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NOVEL SARS-COV-2 PANDEMIC TRANSMISSION WITH ONGOING ANTIVIRAL THERAPIES AND VACCINE DESIGN

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Abstract: Starting from the end of 2019 the new SARs-CoV-2 virus, in the period of a few months, had spread to 210 countries and its territories. The Wuhan wild animal market, in Hubei province, China is considered the epicenter of this pandemic. WHO declared the name COVID-19 to designate the disease caused by the SARS-CoV-2 virus. It is the third coronavirus pandemic after SARS in 2002–2003 and MERS-CoV in 2012. Genome sequencing of this new COVID-19/SARS-CoV-2 virus shows slight genetic diversity when compared to other coronaviruses. Owing to its pathogenesis, and less known replication cycle, no universal antiviral treatment can be applied and vaccine preparation is still a larger challenge. The present article will highlight transmission, pandemic status, genetic diversity current antiviral therapy, and vaccine trials for COVID-19.

Keywords: SARs-CoV-2, WHO, viral genome, COVID-19

1. Introduction

Coronaviruses (CoVs) are a group of viruses named after their crown-shaped spike proteins. Coronaviruses are known for infecting a broad range of classes in the Animalia kingdom, including humans, mice, snakes, and other vertebrates [37]. Till the mid-1960s only six human coronaviruses were known HCoV-229E, HCoV--OC43, HCoV-NL63, HCoV-HKU1s, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS--CoV) [29, 30]. These six HCoVs can be divided into two groups based on the severity of the infection they cause. Group A includes HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 usually causes a less virulent disease, in one study HCoV-229E and HCoV--OC43 accounted for 15–29% of the respiratory pathogen with low virulence for humans [29, 30].

Group B includes SARS-CoV and MERS-CoV. These two have different pathogenicity but have a high fatality rate when compared to other members of coronaviruses. MERS-CoV caused renal failure and acute pneumonia in its first patient from Saudi Arabia in 2012. That virus infected 2494 people with 858 deaths reported from 27 countries with a case fatality rate (CFR) of 34.4%. SARS-CoV caused respiratory failure in patients firstly recognized and reported from China and infected 8422 people with 919 deaths from 32 countries between November 2012 and August 2013 with CFR of 11% [41].

Emerging at the end of 2019 in Wuhan, China, SARS-CoV-2 was initially recognized as a pneumonia--causing unknown agent related to coronavirus, after which it was declared as a Public Health Emergency by WHO on 30 January 2020. On 11 February 2020 WHO officially declared the name "COVID-19" for this novel coronavirus disease [13]. It has become an international calamity affecting over 32.1 million people worldwide with over 980,000 deaths overall and these numbers are still increasing day by day [38]. The countries severely affected by COVID-19 included the USA, India, Brazil, Russia, France, Italy, China, Spain, Germany, and in short the rest of the world, however, the highest deaths

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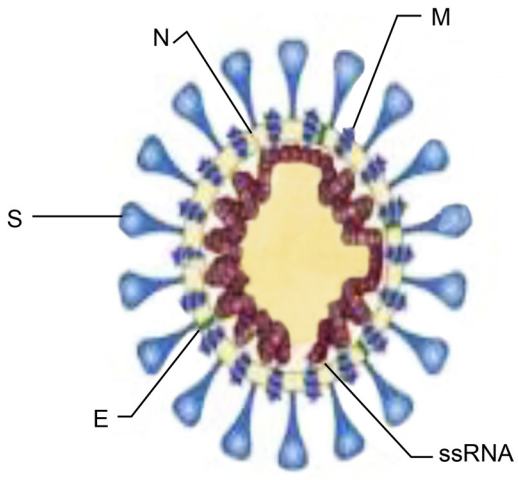

Fig. 1. The structure of SARS-CoV-2. ssRNA genome (26–32 kb) in the center, four structural proteins: spike glycoprotein (S), envelope protein (E), matrix protein (M), and nucleocapsid protein (N). Apart from these, many accessory proteins are also present but not shown in the figure [22].

are being reported from the USA, India, Italy, France, Spain, and UK [39]. The new variant SARS-CoV-2 causes severe acute respiratory syndrome and leads to death [26]. On 22 April, CFR worldwide of COVID-19 is calculated to be 6.89% [39] compared to on March 3 was 3.4% [38]. However, if we take account of mortality rate between different countries for example, in Italy the virus has a mortality rate of 7.2% vs 2.1% in China. According to current information, the suggested source of SARS-CoV-2 is likely bats (it is normally host to many CoVs), but there is no absolute evidence on its origin [2].

