the host cell receptors recognized by H, which specify for morbillivirus lymphotropism and epitheliotropism, respectively.[12] While the nectin-4 amino acid sequence is conserved among all known hosts,[13] the one of SLAM displays divergence across marine mammal species.[14] In silico modeling based on homolog structures from measles virus (MeV) H in complex with SLAM has mapped the region in the cetacean receptor that provides an interface for binding to H.[14,15] Lying within the β-strands of the SLAM membrane-distal, immunoglobulin-like variable (Ig-V) domain, this region (aa 63–130) consists of four binding sites with 35 residues putatively involved in interactions with CeMV H. Of these, half are conserved among all known morbillivirus-susceptible species, whereas 11 residues in the variable half vary between pinnipeds and cetaceans, and six residues differ between odontocetes (toothed whales) and mysticetes (baleen whales).[16] Moreover, both CeMV and PDV were shown to be capable of indifferently using dolphin and seal receptors,[6,17] thereby supporting the hypothesis that low binding specificity between H and SLAM may facilitate CeMV—and possibly also PDV—cross-species transmission. Thus far, not only the molecular basis for the CeMV H-SLAM complex formation has not been yet biochemically elucidated, but evidence suggests that residues located out of the SLAM Ig-V domain may also be involved in the interaction. In fact, an additional binding site for MeV H was recently identified on the extreme N-terminal region (ExNTR) of the human SLAM, where interaction between methionine 29 in the receptor and phenylalanine 549 in the viral glycoprotein increased MeV infectivity by 10 times.[18] Similarly, histidine 28 in the N-terminal region of Macaca SLAM was crucial for the interaction with CDV H,[19] whereas only a minimum number of glycoprotein mutations was required for CDV to interact with the human SLAM and lethally infect nonhuman primates.[20–22] Noteworthy, a serine is present at position 29 of the cetacean receptor, and mutation M29S in the human SLAM was sufficient to abolish the interaction with MeV H. Therefore, it can be anticipated that deciphering residue interactions underlying the formation of CeMV H-SLAM and H-nectin-4 complexes will be a research milestone of utmost importance. In fact, assessing the role of SLAM ExNTR for CeMV H binding could help to understand why this virus is able to use the pinniped receptor but is unable to infect human cells on the one hand,[6,12,17] and to predict the zoonotic potential of CeMV H mutations that could provide adaptation to the human SLAM on the other (Figure 1a).

PRIORITY 2: MOLECULAR BASIS FOR DIFFERENT DISEASE PHENOTYPES DURING CeMV INFECTION

A second research direction should focus on the molecular determinants responsible for the different disease phenotypes observed during CeMV infection. In addition to severe bilateral, interstitial pneumonia associated to lymphoid cell depletion and immunosuppression, a multifocal, non-suppurative meningo-encephalitis is observed. Within this pathological framework, of special concern is the "brain-only form of dolphin morbillivirus infection" (BOFDI), which mostly affected striped dolphins (*Stenella coeruleoalba*)[23,24] but was reported recently also in a long-finned pilot whale (*Globicephala melas*) specimen.[25] The main feature of this neuropathy, displaying morpho-pathological similarities with both subacute sclerosing panencephalitis (SSPE) of MeV-infected humans and old-dog encephalitis (ODE) of CDV-infected dogs, is that CeMV antigens and/or genome are exclusively found in the brain.[23,24,26] Neuronal and nonneuronal cell populations from BOFDI-affected striped

