Review Article

Biology and molecular basis of the pathogenesis and control of Corona viruses with a focus of the COVID-19: Mini Review

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Abstract

This brief review, which was presented as an introduction to the CAS/IAP/NASCA Workshop on scientific evidence response to the COVID-19 in Cameroon and Africa, covers the classification of viruses based on the coding nucleic acid type, the structure of the genomes of corona viruses that have infected humans in the 21st century ie SARS–CoV, MERS–CoV and SARS-CoV-2. It is recalled that SARS-CoV-2 has a genome size of 29.8 kb very similar to those of SARS–CoV (29.10 kb) and and MERS-CoV (30.1kb). The functions of main proteins featuring on surface the SARS–COV-2, namely, spike (S), membrane (M) and the envelope (E) protein as well as the nucleocapsid (N) protein that is expressed in the core of the viral particle were described. An overview of the pathogenesis showed that the three viruses cause similar symptoms, the most severe of them being the severe respiratory syndrome that could lead to death. A deep understanding of the roles of the viral proteins has facilitated the development of diagnostic tests, vaccines and drugs to combat the COVID-19 pandemic. The review also cites COVID-19 vaccines currently approved by the WHO as well as patent drugs in current usage and points out that none of these were developed in Africa, which is why local capacity has to be built to better combat the current and future pandemics.

Key Words: COVID-19, SARS-CoV-2, classification, pathogenesis, vaccines, symptoms, drugs

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Résumé

Cette brève revue, qui a été présentée comme une introduction à l'atelier CAS/IAP/NASCA sur la réponse des preuves scientifiques au COVID-19 au Cameroun et en Afrique, couvre la classification de la classification des virus basée sur le type d'acide nucléique codant, la structure de les génomes des virus corona qui ont infecté les humains au 21e siècle, c'est-à-dire le SARS-CoV, le MERS-CoV et le SARS-CoV-2. Il est rappelé que le SARS-CoV-2 a une taille de génome de 29,8 kb très proche de ceux du SARS-CoV (29,10kb et et du MERS-CoV (30,1kb). Les fonctions des principales protéines présentant en surface le SARS-COV- 2, à savoir, la protéine de pointe (S), la membrane (M) et la protéine d'enveloppe (E) ainsi que la protéine de nucléocapside (N) qui est exprimée dans le noyau de la particule virale ont été décrites. Un aperçu de la pathogénie a montré que la trois virus provoquent des symptômes similaires, le plus grave d'entre eux étant le syndrome respiratoire sévère pouvant entraîner la mort. Une compréhension approfondie des rôles des protéines virales a facilité le développement de tests de diagnostic, de vaccins et de médicaments pour lutter contre la pandémie de COVID-19. La revue cite également les vaccins COVID-19 actuellement approuvés par l'OMS ainsi que les médicaments brevetés actuellement utilisés et souligne qu'aucun d'entre eux n'a été développé en Afrique, c'est pourquoi les capacités locales doivent être renforcées pour mieux lutter contre les pandémies actuelles et futures.

Mots clés : COVID-19, SARS-CoV-2, classification, pathogenèse, vaccins, symptômes, médicaments

Introduction

Before the outbreak of the Corona Virus Disease 2019 (COVID-19) in Wuhan, China in December 2019, viruses were notorious for being the causes of deadly diseases such as HIV/AIDS, EBOLA, smallpox and polio, just to name these few. This notwithstanding, the perception of what a virus is varies among the experts, not to talk of the general population. It is therefore pertinent to define this term at the onset for the sake of clarity and consistency.

Viruses are submicroscopic obligate intracellular parasites (Cann, A.J 2001)

As obligate parasites viruses cannot survive and propagate independently outside the host cells. Viruses are thus not living organisms *per se* as they lack a metabolism and depend on the host cells for their metabolic energy. It should be pointed out that viruses are produced from the assembly of pre-formed parts rather than from division, which sets them apart from other intracellular obligate parasites such as Rickettsia and Chlamydia. Viral particles also known as **virions** and usually smaller than cells or bacteria, though some viruses may be as large as bacteria.