Coronaviruses have been known for years since the 1960s but how long they had existed is not known. Commonly they cause mild disease, but some highly pathogenic strains do occur that are noted by being given a distinct name after causing an outbreak. COVID-19 is the current pandemic the whole world is fighting. The pathogenesis of this novel virus is still unclear. In this article, we aim to discuss the transmission, pandemic, genetic diversity, and antiviral treatments, and precautionary measures against COVID-19.

2. Pathogenesis of coronaviruses

CoVs enters a human body when coming in contact with a source animal, or infected human body fluids via sneezing droplets, coughing, sharing food, touching virus soiled inanimate objects, etc. In the case of SARS-CoV2, the virus will bind to Angiotensin converting enzyme 2 (ACE2) in the lower respiratory tract of an infected individual using its spike (S) proteins [9, 10]. For SARS-CoV, only single stranded (ss) positive sense RNA genome is released inside the cytoplasm of a cell through fusion between a host cell's membrane and the virus [28]. But the same entry mechanism used by SARS-CoV-2 still needs to be confirmed. Once inside the cell ss+RNA act as mRNA and the host ribosome initiates translation of viral proteins: two polyproteins and structural protein (NS and S) which help in viral genomic replication and capsid formation [23]. Newly formed envelope glycoprotein migrate to the Golgi apparatus or Endoplasmic reticulum (not shown in figure 2), after which packaging of viral RNA inside a capsid occurs [9]. Once the virion particles are mature they are released through lysis or exocytosis from the cell. Due to lack of knowledge about this new virus and lack of detailed insight about which proteins are involved in causing host cell disruption and overcoming the host immune system, no particular treatment is present for it.

3. Genetic diversity

SARS-CoV-2 was previously shown to be a close relative of SARS-CoV and their Receptor binding domain of S-proteins also resemble each other [15]. The known differences in proteins encoded by both viruses are presented in table I. The phylogenetic trees' comparison has shown that SARS-CoV-2 is most closely related to the SARS-like bat viruses than human SARS-CoV [19]. Whole genome sequences of SARS-CoV-2 and coronavirus of bats has shown 96% similarities [40].

Table I
The differences found in proteins of SARS-CoV and SARS-CoV-2

Protein	SARS-CoV	SARS-CoV-2
8a	Present	Absent
8b	84 amino acids	121 amino acids
3b	154 amino acids	22 amino acids

The coronaviruses are the largest RNA viruses, with a genome size range of 26–32 kb [8]. A variable number of ORF (open reading frames), in the range of 6 to 11, exists in the genome of the coronavirus. ORF's are shown in figure 3. The 1st ORF, which is 67% of the whole genome, encodes 16 non-structural proteins. Genes for eight accessory proteins and four structural proteins are encoded at the 3' terminus of RNA, while genes encoding orf1a and orf1b proteins (comprise non-structural proteins) are located at the 5' terminus [15, 40]. There are five structural genes E, N, M, SM, and S, which encode envelope, nucleocapsid, membrane glycoprotein, small membrane protein, and spike protein, respectively [32]. N-proteins of SARS-CoV and SARS-CoV-2 have a 90% similarity in sequences.