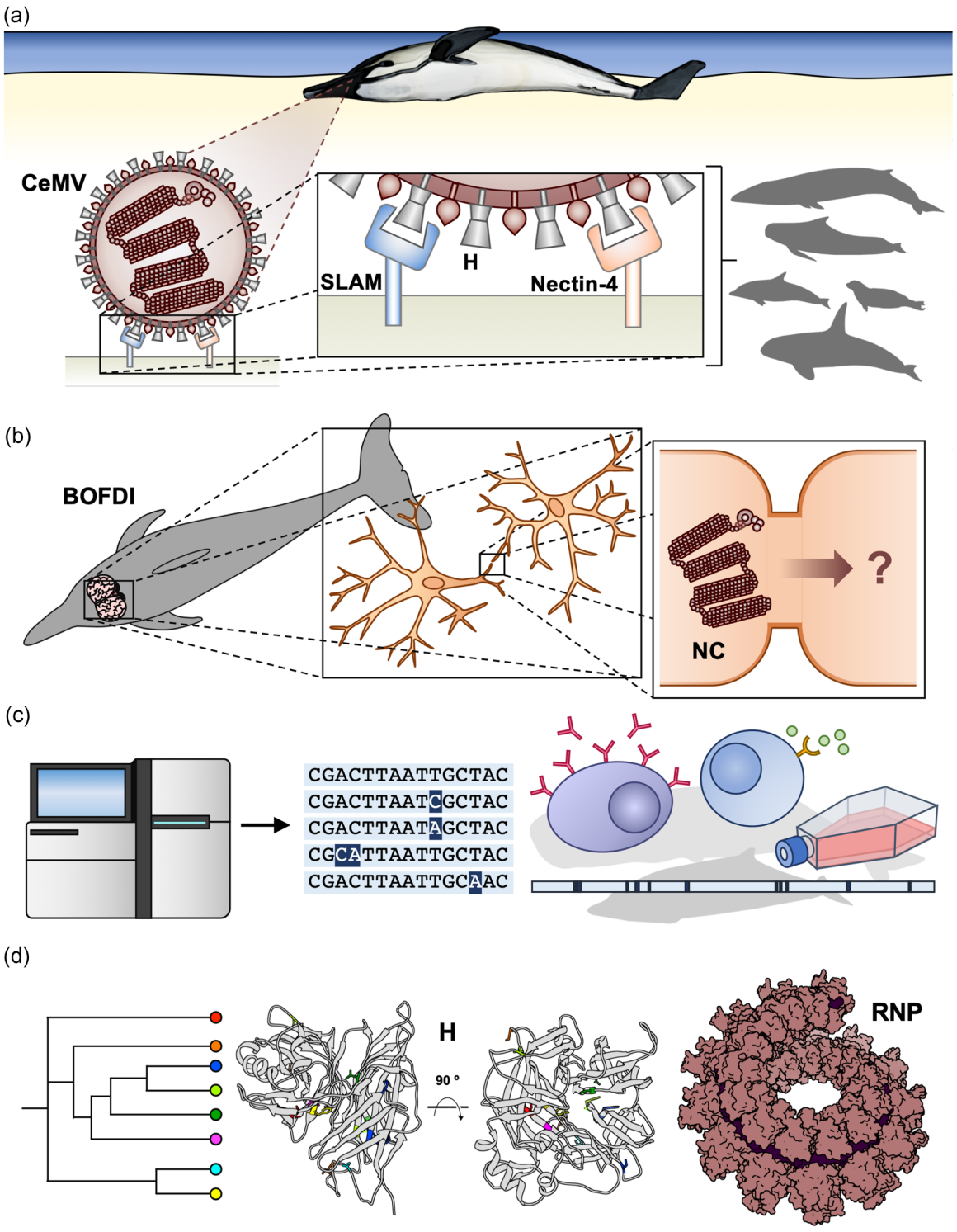

FIGURE 1 Priority directions on Cetacean morbillivirus (CeMV) molecular biology research. (a) Elucidating the molecular basis for CeMV transmission across multiple species requires characterizing the interactions underlying formation of the H-SLAM and H-nectin-4 complexes. (b) Deciphering the molecular basis for different disease phenotypes such as brain-only form of dolphin morbillivirus infection (BOFDI) requires assessment of the role played by P, M, F, and H proteins in CeMV cell-to-cell spread. (c) Understanding the molecular basis for different host susceptibility to CeMV infection involves genome-wide comparative analysis among survivor and nonsurvivors, mapping of genes involved in innate and adaptive immune response and characterization of differential gene expression upon viral challenge. (d) Unveiling the molecular basis for differences in virulence among circulating CeMV strains may take advantage of in silico and in vitro technologies aimed at characterizing the structural and functional properties of CeMV proteins (structure of CeMV H was homology-modeled on the template PDB:3ALZ; structure of CeMV RNP refers to PDB:7OI3; credits for marine mammal silhouettes: Chris huh/PhyloPic.org)