Classification

Viruses abound in the millions and infest all major living organisms: Planta, Animalia, Bacteria and Archaea. Because viruses are not living organisms, their classification and nomenclature follows a system that is distinct from the Linnean binominal system, where each organism has a genus and specie name written in Latin eg *Homo sapiens* for human beings. The naming of viruses follows the recommendations of the International Committee on the Taxonomy of Viruses (ICTV) as reported by Cann (2001) and on their website at https://talk.ictvonline.org. The main families/subfamilies of viruses are grouped according to the type of nucleic acids that code for them (Table 1)

Table 1: Major Groups of Viruses according to nucleic Acids coding them

Group	Coding Nucleic Acid
I	Double stranded DNA viruses (ds DNA viruses)
II	Single stranded DNA viruses (ssDNA viruses)
III	Double stranded RNA viruses (ds RNA viruses)
IV	Positive sense RNA viruses (+) sense RNA) viruses
V	Negative Sense RNA Viruses (-) sense RNA viruses
VI	RNA reverse transcribing virus
VII	DNA Reverse transcribing virus
VIROIDS	Sub viral agents
SATELLITES and PRIONS	Sub viral agents

Table 2 gives a comprehensive classification of the COVID-19 virus, which belongs to viruses Group IV, sub-family Coronaviridae, genus Coronavirus. In the remaining part of this review I will focus on SARS-CoV-2, only referring to its two relatives MERS and SARS-CoV for comparison. (For extensive reviews see Tang, Cornish and Kang (2020) Fehr and Stanley (2015).)

Table 2 : Corona virus disease- 2019 (COVID-19) classification

Group IV : (+) sense RNA
Order : Nidovirales
Family : Coronaviridae
Genus : Coronavirus
Type /Species : Coronavirus disease virus-2019 (COVID-19)
Hosts : Vertebrates including bats and humans

Biology of corona viruses: Life Cycle, Electron micrograph and model

The natural host of SARS-CoV-2 has not yet been definitively determined although the bat and the pangolin have been implicated respectively as natural and intermediate host. The structure of the SARS-CoV-2 has been revealed by electron and scanning microscope studies from which models have been built (Fig 1 A, B & C).

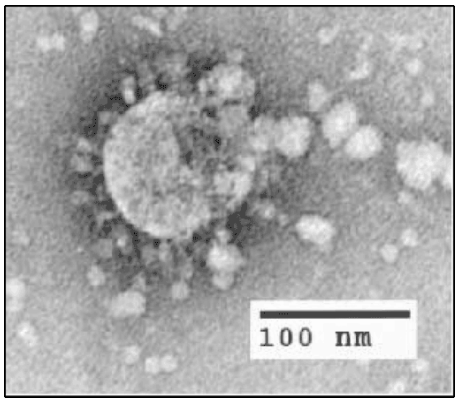

Fig 1A. Photomicrograph of SARS-CoV-2. Credit: www.medical graphics.de

Fig 1B. Model of SARS-Cov-2: Credit: www.medical graphics.de

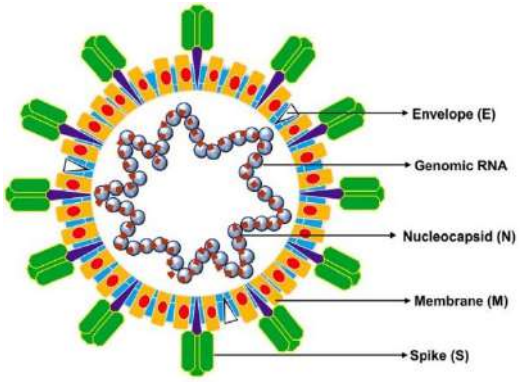

Fig 1C. Cross-sectional diagram of the SARS-CoV-2. Credit: Kirtipal *et al.* 2020

The corona virus is a spherical particle which cross-section presents as two concentric circle (the viral membrane) surrounded by circular protrusions attached to the membrane giving an overall picture of a crown (hence the name Corona virus. *Corona* is Latin for crown).

