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Review Article

Review on Virology of Coronaviridae

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Abstract:

Coronaviridae are a group of enveloped, positive single strand RNA viruses which can infect three classes of vertebrates including mammals (corona -and toro¬viruses), birds (coronaviruses) and fish (bafiniviruses). They are the largest RNA viruses that identified so far. Based on phylogenetic trees there are four types of coronaviruses, Alpha-, Beta-, Gamma and Deltacoronavirus which the latter has been recently identified. Virions use their spikes for attaching to host cell surface receptors and release their genome into the target cell by fusing to the viral envelope with the plasma membrane and/or the limiting membrane of an endocytic vesicle. All of these procedure takes place in the cytoplasm. In this review, we studied virology of the family coronaviridae and by reading 16 articles and 2 chapters of 2 books in 10 days, we express their morphology, physicochemical and physical properties, nucleic acid, proteins, lipids, carbohydrates, genome organization and replication and antigenic properties.

Key words: coronaviridae; positive single strand RNA viruses; virions; morphology; replication; antigenic properties

Introduction:

Coronaviridae are a group of enveloped, positive single strand RNA viruses [1], [2], [3] which can infect three classes of vertebrates [4] including mammals (corona -and toro¬viruses), birds (coronaviruses) and fish (bafiniviruses). They are the largest RNA viruses that identified so far. Based on phylogenetic trees there are four types of coronavirus clusters Alpha-, Beta-, Gamma and Deltacoronavirus which the latter has been recently identified [5]. Virions use their spikes for attaching to host cell surface receptors and release their genome into the target cell by fusing to the viral envelope with the plasma membrane and/or the limiting membrane of an endocytic vesicle. All of these procedure takes place in the cytoplasm and involves the production of full-length and subgenome-sized (sg) minus-strand RNA intermediates with the viral genome serving both as mRNA for the replicase polyproteins and a pattern for minus-strand synthesis. RNA synthesis is catalyzed by an characterized replication–transcription complex of viral and host proteins and associated (at least in coronaviruses) with an interconnected network of modified intracellular membranes and double-membrane vesicles that are presumably endoplasmic reticulum (ER)-derived [5].

Coronavirus enter to the target cell via direct fusion with the plasma membrane or endocytosis and subsequent fusion to the endosomal membrane. Viruses like SARSCoV and HCoV-229E use pH-dependent endocytosis, thus they are sensitive to treatment with lysosomotropic agents that lower the endosomal pH [15,16,17]. Lysosomotropic agents like bafilomycin A, chloroquine, and NH4Cl use this in order to inhibit the entry of these viruses [6].

All members of the Coronaviridae family have:

1-enveloped virions which is decorated with large surface projections,

2-helical nucleocapsid contain genome and multiple copies of a single basic phosphoprotein species (N).

3-an envelope with a number of viral membrane protein species which two of them are essential for virion morphogenesis and/or infectivity

4-an integral membrane protein M with 200-250 amino acids

5-an extensively N-glycosylated protein S with 1100-1600 amino acids to form peplomers

6-positive sense RNA, linear, unimolecular, poly adenylated and structurally polycistronic

Organization of general genome consists of 5-UTR-replicase-S-M-N-UTR-3'with the genome functioning as mRNA for the replicase gene [5]. Replicase gene comprised of overlapping ORFs 1a and 1b which are necessary for coding two huge polyproteins, pp1a and pp1ab, production of the pp1ab needs a programmed 21 ribosomal frameshift; pp1a and pp1ab are processed autoproteolytically [5].

7-a 3'capped and polyadenylated co-terminal nested set of two or more subgenomic mRNAs that expressed ORFs downstream of the replicase gene [5].

The genome contains multiple ORFs. Its 5'-most two-thirds are occupied by the replicase gene comprised of two overlapping ORFs 1a and 1b. The translation of replicase gene produce polyprotein pp1a and, subject to programmed 1 ribosomal frameshifting, a C-terminally extended product, pp1ab. The polyproteins are translated by a set of virus-encoded proteinases and, thus, are not detectable as full-length proteins in virus-infected cells. One or two papain-like proteinases are responsible for the coding of the N-terminal of pp1a and pp1ab, while the main proteinase (Mpro or 3CLpro), a nidovirus-wide conserved enzyme with a chymotrypsin-like fold, a poliovirus 3C proteinase-like substrate specificity and either a serine (torovirus, bafinivirus) or a cysteine (coronavirus) as active site nucleophile are doing so for the C-terminal half of coronavirus pp1a and the ORF1b-encoded part of pp1ab cleaved at 11 well-conserved . In coronaviruses, proteolytic processing produce 15 (in viruses belonging to the species Avian coronavirus) or 16 mature products, generally referred to as non-structural proteins (nsp's) and numbered according to their position – from N- to C-terminal – in the viral polypro¬teins. Many of these nsp's enzymes involved in one or more essential step(s) in viral replication. Others appear to be solely involved in virus–host interactions (including immune evasion) and are dispensable for virus propagation in vitro [5].