dolphin brains have been characterized,[27] however, neither the involved host cell receptors, nor the viral determinants for CeMV spread and persistence in cerebral tissue were determined.[11] Moreover, while human neurons do not express SLAM and nectin-4, the latter is expressed by cells of the canine central nervous system and is involved in CDV neurovirulence.[28,29] Furthermore, mutations at the phosphoprotein (P) and the matrix (M) genes resulting in defective M protein, or at the fusion (F) gene producing hyperfusogenic F protein[30–32] have been reported to promote cell-to-cell spread of MeV nucleocapsid (NC) in infected human brains and to correlate with the aforementioned neuropathogenic phenotype. In addition, a novel molecular mechanism was described recently, where host cell adhesion molecules 1 (CADM1) and 2 (CADM2) interact in *cis* with MeV H in neurons as well as in other cells lacking SLAM and nectin-4, thereby allowing membrane fusion and cell-to-cell trans-synaptic spread.[33] Given that similar studies have not been conducted in CeMV-infected neurons, caution should be taken before crediting the striped dolphin BOFDI as a comparative model for human SSPE and SSPE-like neuropathies. Nonetheless, a detailed analysis of P, M, F, and H gene mutations in circulating CeMV isolates traceable to BOFDI cases will be helpful to shed light on how CeMV spreads and persists in the cetacean brain (Figure 1b).

PRIORITY 3: MOLECULAR BASIS FOR DIFFERENT HOST SUSCEPTIBILITY TO CeMV INFECTION

A third area of investigation priority should elucidate the peculiarities of cetacean immune response to viral infections, meaning the genetic basis that determines resistance or susceptibility to CeMV, either at taxonomic or at ecological levels. The evolutionary transition from land that brought cetacean ancestors back to water correlates with various genomic changes consisting in the loss of at least 85 genes that were kept instead by terrestrial mammals, among which tripartite motif 14 (TRIM14) and triggering receptor expressed on myeloid cells 1 (TREM1) are involved in innate immune response against viral and bacterial pathogens.[34] Furthermore, odontocetes were reported to have lost the functionality of both dynamin-like GTPase Myxovirus 1 (Mx1) and Mx2 genes at approximately the same time frame during which they diverged from mysticetes, namely 33–37 million years ago.[35] Since the complete gene loss or loss-of-function mutations in Mx1 and Mx2 proteins are known to decrease antiviral immunity and to enhance viral infectivity, this deficiency could at least in part explain why, compared with whales, dolphins experience mass die-offs during CeMV epidemics,[35] like those that occurred throughout the past 35 years along the North-western Atlantic coast and in the Western Mediterranean Sea.[6,11,36] In this regard, it is worth noting that, while here the focus is on molecular factors that modulate the outcome of CeMV infection in its naturally susceptible hosts, the role potentially played by behavioral patterns and ecological habits that set apart odontocetes from mysticetes should not be ruled out. Nonetheless, different responses to CeMV infection can be ascribed, at the species level, to genetic features leading to resistance or susceptibility to CeMV within geographically isolated populations. In this respect, genome-wide comparative analysis of the Indo-Pacific bottlenose dolphin (*Tursiops aduncus*) Australian population hit by a CeMV outbreak in 2013 revealed that single nucleotide polymorphisms (SNPs) among survivor and nonsurvivor dolphins mapped to genes involved in innate and adaptive immune response, as well as in cytokine signaling pathways.[37,38] Likewise, recent full-length RNA sequencing of the Sperm whale (*Physeter macrocephalus*) skin transcriptome led to the identification of gene products with essential functions in the antiviral innate immune response, including nucleotide-binding oligomerization domain-containing protein 1 (NOD1), NOD2 and nuclear factor kappa B (NF-kB) proteins.[39] Furthermore, at the population and individual levels within a single species, the immune status can be influenced by both intrinsic factors such as given physiological conditions (e.g. pregnancy, breastfeeding) and extrinsic ones such as chemical pollutants (e.g. dichlorodiphenyltrichloroethane, polychlorobiphenyls, dioxins, methyl-mercury, etc.) or co-morbidities (e.g. brucellosis, toxoplasmosis).[40–42] Also, the possession of a specific immune phenotype and its dominance within a given population can be crucial in driving the outcome of CeMV infection, as the characterization of B and T cells profiles in lymphoid tissues from striped dolphin and common bottlenose dolphin (*Tursiops truncatus*) specimens seems to indicate.[43] Within this picture, future research could certainly benefit from the establishment of dedicated reverse-genetics models that recapitulate the CeMV life cycle, also allowing dissection of its molecular steps in vitro, and of cell–tissue systems (i.e. organoids) through which assessing the differential expression of host genes following viral challenge may shape the cell phenotype along the whole spectrum that goes from increased susceptibility to resistance to CeMV infection (Figure 1c).