Inside the crown is a single stranded positive sense RNA which comprises the genome of the virus to which we shall return later. The main viral capsid proteins are the spike (S) protein, the membrane (M) protein, envelope (E) protein, and the nucleocapsid protein, N (Fig 1C). These proteins have been cloned, crystalized and their 3-D structures determined (Kanimozhi *et al*, 2021). We briefly highlight the roles of these proteins in the life cycle of the virus as a prelude to understanding why some of them have been targeted for diagnosis, therapeutics and vaccine development.

The **spike protein (S)** is a highly glycosylated 150 KDa protein that has been implicated in the attachment of the virus to the host cell during infection. Without the S-protein the virus cannot easily enter the cell which is why the S-protein has been targeted for the production of vaccines. The spike protein is thus the main driving force for cellular recognition.

The **membrane protein** (M) is a 23-30 kDa protein that is abundantly present in the virus and because of its flexibility, it helps to shape the virus into its circular form. Its functions is thus structural.

The **envelope** protein (E) ranges from 8-12 KDa and is even smaller than the M-Protein. It has an ion channel activity and does not play a role in the replication of the virus though it required for pathogenesis.

The **hemaglutinin-esterase** (HE) acts a hemagluninin which binds to sialic acids and on cell surface glycoproteins and contains acetyl esterase activity. It enhances S-protein mediated cell entry and virus spread through the mucosa cells.

The **nucleocapsid protein (N-protein)** ranges from 43-50 KDa. It is folded into two principal domains: the N-terminal domain

(NTD) and the C-terminal domain (CTD). Its main function is to bind RNA through its N-terminal domain (NTD). The CTD on the other hand contains a nuclear localization signal and mediates the dimerization of the N-protein. The N-protein plays a role in the replication and transcription of RNA as well as in the formation and maintenance of the ribonucleoprotein (RBN) complex.

The Coronavirus Genome

Literally millions of Coronavirus-2019 (SARS-CoV-2) genomes have been sequenced since the first sequence was reported by Zhu et al (2019) and as expected there are both conserved features and areas of great variation. Fig 2 taken from Kirtipal et al (2020), Kadam et al (2020) Kanimozhi 2021 shows sketches of SAR-CoV-2 (COVID-19 virus). The genome presents as a single positive sense RNA of 29,891 kb with about 38% GC content packed in a protein envelope. The genomic RNA (gRNA) contains two terminal untranslated regions (UTR) in the 5'-end and 3'- end respectively.

There are two open reading frames (ORF) 1a and 1b. ORF 1a is the longest region and codes for a polyprotein that automatically is cleaved into 16 nonstructural proteins (nsp). All these nsp's are enzymes involved in the viral replication, namely, replicase /transcriptase-complex, RNA-dependent RNA –polymerase, proteases, NSP 13 and helicase.

The 3'end contains 13 ORFs which code for structural proteins including the S, E, M, N proteins which are described in the previous section (Fig 2).

Brief Comparison of major corona viruses that erupted and infected humans in the 21st century SARS-CoV-2, SARS-CoV and MERS-CoV

Three coronaviruses SARS-**CoV-2, SARS-CoV and MERS-CoV** have caused significant epidemics/pandemics in humans in the 21st Century. Their salient properties are summarized in Table 3. The first to emerge among them was the SARS-CoV in 2002 followed by the MERS-CoV in 2012 and currently the SARS-CoV in 2019. It should be noted that both SARS-CoV and MERS-CoV have been contained, and the lessons learnt from these two viruses were critical for devising strategies to fight the ongoing SARS-CoV-2. Table 3 also refers to evidence that the viruses have similarly structured genomes and share extensive sequence homologies as mentioned above. The symptoms of the disease caused are very similar and include **fever, cough and respiratory distress which seem to be shared by** all three infections albeit with varying frequencies**.** Other flulike symptoms such as malaise, myalgia, diarrhea,