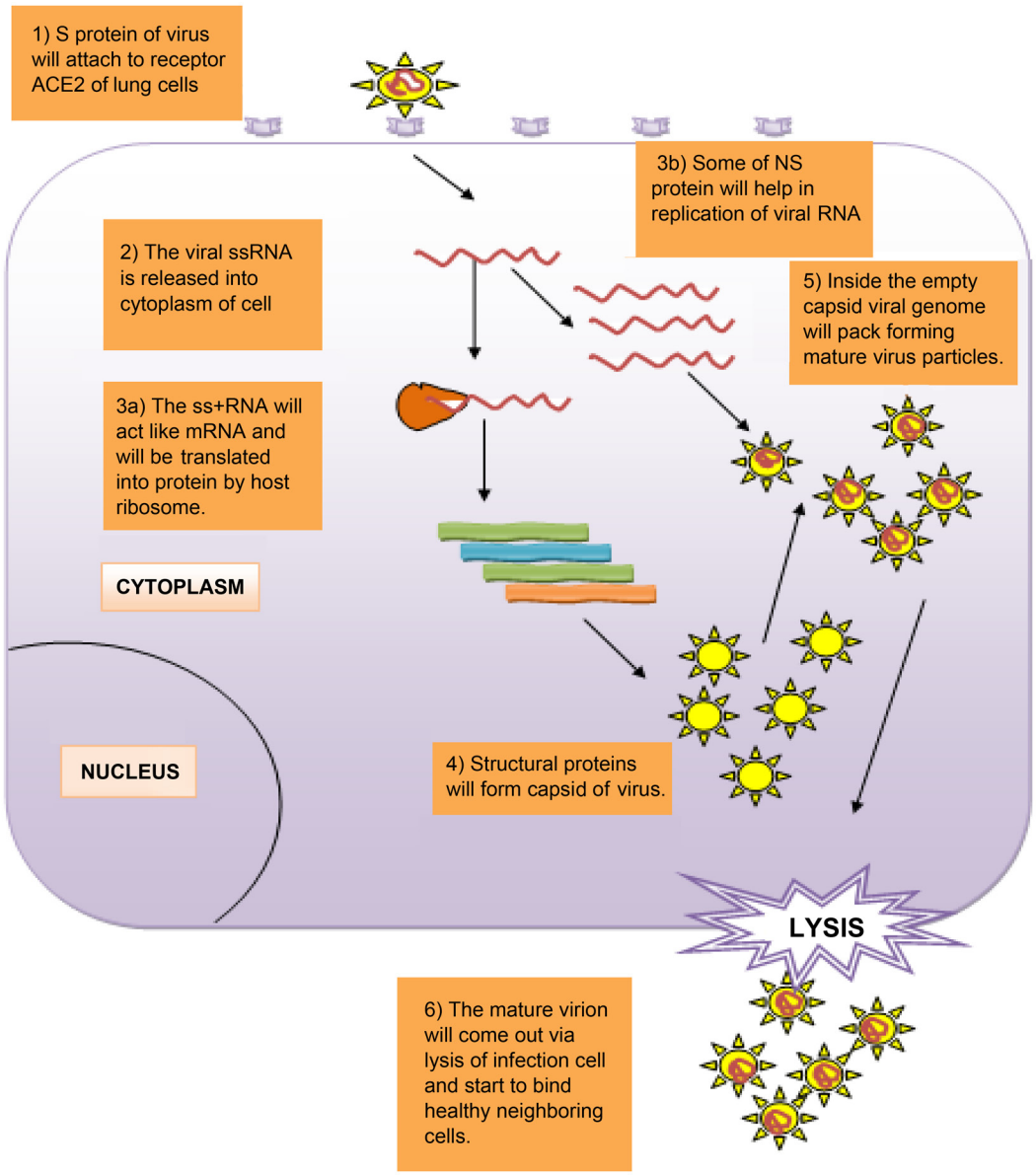

Fig. 2. General mode of replication of SARS-CoV. Starting with the attachment of viral S protein, present on the envelope, with ACE-2 receptor on lung cells the viral RNA is released inside the cytoplasm through membrane fusion. Once inside the cell +ssRNA act as mRNA and the host ribosome will start making viral proteins (2 polyproteins and structural protein) which help viral genomic replication and capsid formation, after which packaging of viral RNA inside a capsid occurs. Once the virion particles are mature they are released through lysis or exocytosis.