PRIORITY 4: MOLECULAR BASIS FOR DIFFERENT VIRULENCE AMONG CIRCULATING CeMV STRAINS

Finally, the fourth priority research theme is represented by the characterization of CeMV proteins that act as molecular determinants of virulence and pathogenesis, coupled with the monitoring of mutations causing loss or gain of functions that correlate with changes in disease severity. To properly address such a challenging goal, obtaining high-quality and genome-wide sequences of CeMV isolates from stranded cetaceans, and possibly also from free-ranging ones, is essential in providing information on circulating CeMV variants. In addition, correlating pathological findings from postmortem examinations to the

genetic features of sequenced viral genomes from a given set of specimens is crucial to address key questions about the molecular basis for a given disease phenotype. In this respect, a recent phylogenetic and phylogeographic analysis of newly sequenced CeMV whole genomes allowed to discriminate between viral strains circulating in the Mediterranean Sea and the North-eastern Atlantic Ocean, and to trace them back to epidemics that occurred in 2008–2015 and 2014–2017, respectively.[44] Moreover, while the amount of genomic data is probably too small at present to allow the unveiling of any genetic determinacy in virulence and pathogenesis between CeMV strains, such investigational approaches are nevertheless of paramount importance for establishing genomic-informed routine surveillance on CeMV epidemiology and pathology in the future. In addition, as the volume of molecular data about the CeMV proteome and that of its putative interactors in the hosts increase, new trends in CeMV molecular studies will be dictated by the need of correlating amino acid sequences to protein functional properties. In this respect, valuable examples come from the recent characterization of protein–protein interactions between MeV and CDV H with their cognate SLAM receptors, undertaken by means of computational technologies such as molecular dynamics, fragment molecular orbital and interfragment interaction energies calculations.[19,45] Furthermore, as CeMV recombinant proteins become available, the obtainment of experimentally solved structures of CeMV macromolecular complexes can be pursued. Within this framework, a new investigational approach was inaugurated by the CeMV ribonucleoprotein (RNP) complex structure recently determined by cryo-electron microscopy, which shed light on the atomic details of CeMV genome packaging, as well as on molecular signatures underlying potential viral replication kinetics diversity among CeMV strains.[46] Arguably, it can be foreseen that such studies will pave the way for better targeted diagnostic, typing and possibly also therapeutic strategies to counter CeMV infection and epidemics (Figure 1d).

CONCLUSIONS

CeMV is a major threat to the health of marine mammals, and deepening our understanding of the pathogen–host interactions underlying CeMV infection is a key step towards the implementation of effective conservation strategies and preventive countermeasures to preserve the ecological status of affected species. Along the imaginary roadmap traced to achieve this goal, we have identified four areas in molecular research that we consider as priority, summarizing the most recent findings and urging on what the forthcoming CeMV studies should focus on. The common denominator to those areas is the elucidation of the molecular determinants in the CeMV proteome that are responsible for virulence and pathogenesis, and what are those in the proteomes of CeMV hosts that modulate the immune response to infection, altogether ultimately determining both the disease phenotype and the outcome. For viral determinants such elucidation requires moving on from molecular sequencing for diagnostic purposes—often limited to a few viral gene portions—to whole-genome sequencing of CeMV. This could produce genomic-informed epidemiological data and allow the correlation of genetic information with pathological findings, almost in real-time with respect to stranding events. Similarly, elucidation of the molecular mechanisms underlying the cetacean immune response to CeMV infection, requires the characterization of genes involved in such a response and of their expression products in different physio-pathological conditions. This could be achieved by performing comparative genomics and transcriptomics analysis of specimens obtained from either stranded cetaceans or free-ranging ones, and also from animals that are kept in captivity. In particular the latter could serve—notwithstanding the absence of any chronic stress condition—as the best available baseline data for immune function under a physiological state. In addition, the study of such viral and host determinants requires biochemical and biomolecular tools such as recombinant proteins and cell-based assays, through which the molecular aspects of the CeMV life cycle can be recapitulated in vitro. Finally, since the fatal outcome of CeMV infection may result from the overlapping effects of co-infecting pathogens including herpesviruses, *Brucella ceti* and *Toxoplasma gondii*, or after immunosuppression induced by pollutants, environmental changes, or other anthropogenic factors, it must be emphasized that, for the elucidation of molecular determinants in the CeMV proteome and those of its hosts, conducting research under a multidisciplinary framework and a "One-Health" approach remains essential.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DISCLOSURE

None.