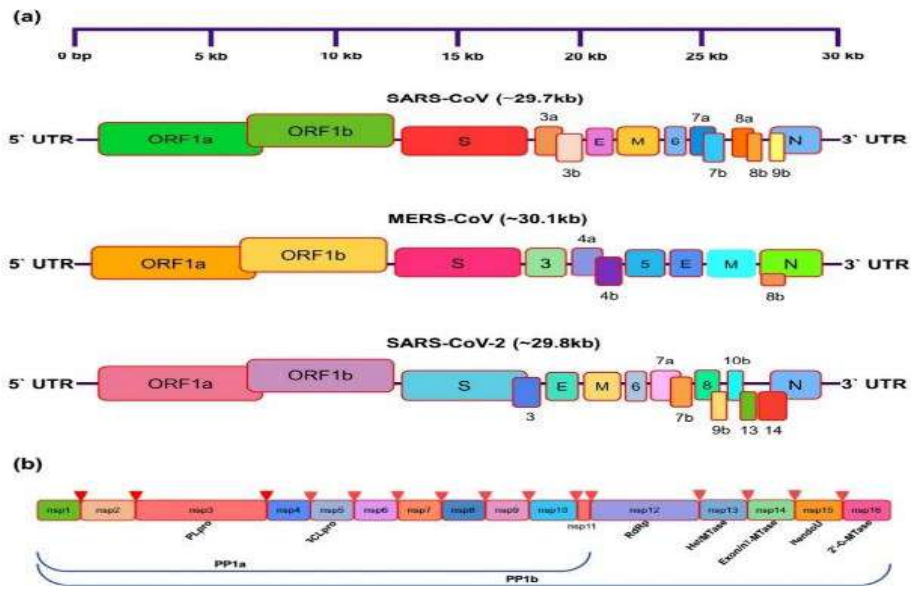

Fig 2: Schematic representation for (a) genome organization and (b) functional domains in the genome of SARS-CoV, MERS-CoV, and SARS-CoV-2. Credit: **Kirtipal, *et al.*; 2020**

loss of taste (dyspnea) have been reported. MERS-CoV seems to be the deadliest of the three, followed by SARS-CoV, and SARS-CoV-2 in decreasing order of magnitude. However, because SARS-CoV-2 has been more widely spread practically all over the world the number of cases and fatalities have been by far greater than those caused by MERS-CoV and SARS-CoV.

SARS-CoV-2, the etiologic agent of COVID-19 pandemic.

SARS-CoV-2 is transmitted from person to person through aerosol droplets produced by the infected persons during sneezing, coughing or otherwise releasing sputum. SARS-CoV-2 enters the lung's alveolar epithelial cells using the viral spike protein which binds to the

Table 3: Some characteristics of major coronaviruses that caused epidemics/ pandemic in the 21st Century

Parameter	SARS-CoV-2	SARS-CoV	MERS-CoV
Genome Size	29.8kb	29.7kb	30.1kb
Homology	-	79.5%	40%
Possible Intermediate hosts	Bat, Pangolin	Bat, palm civets, Racon dogs	camel
Predominant Cellular Receptor	ACE2	ACE2	Dipeptidylpeptidase (CD26)
Symptoms shared	Fever, cough, respiratory distress	Fever, cough, respiratory distress	Fever cough respiratory distress
Disease Caused	Severe Acute Respiratory Syndrome, SARS (COVID-19)	(Severe) Acute Respiratory Syndrome (SARS, ARS)	Mediterranean respiratory Syndrome (MERS)
Mortality rate	3.6-4.2 % (ongoing)	9.6-11% (ended	34% (ended)
Vaccines	7 registered with the WHO	N.D.	N.D.
Emergence	2019	2002	2012

Pathogenesis

Pathogenesis can be defined as the process by which one organism causes disease in another. The disease- causing organism is known as the **pathogen** and the organism targeted known as the **host**.

Pathogens abound in nature and these include viruses, bacteria, fungi and parasites. The mechanisms of pathogenesis vary depending on the pathogen-host interactions.

Pathogenesis can be achieved either directly through the injury inflicted on the host cells and tissues or indirectly through an inflammatory response that may be either innate or immune mediated. The pathogenesis of coronavirus infection humans have been extensively reviewed ((Fehr and Perlman (2015) Kirtipal *et al* (2020) Sood *et al* (2020) Kammozhi *et al* (2021)) Herein we focus on angiotensin-converting enzyme-2 (APC-2) receptor. After binding, the virus enters the cell through the process of endocytosis. Once in the cell the viral particle uses the cellular machinery to multiply / replicate itself. This process include un-coating, transcription, replication, translation and assembly of new viral particles and their expulsion from the cell through exocytosis and finally maturation finally. The viral life cycle has been elegantly summarized by Tang et al (2020) as shown in fig 3 below.

