COVID-19 PHYSIOLOGICAL AND MOLECULAR MECHANISM RESULTING IN THREAT TO HUMAN SOCIETY-A REVIEW

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ABSTRACT

Human Corona Viruses (HCoVs) are the displaying pandemic disease globally. It is commonly regarded as the pathogens of the respiratory system coupled in the midst of broad assortment of respiratory diseases. These HCoVs also revealed to possess an enveloped positive-sensed RNA viruses and multiplies mainly in the protoplasm of the host. It is been acknowledged that the virus common route of its entry is by contacting and later coalescing with the external surface of the host. Once entered the niceties of the corona virus need to be clearly understood. Although several advancements acknowledged about its structural properties as well as emphasized physicochemical and molecular mechanism of the coronavirus yet unable to distinctively comprehend on the unusual property of trimeric S protein. Characteristically the action of the coronavirus fusion peptide (FP) and induction of consensual alteration in the viral fusion proteins necessitate for comprehension. In our present review, we have imparted a concise introduction to corona viruses and discussed on their replication, physiology and molecular mechanism of pathogenicity, further portray different types of corona viruses. Hence this review noticeably highlights the outbursts of the mutated form of (SARS-CoV) commonly named as Severe Acute Respiratory Syndrome. Corona virus now basically regarded COVID-19 all over world.

Keywords: *SARS-CoV, COVID-19, Corona virus, Pandemic disease, Positive stranded RNA virus*

1. Introduction

Approximately the last few months, globally there has been the subsistence rise of latest mutant forms of viruses that shroud insistent menace among worldwide well being. Lately, in December 2019 especially numerous patients from Wuhan, China were the first to exhibit conditions that were similar to flu as well as pneumonia and lead to outbursts throughout the world at a robust rate. Eventually, after understanding the severity of the cases the World Health Organization (WHO) acknowledged the growth of virus and arrived at a conclusion that this virus was quite different from SARS. Hence, renamed first as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its similar symptoms[1]. Although, it belongs to Coronaviridae family but regarded as new virus as well as initially been acknowledged in the year 2019 so, regarded as novel coronavirus (2019-nCoV). Recently, the pathological diseases it aggravates lead to be recognized as COVID-19. Both the viruses COVID-19 as well as SARS-CoV are positive-sensed RNA virus originating from the family Coronaviridae [2-3].

In fact the strains belonging to coronavirus family reported in early 1930s [4]. Later the popularity of corona viruses acknowledged after the (SARS) sudden occurrence which juddered the humankind in 2002–2003. Repercussion of epidemic virus, interestingly hue again on this family of viruses and lead to the identification of COVID-19 belonging to these family members. At present the chaos it is causing and the enormity for society physical conditions in relation with diseases connected among humans and animals was raising interest. In fact this Corona viruses is not only persistent to humans but infects a vast variety of animal creatures as well as avians, resulting in breathing problems as well as gastrocolic diseases and in few abnormal cases leads to liver cirrhosis as well as brain related diseases. Although the viral infection can result either in acute condition or continuous condition[5]. Based on the serological and genetic analysis, corona virus was recognized with four diverse subfamily such as α, β, ɣ, and δ-CoV [6] .

All the four subfamily possess a protected spike protein which is anchored on the external surface as well as provides channel for the corona virus ingress into host cells [7]. Literally the protein spike known to be epitomized in different forms i.e basically the pre-fusion structure existing on developed virions along with post-fusion shape which is formed later blending along with the host outer membrane. Hence in our study we have focussed on the ingress strategies of corona viruses and unravel how these mechanisms are related to host tropism as well as pathogenicity. Since the virus is spreading globally, the WHO on March 11, 2020, officially described the COVID-19 outbreak as a pandemic in upcoming days and strategies needed to be undertaken to break the chain and manage the disease spreading.