AUTHOR CONTRIBUTIONS

Luca Zinzula and Giovanni Di Guardo drafted the manuscript. Sandro Mazzariol commented on the manuscript. All authors revised the manuscript.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

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REFERENCES

1. Jo WK, Kruppa J, Habierski A, et al. Evolutionary evidence for multi-host transmission of cetacean morbillivirus. Emerg Microbes Infect. 2018;7(1):201. https://doi.org/10.1038/s41426-018-0207-x

2. Groch KR, Blazquez DNH, Marcondes MCC, et al. Cetacean morbillivirus in Humpback whales' exhaled breath. Transbound Emerg Dis. 2021;68:1736–43. https://doi.org/10.1111/tbed.13883
3. Groch KR, Groch KR, Kolesnikovas CKM, et al. Cetacean morbillivirus in Southern Right Whales, Brazil. Transbound Emerg Dis. 2019; 66:606–10. https://doi.org/10.1111/tbed.13048
4. Groch KR, Jerdy H, Marcondes MC, et al. Cetacean morbillivirus infection in a killer whale (*Orcinus orca*) from Brazil. J Comp Pathol. 2020;181:26–32. https://doi.org/10.1016/j.jcpa.2020.09.012
5. West KL, Silva-Krott I, Landrau-Giovannetti N, et al. Novel cetacean morbillivirus in a rare Fraser's dolphin (*Lagenodelphis hosei*) stranding from Maui, Hawai'i. Sci Rep. 2021;11(1):15986. https://doi.org/10.1038/s41598-021-94460-6
6. Jo WK, Osterhaus AD, Ludlow M. Transmission of morbilliviruses within and among marine mammal species. Curr Opin Virol. 2018;28: 133–41. https://doi.org/10.1016/j.coviro.2017.12.005
7. Mira F, Rubio-Guerri C, Purpari G, et al. Circulation of a novel strain of dolphin morbillivirus (DMV) in stranded cetaceans in the Mediterranean Sea. Sci Rep. 2019;9(1):9792. https://doi.org/10.1038/s41598-019-46096-w
8. Mazzariol S, Peletto S, Mondin A, et al. Dolphin morbillivirus infection in a captive harbor seal (*Phoca vitulina*). J Clin Microbiol. 2013;51:708–11. https://doi.org/10.1128/JCM.02710-12
9. Padalino I, Di Guardo G, Carbone A, et al. Dolphin morbillivirus in Eurasian otters, Italy. Emerg Infect Dis. 2019;25:372–374. https://doi.org/10.3201/eid2502.180256
10. Petrella A, Mazzariol S, Padalino I, et al. Cetacean morbillivirus and *Toxoplasma gondii* co-infection in Mediterranean monk seal pup, Italy. Emerg Infect Dis. 2021;27:1237–39. https://doi.org/10.3201/eid2704.204131
11. Di Guardo G, Mazzariol S. Cetacean morbillivirus-associated pathology: knowns and unknowns. Front Microbiol. 2016;7:112. https://doi.org/10.3389/fmicb.2016.00112
12. Takeda M, Seki F, Yamamoto Y, Nao N, Tokiwa H. Animal morbilliviruses and their cross-species transmission potential. Curr Opin Virol. 2020;41:38–45. https://doi.org/10.1016/j.coviro.2020.03.005
13. Delpeut S, Noyce RS, Richardson CD. The tumor-associated marker, PVRL4 (nectin-4), is the epithelial receptor for morbilli viruses. Viruses. 2014;6:2268–86. https://doi.org/10.3390/v6062268
14. Shimizu Y, Ohishi K, Suzuki R, et al. Amino acid sequence variations of signaling lymphocyte activation molecule and mortality caused by morbillivirus infection in cetaceans. Microbiol Immunol. 2013;57: 624–32. https://doi.org/10.1111/1348-0421.12078
15. Ohishi K, Ando A, Suzuki R, et al. Host-virus specificity of morbilliviruses predicted by structural modeling of the marine mammal SLAM, a receptor. Comp Immunol Microbiol Infect Dis. 2010;33: 227–41. https://doi.org/10.1016/j.cimid.2008.10.003
16. Ohishi K, Maruyama T, Seki F, Takeda M. Marine morbilliviruses: diversity and interaction with signaling lymphocyte activation molecules. Viruses. 2019;11(7):606. https://doi.org/10.3390/v11070606
17. Seki F, Ohishi K, Maruyama T, Takeda M. Phocine distemper virus uses phocine and other animal SLAMs as a receptor but not human SLAM. Microbiol Immunol. 2020;64:578–83. https://doi.org/10.1111/1348-0421.12788
18. Seki F, Yamamoto Y, Fukuhara H, et al. Measles virus hemagglutinin protein establishes a specific interaction with the extreme N-terminal region of human signaling lymphocytic activation molecule to enhance infection. Front Microbiol. 2020;11:1830. https://doi.org/10.3389/fmicb.2020.01830
19. Yamamoto Y, Nakano S, Seki F, et al. Computational analysis reveals a critical point mutation in the N-terminal region of the signaling lymphocytic activation molecule responsible for the cross-species infection with canine distemper virus. Molecules. 2021;26(5):1262. https://doi.org/10.3390/molecules26051262