Infection by SARS-CoV-2 can be both asymptomatic and symptomatic. In either case, both the innate and adaptive immune systems are activated. SARS-CoV-2 infection is sensed by macrophages, dendritic cells and monocytes which produce pro-inflammatory cytokines including IL-6, TNF-gamma, IL-B, IL-2, chemokine CXC10, chemokine CCL2, TNF-alpha leading to the so-called **cytokine storm**.

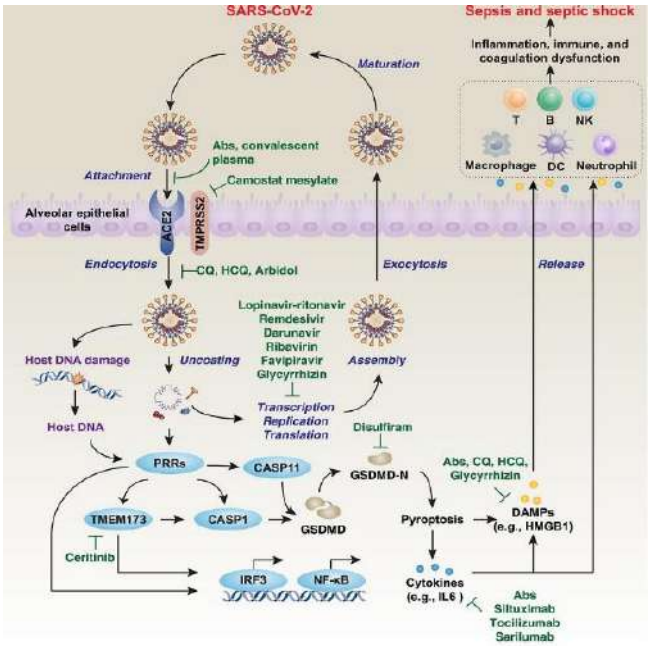

Fig 3. A model of the life cycle and immune response to SARS-CoV-2 in host cells. Credit: Tang et al., 2020

Interleukin-6 (IL-6) was frequently mentioned among the early reports of the cytokine storm and has come to be regarded as being diagnostic of the symptom.

Thrombosis caused by COVID-19 vaccination does occur, but its prevalence is by far lower than what occurs in the unvaccinated persons, or in persons infected with COVIID-19. The benefit of vaccination against COVID-19 by far outweighs the threat of thrombosis caused by COVID-19 vaccination (Iba and Levy, 2022)

Diagnosis of COVID-19

A wide variety of laboratory tests have been introduced for the accurate diagnosis of COVID-19 since the flu-like symptoms it causes cannot be used for definite diagnosis (Pascarella, 2020; Table 4). All tests approved for routine use must be specific, sensitive with a more than 90% positive and negative predictive values. Brief comments on some of these tests follow:

- At the level of the hospital, radiological findings including MRI have been used though the expensive instrumentation precludes usage in rural areas (Udugama, 2020).

- **Polymerase Chain reaction (PCR)** based assays target and amplify a segment of the N-protein. These tests can be conducted using a classical PCR approach or preferably the real time PCR. Earlier versions of the PCR test were prone to causing false negatives especially at the onset of the infection. Later versions are more specific and can give accurate results within 24-48 hours. The WHO has published a list of specific primers that can be used in configuring local PCR tests (Bellini, WJ, 2022).

- **Antigen detection tests**. These are deigned in the Rapid Test format to detect viral proteins. One or several viral proteins could be targeted by specific antibodies. The tests can be relatively rapid 10-15 minutes. Compared to the PCR their sensitivity is relatively lower, but they serve well as screening tests eg at airports and other gatherings were testing negative for COVID-19 is required.