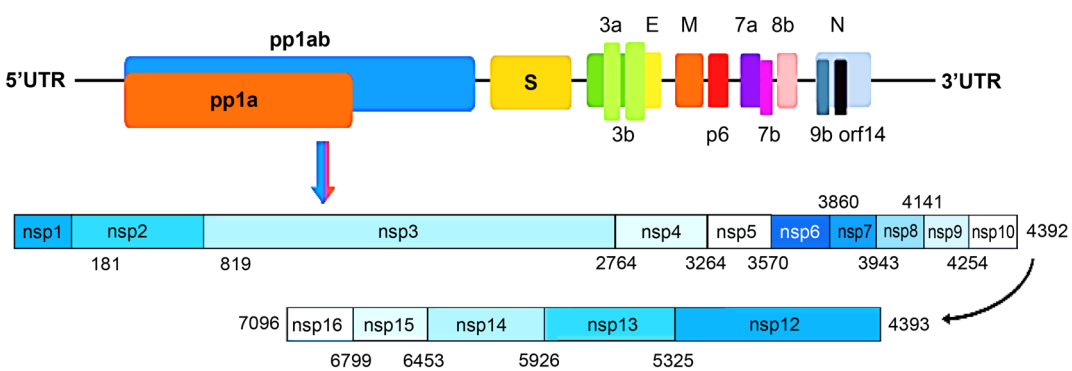

Fig. 3. ORF's of the genome of HB01 strain of SARS-CoV-2 (previously called 2019-nCoV) are shown. Structural proteins are encoded at the 3' terminus and non-structural at the 5' terminus (Modified from [40]).

Table II
The functions of non-structural proteins in the replication of coronaviruses are shown (Modified from [8])

Nsps	Functions
Nsp1	Degrade Cellular mRNA and constrain signaling of IFN
Nsp3	Blocking of host innate immune response and cut polypeptides
Nsp4	Development of double membrane vesicles
Nsp5	Constrain IFN signaling and cleave polypeptides
Nsp6	Restrict expansion of auto phagosomes
Nsp7	Nsp8 and Nsp12 co-factor
Nsp8	Nsp7 and Nsp12 co-factor
Nsp9	Interact with RNA binding and dimerization
Nsp10	Nsp14 and Nsp16 support protein
Nsp12	Primer, which function depends upon Rd-Rp
Nsp13	5 prime triphosphatase and RNA helicase
Nsp14	Exo ribonuclease activity
Nsp15	Exo ribonuclease activity
Nsp16	Regulate immune responses negatively and 2'-O-MTase

The N-protein of SARS-CoV acts as a viral suppressor protein of RNAi, to overcome the host immunity. The N-protein of SARS-CoV-2 can also have the same effect [15, 34]. The functions of non-structural proteins (Nsp) of coronaviruses are mentioned in table 2, except Nsp 2 and 11, whose functions are currently unknown.

4. Transmission

The natural host reservoir for SARS-like coronaviruses are reported to be bats, the intermediate host for the viruses are reported to be civets or camels and then they are transmitted to humans hence these viruses are capable of a host-species jump [16]. One of the major transmission routes of SARS-CoV-2 is human-to-human transmission within close contact and has caused an exponential increase in the number of cases. Aerosol transmission happens when an infected person coughs or sneezes shedding the virus in the air and touching inanimate objects infected with the virus are possible transmission routes [14, 17].

The current epidemic started when the earliest patients who went to Huanan seafood market in Wuhan city, Hubei province, China got infected with SARS-CoV-2 after coming in contact with some animals; the intermediate animal source is yet to be confirmed. These infected patients became a source of infection for other healthy people [20]. Reportedly a large number of infected people did not have exposure to the seafood market so it is likely they got infected from the earliest patients hence person-to-person contact became a major reason for the spread of this epidemic [5]. The reason why coronavirus caused havoc throughout the world and became a cause of lockdown in multiple countries is its high transmission rate [3].

One recently published study indicated a whole family of 6 was infected with this novel coronavirus although none of the family members visited the Wuhan seafood market, only 2 persons of the family visited Wuhan hospital where they might have caught the virus from infected patients. From the two infected family members the whole family got infected. Real time RT-PCR was used to test the RNA extracted from patient samples with new coronavirus virus specific primers and probes [17]. The patients had symptoms such as fever, upper or lower respiratory tract infections however, older patients (> 60 years) showed more systemic symptoms [5].