2. Corona Virus Genome and domains of Spike Protein

The Corona viruses are pleiomorphic spherical, enveloped viruses, with varying dimensions from 80 to 120 nm. The 5' capped positive stranded RNA viral genome with was found to be approximately in the range of 27 and 34 kb, the largest in midst of all RNA viruses. The organization of the genome with approximately six to ten open reading frames (ORFs). Nevertheless the beginning ORF occupies major part of the genome and ascertain to posses the replication proteins, while the final end possess the structural gene proteins arranged in a predetermined order: (HE)-S-E-M-N as shown in (Figure 1A). The genome is protected with envelope made of helical nucleocapsid surrounding the host-derived lipid bilayer. The three viral proteins were found on the outer virion envelope, one among them included the spike protein (S), the (M) protein referred as Membrane protein and third enveloped protein (E) (Figure 1B). Additionally, few corona viruses encompassed hemagglutinin esterase (HE) along with membrane and enveloped proteins present on the envelope are essentially indulging in assembly of viruses, the S protein is the principal mediator for viral entry. [8-12].

Figure 1A

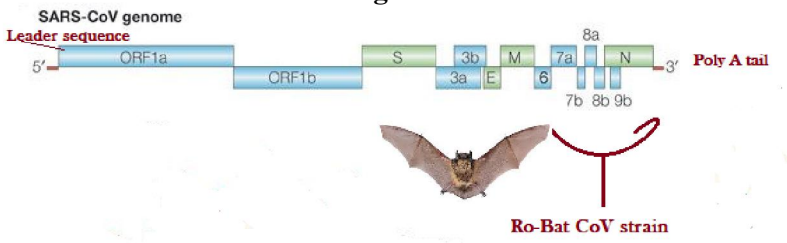

Figure-1B

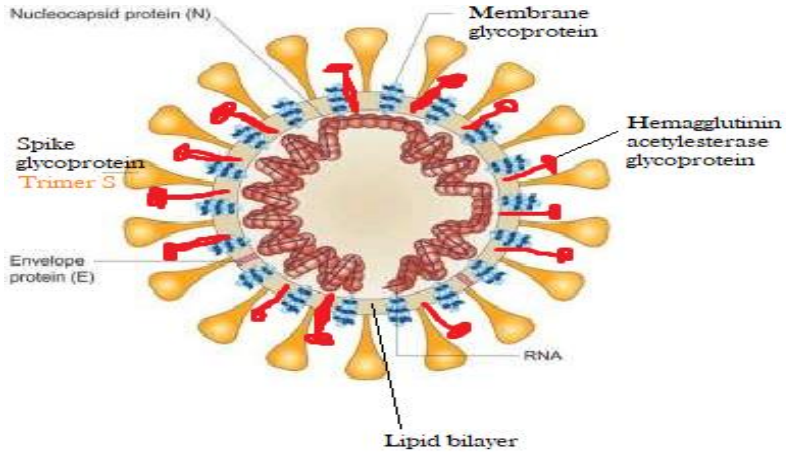

Figure-1A & 1B: The genome organization of Corona virus and Structure of Corona encompassing diverse viral proteins

3. The spike type I transmembrane protein Morphology

The physiology as well as the morphological structure of trimeric (S) spike protein revealed to possess trimeric receptor-binding structure identified as S1 and S2, heads are on top of a three membrane fusion regarded as S1 and S2 forms the stalk [9–12]. While the post-fusion structure is a twisted-loop structure, enclosing S2 only [13, 14]. During entry process into cell, spike is hewed consecutively by proteases present in host at two sites of the virion. The first at the S1/S2 boundary and later in the interior of S2 site [15–17]. Subsequently the chopping, releases S1 from S2 and further accepting the S2 to transition to the twisted loop structure. Nevertheless HCoV transition stage from binding, merging to twisted loop form is not reversible once covalently fused after attachment onto lipid bilayer during the entry process [18]. Regardless, this novel/mutated HCoVs has again displayed greater chaos and deadly disease in humans earlier in the 2002/2003. SARS-CoV spread earlier as well as later recently MERS-CoV in the Middle East and again in 2019 to be pandemic [19-20]. Additionally now novel COVID-19 causing catastrophe among the world wide disturbing the economic background and rise of death polls from stage-I to stage-IV.