The replicase polyproteins of the Coronaviridae have some conserved domains like two ORF1a-encoded replicase domains, an ADP-ribose-1'-phosphatase (ADRP, also called macrodomain; located in coronavirus nsp3) and a noncanonical "secondary" RdRp with possible primase activity (coronavirus nsp8) may represent diagnostic markers that makes members of the family Coronaviridae different from viruses in other nidoviruses [5].

Open reading frames (ORFs) (1a and 1b) which code necessary and nonstructural proteins for RNA replication are located at 5 two-thirds of the genome and ORFs that code structural proteins such as hemagglutinin esterase (HE), spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein (N) [7,8,9]. At upstream of the 5 end of each ORF, a common transcription regulatory sequence (TRS) is located for the formation of subgenomic mRNAs [6,5]. Leader–body fusion occurs during the synthesis of genome-templated sg minus-strand RNAs by 3'-discontinuous extension via a mechanism resembling homology-assisted RNA recombination. This process obviously done by sequence complementarity between the anti-TRS at the 3' end of the nascent minus-strand and the 5' genomic TRS. This is the usual model for transcription. It is assumed that each mRNA is transcribed from its corresponding sg minus-strand RNA template through a process of "continuous" RNA synthesis [5].

At the 5' end of the genomic RNA, there is a leader sequence of about 70 nucleotides for the subgenomic mRNAs which are generated by discontinuous minus strand synthesis and are copied into plus-strand mRNAs. Each subgenomic mRNA and the viral genomic RNA, in most cases is translated to only a single protein encoded by the ORF located immediately downstream of the TRS sequence [7,10,11]. Translation of bicistronic F depends on an internal ribosomal entry site [12]. The synthesitization of replicase proteins done by overlapping ORF1a and ORF1b. Also, by a hairpin-pseudoknot structure that acts as a ribosomal frame shifting element (RFS) ribosomal access to ORF1b is regulated [13]. Translation of the coronavirus ORF1ab is done as a single polyprotein that is cotranslationally cleaved by two proteases encoded in the 5 region of the 1ab protein gene. Near the 5 terminus of the genome, the nonstructural protein 3 (nsp3) gene encoded papain-like protein consisting of two domains: PL1pro and PL2pro. The second protease of coronaviruses is encoded by nsp5 gene. It has a predicted serine-like protease activity and is nominated the "main" protease (Mpro) to express its main function. The majority of cleavage sites between the protein domains of the 1ab polyprotein is done by this protease [14, 6].

In addition to RNA the coronavirion nucleocapsid contains a non-glycosylated protein of 50000 to 60000 mol. Wt which is phosphorylated and purified. Coronavirions have two major envelope proteins, the matrix protein and the surface peplomer. The latter is responsible for eliciting neutralizing antibodies during infection [1]. The matrix protein is a transmembrane glycoprotein with the weight of 20000 to 35000mol. The exterior region to the envelope of the protein is glycosylated mostly at the N-terminus of the polypeptide. Peplomer protein is acylated and complex and consists of mannose-rich carbohydrate side-chains that are N-glycosylated and linked to the polypeptide. Virions grown with the lack of the peplomer protein are unable to attach to cells or induce infection. Researches show that the peplomer protein may be involved in activating functions such as virus-induced cell fusion [1].

The virion envelope like plasma membrane contains phospholipids, glycolipids, cholesterol, di- and triglycerides and free fatty acids but unlike the plasma membrane, cholesteryl and fatty acid esters do not exist in the virion membrane. When virus grows in different cell types, the virion envelope changes. Thus the virion envelope reflects the lipid content of the host cell membrane [5].

The 3'proximal genes code structural proteins and, about coronaviruses, a variable number of "accessory" or "niche-specific" proteins. These genes are typical for nidoviruses [5].

All of the members of Coronaviridae family have two envelope protein species, the membrane (M) and spike (S) proteins. These similarities show a common ancestry. Virus assembly consist of budding of preformed nucleocapsids at membranes of the endoplasmic reticulum and early Golgi compartment and releasing the completed virions to the exocytotic pathway. The mechanism of this releasing has not been clarified [5,1].