A recent report suggested that the virus can also take an ocular route of transmission [18]. Vertical

Table III
Different Vaccine Strategies with their Advantages and Disadvantages

Vaccine strategy	Advantages	Disadvantages	References
mRNA vaccines	Easy preparation, High Adaptability, Can induce strong immune responses	High unstable under physiological conditions	[24]
DNA vaccines	Easy preparation Neutralizing antibodies with high titer	Low immune responses May induce toxicity with repeated doses	[24]
Viral vector vaccines	Induces high humoral and cellular immune responses	Pre-existing immunity will be a problem	[11]
Subunit vaccines	Neutralizing antibodies with high titer, Induces high humoral and cellular immune responses	High cost Low immunity, Repeated doses may require	[11]
Attenuated virus vaccines	Quick development, High immune responses	Genotypic & phenotypic reversion possible	[25]
Inactivated virus vaccines	Easy preparation, Neutralizing antibodies with high titer	Not applicable for immunosuppressed individuals	[25]

Table IV
In process-Vaccines with its Candidates & Phase Trials

Manufacturer	Vaccine candidate	Phase trials [31]	References
Moderna	DNA-based vaccines which code or a stabilized form of of SARS-CoV-2 spike protein	Phase 3 starts in the 1st week of July. It will include the study of 30,000 patients	[4]
Curevac	Lab-made RNA to spur the production of corona proteins	Begins the human trials	https://www.curevac.com/en/covid-19/
Inovio	DNA-based vaccines	Human trials to start in later June	https://www.inovio.com/our-focus-serving-patients/covid-19/
Takis Biotech	DNA-based vaccines	Results of dose-response trials to be published in June	[27]
Zydus Cadila	DNA-based vaccines	Project is in pre-clinical trials	https://zyduscadila.com/
Stemirna Therapeutics	mRNA-based vaccines	Clinical trials expected to start in Mid-April	http://www.stemirna.com/en/index.aspx
Imperial College London	DNA-based vaccines	Human trial started	https://www.imperial.ac.uk/covid-19-vaccine-trial/
Novavax	Recombinant-protein nanoparticles derived from spike proteins of SARS-CoV-2	Phase I/II started in May 2020	https://www.novavax.com/covid-19-coronavirus-vaccine-candidate-updates
Vaxart	Oral vaccine half of 2020	Phase I begins in the second	https://vaxart.com/
GlaxoSmithKline (GSK)	A protein-based vaccine with the use of adjuvant	Animal trials	https://www.gsk.com/en-gb/media/press-releases/gsk-and-curevac-to-develop-next-generation-mrna-covid-19-vaccines/
University of Saskatchewan	A protein-based candidate	Animal trials	https://www.vido.org/covid19/covid-19-news/
Sanofi	Recombinant DNA platform swapping the part of corona-virus with genetic material from a harmless virus	Phase 1 to be started in the last quarter of 2020	https://www.sanofi.com/en/about-us/our-stories/sanofi-s-response-in-the-fight-against-covid-19
Geovax Labs/ Bravovax	Develop a live horsepox virus which will be modified to express protein fragments from SARS-CoV-2	Pre-clinical stage	https://www.geovax.com/news/geovax-progresses-in-coronavirus-covid-19-vaccine-development-program
Cansino Biologics	Viral vector-based vaccine	Phase II – All volunteers developed neutralizing antibodies	[42]
Greffex	DNA-based vaccines: Adenovirus based vector vaccines that involve a harmless virus that will express foreign genes like SARS-CoV-2 spike protein	Pre-clinical stage	https://www.greffex.com
Generex Biotechnology	The firm uses insect cells from fruit flies to produce viral antigens	Ex-Vivo Human Immune System screening of 33 Ii-Key-SARS-CoV-2 peptides	https://www.generex.com/covid-19

transmission is not found to be a route for this virus, as pregnant women with COVID-19 had virus negative newborns [6]. The best way suggested by the World Health Organization to limit the epidemic is by social distancing along with practicing good hygiene such as washing your hands regularly and wear protective masks.

5. Vaccination strategies against COVID-19

A study found a correlation between the universal BCG vaccine policy and reduced mortality and morbidity ranges for COVID-19. They found that countries without a universal BCG vaccine policy were more adversely affected by the pandemic compared to

countries having a universal BCG vaccine policy. They also found that BCG vaccination reduced the number of cases in a country [21].