20. Sakai K, Yoshikawa T, Seki F, et al. Canine distemper virus associated with a lethal outbreak in monkeys can readily adapt to use human receptors. J Virol. 2013;87:7170–5. https://doi.org/10.1128/JVI.03479-12
21. Bieringer M, Han JW, Kendl S, Khosravi M, Plattet P, Schneider-Schaulies J. Experimental adaptation of wild-type canine distemper virus (CDV) to the human entry receptor CD150. PLoS One. 2013; 8(3): e57488. https://doi.org/10.1371/journal.pone.0057488.
22. Feng N, Liu Y, Wang J, et al. Canine distemper virus isolated from a monkey efficiently replicates on Vero cells expressing non-human primate SLAM receptors but not human SLAM receptor. BMC Vet Res. 2016;12(1):160. https://doi.org/10.1186/s12917-016-0757-x
23. Di Guardo G, Cocumelli C, Scholl F, et al. Morbilliviral encephalitis in a striped dolphin *Stenella coeruleoalba* calf from Italy. Dis Aquat Organ. 2011;95:247–51. https://doi.org/10.3354/dao02355
24. Soto S, Alba A, Ganges L, et al. Post-epizootic chronic dolphin morbillivirus infection in Mediterranean striped dolphins *Stenella coeruleoalba*. Dis Aquat Organ. 2011;96:187–94. https://doi.org/10.3354/dao02387
25. Wessels ME, Deaville R, Perkins MW, et al. Novel presentation of DMV-associated encephalitis in a long-finned pilot whale (*Globicephala melas*). J Comp Pathol. 2021;183:51–6. https://doi.org/10.1016/j.jcpa.2021.01.004
26. Di Guardo G, Giacominelli-Stuffler R, Mazzariol S. Commentary: SLAM- and nectin-4-independent noncytolytic spread of canine distemper virus in astrocytes. Front Microbiol. 2016;7:2011. https://doi.org/10.3389/fmicb.2016.02011
27. Lucá R, Giacominelli-Stuffler R, Mazzariol S, Roperto S, Cocumelli C, Di Guardo G. Neuronal and astrocytic involvement in striped dolphins (*Stenella coeruleoalba*) with morbilliviral encephalitis. Acta Virol. 2017;61:495–497. https://doi.org/10.4149/av_2017_414
28. Pratakpiriya W, Seki F, Otsuki N, et al. Nectin4 is an epithelial cell receptor for canine distemper virus and involved in neurovirulence. J Virol. 2012;86:10207–10. https://doi.org/10.1128/JVI.00824-12
29. Pratakpiriya W, Ping Teh AP, Radtanakatikanon A, et al. Expression of canine distemper virus receptor nectin-4 in the central nervous system of dogs. Sci Rep. 2017;7(1):349. https://doi.org/10.1038/s41598-017-00375-6
30. Watanabe S, Shirogane Y, Sato Y, Hashiguchi T, Yanagi Y. New insights into measles virus brain infections. Trends Microbiol. 2019; 27:164–75. https://doi.org/10.1016/j.tim.2018.08.010
31. Busch J, Chey S, Sieg M, Vahlenkamp TW, Liebert UG. Mutated measles virus matrix and fusion protein influence viral titer in vitro and neuro-invasion in lewis rat brain slice cultures. Viruses. 2021; 13(4):605. https://doi.org/10.3390/v13040605
32. Ikegame S, Hashiguchi T, Hung CT, et al. Fitness selection of hyperfusogenic measles virus F proteins associated with neuropathogenic phenotypes. Proc Natl Acad Sci U S A. 2021;118(18): e2026027118. https://doi.org/10.1073/pnas.2026027118
33. Shirogane Y, Takemoto R, Suzuki T, et al. CADM1 and CADM2 trigger neuropathogenic measles virus-mediated membrane fusion by acting in *cis*. J Virol. 2021;95(14):0052821. https://doi.org/10.1128/JVI.00528-21. e0052821.
34. Huelsmann M, Hecker N, Springer MS, Gatesy J, Sharma V, Hiller M. Genes lost during the transition from land to water in cetaceans highlight genomic changes associated with aquatic adaptations. Sci Adv. 2019;5(9):eaaw6671. https://doi.org/10.1126/sciadv.aaw6671
35. Braun BA, Marcovitz A, Camp JG, Jia R, Bejerano G. Mx1 and Mx2 key antiviral proteins are surprisingly lost in toothed whales. Proc Natl Acad Sci U S A. 2015;112:8036–40. https://doi.org/10.1073/pnas.1501844112
36. Di Guardo G, Mazzariol S. Cetacean morbillivirus: a land-to-sea journey and back? Virol Sin. 2019;34:240–242. https://doi.org/10.1007/s12250-019-00128-x
37. Batley KC, Sandoval-Castillo J, Kemper CM, et al. Genome-wide association study of an unusual dolphin mortality event reveals candidate genes for susceptibility and resistance to cetacean morbillivirus. Evol Appl. 2018;12:718–32. https://doi.org/10.1111/eva.12747
38. Batley KC, Sandoval-Castillo J, Kemper CM, et al. Whole genomes reveal multiple candidate genes and pathways involved in the immune response of dolphins to a highly infectious virus. Mol Ecol. 2021. https://doi.org/10.1111/mec.15873