Virion properties:

Morphology

By conventional negative-staining electron microscopy, the followings has been achieved:

Corona viruses are spherical,pleiomorphic, 120-160 nm in diameter and have a characteristic fringe of large, petal-shaped sur¬face projections t consists of trimers of the spike (S) glycoprotein. Group A beta¬coronaviruses have second type of surface projection, 5–7 nm in length, consists of the homodimeric hemagglutinin-esterase (HE) glycoprotein. The envelope is extremely thicker than typical biological membranes. The nucleocapsid folded to form a compact core that seems to be separated from the envelope by a gap of about 4 nm [5].

Physicochemical and physical properties

Particles of virions are sensitive to heat, lipid solvents, non-ionic detergents, formaldehyde, oxidizing agents and UV irradiation [5].

Nucleic acid Genome compromised of a unimolecular, positive stranded RNA genome, which is capped, polyadenylated and infectious and its lengths range from 26.4 to 31.7 kb [5].

Proteins:

1-the spike protein (S), is a large (1128–1472 aa), homo-trimeric type I membrane anchored glycoprotein and from class I fusion protein which is responsible for receptor-binding and membrane fusion. The N-terminal of the protein (S1) acts as the receptor binding domain and the C-terminal (S2) is the membrane anchored domain with fusogenic activity. Like class I fusion proteins which have a hydrophobic fusion peptide at or close to the N terminus of the membrane fusion subunit, the S2 domain contains two heptad repeat (HR) regions located close to the transmembrane anchor [18]. Thus, the spike protein shows strong similarities to class I virus fusion proteins, but unlike other class I fusion proteins, it does not require cleavage into S1 and S2 for coronavirus infection [6].

2-the membrane glycoprotein M, is an integral type III membrane protein with 218 to 263 aa. Based on the species of each virus, at the amino-terminal ectodomain N- or O-linked glycans are located and C-terminal endodomain, including an amphiphilic region and a hydrophilic tail, is associated with the inner leaf¬let of the membrane in order to form a matrix-like lattice, which would explain the notable thickness of the coronavirus envelope.

3-the envelope protein (E), is a small (74–109 aa) pentameric integral membrane protein with ion channel for membrane permeabilizing (viroporin) activities. It is a minor structural component and plays a role in virion assembly and morphogenesis and has been recognized as a virulence factor for the severe acute respiratory syndrome-coronavirus (SARS-CoV);

4-the nucleocapsid protein N, is a 349 to 470 aa RNA-binding phosphoprotein. It is involved in genome encapsidation, RNA synthesis and transla¬tion, shows RNA chaperone activity, and acts as a type I interferon antagonist [5].

Lipids:

Coronaviruses need the lipids of their envelopes for attaching to the membranes of the endoplasmic reticu¬lum, intermediate compartment and/or Golgi complex.

Carbohydrates

Coronavirus S and HE proteins are heavily glycosylated and contain multiple N-linked glycans (20–35 and 5–11, respectively) while the M protein contains a small number of N- or O-linked glycans, depending on the virus species, located near the amino-terminus. E proteins are not glycosylated [5].

Genome organization and replication:

The 5’ and 3’ UTRs in the genome of the coronaviruses ranging in size from 200 to 600 and from 200 to 500 nt, respectively. Not only these UTRs send signals for genome replication and encapsidation, but also adjacent and more internal coding regions do so. Six conserved ORFs are: ORFs 1a and 1b which together comprise the replicase gene, and the ORFs for the structural proteins S, E, M and N. Downstream of ORF1b and interspersed between the structural protein genes, there are at least eight accessory genes that are also called “group” or “niche-specific” genes, the products of which are unnecessary for replication in vitro, but are important for replication during natural infection. These accessory genes were obtained in horizontal gene transfer and sometimes lost again as the evolution and divergence of viruses to new hosts and niches. This diversity of accessory genes displays the plasticity and highly dynamic nature of the coronavirus genome [5].

The whole genome serves as an mRNA for the replicase polyproteins. The 3’ proximal genes are expressed from a nested set of sg mRNAs that are located at (the “body” sequences) 3’-coterminal with the genome (the “body” sequences). Each of these mRNAs has a short 5’ leader sequence located at the 5’-terminal end of the genome. Leader and body sequences are not near each other and may have 20000 nts distance), but they join in a proc¬ess of discontinuous minus-strand RNA synthesis.

Antigenic properties:

Among Coronaviruses in the same genus, cross-reactivity is limited. The S protein, the major inducer of virus-neutralizing antibodies, is located principally by epitopes in the amino terminal half of the molecule. The infectivity of virus is neutralized by the antibodies that are produced by surface-exposed amino-terminus of the M protein. Also, the antibodies produced by HE protein of group A betacoronaviruses prevent virion binding to O-acetylated sialic acids or inhibit sialate-O-acetylesterase activity. The N protein is a chief antigen for natural infection. Although N-specific antibodies provide little immune protection, they are using in serology diagnostic.