- **Antibody tests** are used to screen for specific antibodies in the plasma of patients exposed with COVID-19. Antibody tests are be very sensitive, but they cannot discriminate between past and ongoing infection.

Vaccines against COVID-19

At least 7 vaccines have been approved by the WHO and these are now widely used worldwide. The vaccines typically target either the whole virus or the spike protein that is projected as a crown on the surface of the viral particle.

Table 5 summarizes the properties of the COVID vaccines according to the platform used. Perhaps the most noteworthy of them are the mRNA vaccines (Pfizer and Moderna)

which came into use for the first time during the COVID pandemic. The public was generally worried that the mRNA vaccines had not been tried before and that these vaccines were developed too rapidly (in about a year) whereas vaccines usually take about 10 years to be developed and deployed. It has been explained herein that a lot of background research had been done in the two decades prior to the pandemic with similar coronaviruses, the results of which helped to accelerate the production of vaccines and drugs against COVID-19.

Table 4. World Health Organization (WHO)-approved COVID-19 vaccines

No.	Name	Description/ Platform	Country of Origin
1.	Moderna mRNA-1273	Messenger RNA	USA
2.	Pfeizer BioNtech BNT162B2	Messenger RNA	USA with Germany
3.	Janssen (Johnson & Johnson) Ad26CoV2.S	Adenovirus (non-replicating viral vector)	USA
4.	Oxford/ ASTRA/ Zeneca AZD1222	Non-replicating viral vector	UK with Sweden
5.	Serum Institute of India Covisheld (Astra Zeneca Formulation)	Non-replicating Viral Vector	UK/India
6	Sinopharm (Beijing) BB1Bp-CorV	Inactivated virus	China
7.	Sinovac (Corona Vac)	Inactivated virus	China

Sources: https://covid19.trackvaccine.org/agency/who/ Accessed 6 August 2021 complied by Titanji,VPK (2021)

New Drugs against SARS-CoV

The early sequencing of the SARS-CoV-2 by Chinese scientists considerably aided in the rational development of new drugs against COVID-19. On table – are shown the drugs developed and registered since the emergence of COVID-19 in December 20 (Table 5). As was the case with the vaccines, detailed knowledge about the biology, molecular structure and pathogenesis of SARS-Cov-2 also accelerated the rational development drugs targeting the virus and the symptoms it causes. However, the development and registration of effective drugs lagged behind that of vaccines.

Table 5: Selected drugs used for COVID-19 treatment/management

Drug Type	Examples fo drigs	Mechanism
Direct Acting (causative)	Monoclonal antibodies (Mabs): bamlanivimab; etesevimab; **	Several have been developed and authorized. Mabs act by binding to a neutralizing the virus
	Remdesivir	Blocks viral replication by inhibiting the RNA dependent RNA Polymerase of the coronavirus*
	molnupiravir	Interferes with corona virus replication*; approved in the UK and under review in several other countries including the EU and USA.
Indirect Acting (symptomatic)	baricitinib	Disrupts inflammation by blocking JAK1 and JAK2 protein kinases. *
	dexamethasone	Broad spectrum anti-inflammatory steroid to be used under medical supervision
	Vitamin C	Broad spectrum Anti-oxidant***
	Vitamin D3	Immunomodulator***

Sources *https://go.drugbank.com accessed 05/11/2021; **www.who.int accessed 25/10/2021; ***Recommended by Cameroon Ministry of Health for the management of mild COVID-19 cases alongside other treatments. Table was compiled by Titanji (2021)

Conclusions

This brief introduction to the SARS-CoV-2 also known as the COVID-19 virus has demonstrated pivotal role of scientific research results in designating tools for the control of the COVID pandemic. It is hoped that the application of these tools will eventually lead to the elimination and eradication of the virus. Most of the research was conducted in

advanced countries of the global North almost to the exclusion of Africa. This time around Africa has been lucky not to suffer a great deal of deaths from the COVID-19. Our fate in future pandemics may not be the same unless we learn the appropriate lessons and deliberately prepare for the future. The CAS-IAP-NASAC Capacity building workshop was designed to begin the conversation on lessons learnt and how best to prepare for future epidemics.

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