39. Wang D, Li Y, Aierken R, et al. Integrated full-length transcriptome and RNA-seq to identify immune system genes from the skin of sperm whale (*Physeter macrocephalus*). Genes (Basel). 2021;12(2):233. https://doi.org/10.3390/genes12020233
40. Mazzariol S, Centelleghe C, Beffagna G, et al. Mediterranean fin whales (*Balaenoptera physalus*) threatened by dolphin morbillivirus. Emerg Infect Dis. 2016;22:302–5. https://doi.org/10.3201/eid2202.15-0882
41. Mazzariol S, Centelleghe C, Di Provvido A, et al. Dolphin morbillivirus associated with a mass stranding of sperm whales, Italy. Emerg Infect Dis. 2017;23:144–146. https://doi.org/10.3201/eid2301.160239
42. Centelleghe C, Beffagna G, Palmisano G, et al. Dolphin morbillivirus in a Cuvier's beaked whale (*Ziphius cavirostris*), Italy. Front Microbiol. 2017;8:111. https://doi.org/10.3389/fmicb.2017.00111
43. Centelleghe C, Da Dalt L, Marsili L, et al. Insights into dolphins' immunology: immuno-phenotypic study on Mediterranean and Atlantic stranded cetaceans. Front Immunol. 2019;10:888. https://doi.org/10.3389/fimmu.2019.00888
44. Cerutti F, Giorda F, Grattarola C, et al. Specific capture and whole-genome phylogeography of Dolphin morbillivirus. Sci Rep. 2020;10(1):20831. https://doi.org/10.1038/s41598-020-77835-z
45. Xu F, Tanaka S, Watanabe H, et al. Computational analysis of the interaction energies between amino acid residues of the measles virus hemagglutinin and its receptors. Viruses. 2018;10(5):236. https://doi.org/10.3390/v10050236
46. Zinzula L, Beck F, Klumpe S, et al. Cryo-EM structure of the cetacean morbillivirus nucleoprotein-RNA complex. J Struct Biol. 2021;213(3):107750. https://doi.org/10.1016/j.jsb.2021.107750

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