The ectodomains of the S and HE proteins can vary greatly cause widespread antigenic drift. Some examples of antigenic shifts are intra- and interspecies exchange through RNA recombination of coding sequences of S and HE ectodomains. Studies revealed that both structural and non-structural (replicase) proteins serve as CD4 and CD8 T cell antigens. No serologic cross-reactivity have been observed between corona-, toro- and bafiniviruses [5].

References:

1. Sidell, S, Wege, H, Meulen, V. (1983). The Biology of Coronaviruses, J. gen. Virol. 64, 761-776.
2. Masters, P. S. The molecular biology of coronaviruses. Adv. Virus Res. (2006),66:193–292.
3. Brian, D. A., Baric, R. S. Coronavirus genome structure and replication. Curr. Top. Microbiol. Immunol. (2005), 287:1–30.
4. Holmes, K. V. (2001). Coronaviruses, In D. M. Knipe, P. M.Howley, D. E. Griffin, et al (ed.), Fields virology, 4th ed., vol. 1. p. 1187–1203, Philadelphia, Pa.
5. de Groot, R.J., Baker, S.C., Baric, R., Enjuanes, L., Gorbalenya, A.E., Holmes, K.V., Perlman, S., Poon, L., Rottier, P.J.M., Talbot, P.J., Woo, P.C.Y. and Ziebuhr, J., (2012). Coronaviridae, In *Virus Taxonomy: Ninth Report of the International Committee on Taxonomy of Viruses*, (vol.2, p. 806-828), Elsevier Inc.
6. Pyrc, K, Berkhout, B, Hoek, L. (2007). The Novel Human Coronaviruses NL63 and HKU1, J. of virology. 81, 3051-3057.
7. Gorbalenya, A. E., L. Enjuanes, J. Ziebuhr, and E. J. Snijder. (2006). Nidovirales: evolving the largest RNA virus genome. Virus Res. 117:17–37.
8. Pyrc, K., R. Dijkman, L. Deng, M. F. Jebbink, H. A. Ross, B. Berkhout, and L. van der Hoek. (2006). Mosaic structure of human coronavirus NL63, one thousand years of evolution. J. Mol. Biol. 364:964–973.
9. Siddell, S. Coronavirus JHM. (1983). coding assignments of subgenomic mRNAs. J. Gen. Virol. 64:113–125.
10. Lai, M. M., C. D. Patton, R. S. Baric, and S. A. (1983). Stohlman. Presence of leader sequences in the mRNA of mouse hepatitis virus. J. Virol. 46:1027–1033.
11. Spaan, W., H. Delius, M. Skinner, J. (1983). Armstrong, P. Rottier, S. Smeekens, B. A. van der Zeijst, and S. G. Siddell. Coronavirus mRNA synthesis involves fusion of non-contiguous sequences. EMBO J. 2:1839–1844.
12. Thiel, V., Siddell, S. G. (1994). Internal ribosome entry in the coding region of murine hepatitis virus mRNA 5. J. Gen. Virol. 75:3041–3046.
13. Namy, O., Moran, S. J., Stuart, D. I., Gilbert, R. J., Brierley ,I. (2006). A mechanical explanation of RNA pseudoknot function in programmed ribosomal frameshifting. Nature. 441:244–247.

14. Ziebuhr, J. (2005). The coronavirus replicase. Curr. Top. Microbiol. Immunol. 287:57–94.
15. Blau, D. M., Holmes, K. V. (2001). Human coronavirus HCoV-229E enters susceptible cells via the endocytic pathway. Adv. Exp. Med. Biol. 494:193-198.
16. Delmas, B., Gelfi, J., L'Haridon, R., Vogel, L. K., Sjostrom, H., Noren , O., Laude, H. (1992). Aminopeptidase N is a major receptor for the enteropathogenic coronavirus TGEV. Nature. 357:417–420.sd
17. Simmons, G., Reeves, J. D., Rennekamp, A. J., Amberg, S. M., Piefer , A. J., Bates, P. (2004). Characterization of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) spike glycoprotein-mediated viral entry. Proc. Natl. Acad. Sci. 101:4240-4245.
18. Sainz, B., Jr., Rausch, J. M., Gallaher, W. R., Garry, R. F., Wimley, W. C. (2005). Identification and characterization of the putative fusion peptide of the severe acute respiratory syndrome-associated coronavirus spike protein. J. Virol. 79:7195–7206.