6. In process vaccination strategies against COVID-19

Vaccines help the body enhance the immune response by triggering the generation of antibodies in addition to the development of T and B cells. Vaccines induce active immunity and provide immunological memory which enables the immune system to remember and respond rapidly in case of exposure. Vaccines often provide long-lasting immunity, but sometimes they don't. Scientists at research institutes are working on the development of vaccines all over the world. Vaccine development can take a minimum of 18 months.

7. Lack of antiviral treatment and antiviral treatment studies

In current times, there is no specific antiviral therapy to control this virus only supportive treatment for the coronavirus. Recombinant interferon only has a limited response with ribavirin against a coronavirus infection. The two viral protein inhibitors as an available option of treatment are Baricitinib (Janus and AAK1 kinases inhibitor) and Remdesivir (adenosine analog) [12].

The other antiviral drugs like chloroquine and hydroxychloroquine show an effective response against this virus. The drug chloroquine was first identified in 1934 which is used against SARS-CoV infection, also used to treat other human diseases such as malaria, amoebiosis, HIV, and autoimmune diseases without any side effects.

Leronlimab (CCR5 antagonist) and Galidesivir (nucleoside RNA-polymerase inhibitor) are other possible treatment options [34]. According to guidelines, Interferon-alpha (IFN-alpha) and lopinavir-ritonavir (combined therapy) are recommended antivirals. Chinese medicines, tested to treat influenza H1N1, such as Lianhua Qingwen and ShuFeng Jiedu capsules are also tested against SARS-CoV-2 [7, 18].

The compounds tryptanthrin and indigodole B extracted from the plant Strobilanthes cusia, can reduce the cytopathic effects of human coronavirus NL63. *S. cusia* has also been used to treat SARS-CoV. The spikes of NL63 and SARS-CoV-2 are genetically identical. Hence, *S. cusia* can also be a treatment option for SARS-CoV-2 [33].

Recuperating patients' plasma and antibodies are proposed for treatment. Some vaccine strategies are assessed in animals, including recombinant proteins, DNA vaccines, live and killed attenuated vaccines, and subunit vaccines [6].

8. Precautions

As the virus spread increases with each passing day we have to minimize the transmission cycle by following the different precautionary measures as suggested by the World Health Organization:

- Avoid contact with suspected people.
- Ensure social and physical distancing to prevent the transmission of disease.
- Use of protective surgical masks in public.
- Proper hand washing with sanitizer after every ten minutes.
- Use a mask at all times within an airport facility and outside while traveling.
- Avoid crowded places.
- Avoid contact with unwell people (having flu or cough like symptoms).
- Avoid traveling overseas.
- Ensure good hygiene (wash hand frequently with soap).
- Avoid eating raw or undercooked meat of any type.
- Avoid contact with animals.

9. Conclusion

Coronaviruses are +ssRNA viruses with 7 human coronaviruses, they mainly affect the respiratory system. Group B coronaviruses are the main concern for researchers as it includes the causative virus of the SARS-CoV-2 epidemic. This virus has a high pathogenicity and high virulence rate [41]. SARS-CoV-2 has now spread all around the Globe and is declared a public health emergency by WHO. Its sequence was found to be 96% similar to coronaviruses found in bats [43].

The high transmission rate of the virus is the main concern. Research has been conducted to find effective measures in controlling the speed of the disease with one study reported to minimize person-to-person contact rate to 30% [35]. Real Time Polymerase chain reaction (PCR) with new coronavirus virus-specific primers and probes is the main diagnostic test used to test RNA extracted from a patient [17].

The most commonly reported clinical manifestations are fever, cough, fatigue, and pneumonia. Patients with mild cases recover early, mostly after one week, while serious cases lead to alveolar damage which causes progressive respiratory failure and ultimately leads to death [1]. The genomic nature of this virus is single-stranded RNA which makes it harder to develop vaccines and yet no approved vaccine exists.

Many research groups around the world are working to make vaccines and antivirals as explained in the vaccination and antiviral section above. Some antivirals

that have shown *in-vitro* results against novel coronavirus include chloroquine and remdesivir [36] but the virus has error-prone RNA dependent RNA polymerases that are responsible for mutations and recombination events which are of major concern.

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