All CoV virions revealed to possess multimeric proteins i.e N, M, E along with S. Although viral genomic RNA is encapsulated with nucleocapsid protein (N) which results in the spiral shape nucleocapsid, and outer layer is always enfolded by the lipid bilayer, encompassing membrane glycoprotein (M), there is a diminutive envelope protein (E) along with the trimeric spike glycoprotein (S). The S protein, belongs to type I membrane protein belonging to the class I fusion proteins, that obtrude from the exterior layer of the virion [21-28]. Nevertheless, trimeric S receptor binding protein are split into two functional subunits, the amino terminal S1 subunit having the RBD, while the carboxy terminal S2 subunit forms stalk and has domains for fusion, comprising the combined peptide. It also has heptad replicate domains of (HR) HR1 and HR2 [29-31].

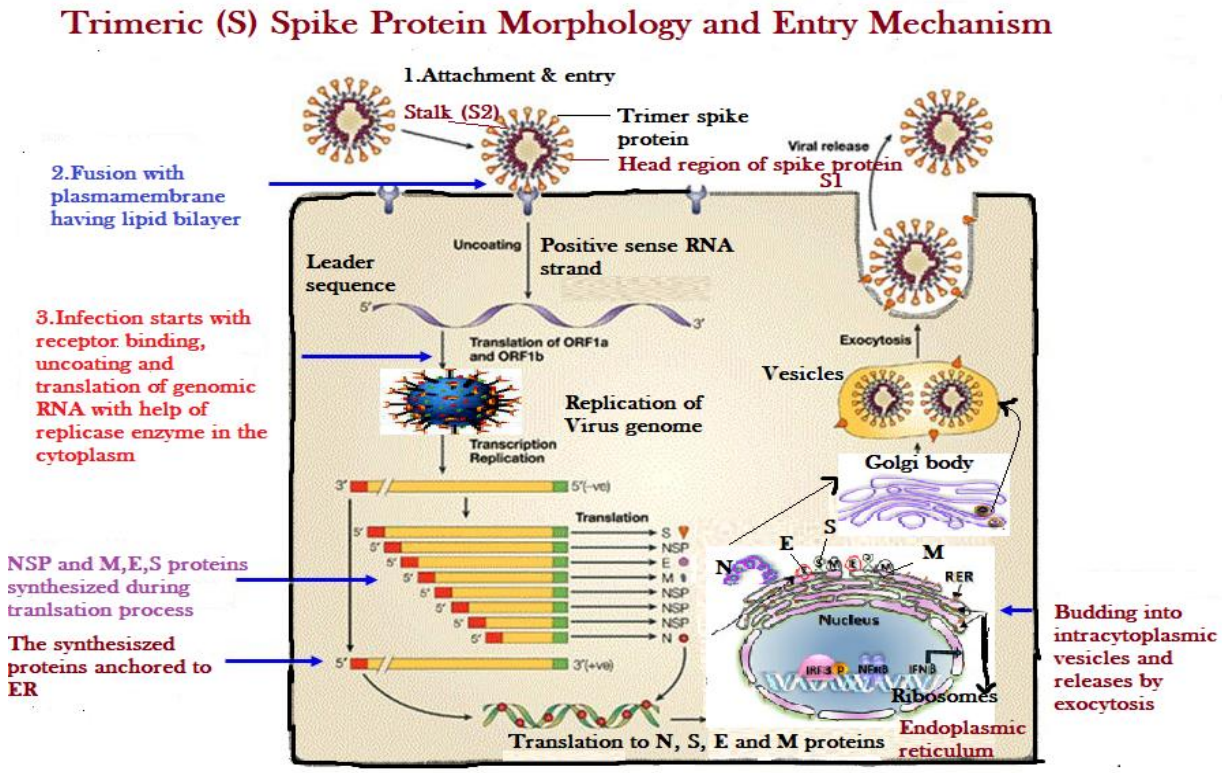

Figure-2: Schematic diagram showing the Trimeric S protein Morphology and Mechanism of action

4. Inhibition of PERK pathway attenuates viral infection

Translation of proteins weakens the viral replication has been broadly monitored as a combat method for the host cells opposed to viral infection. Hence in order to reduce the transportation of viral proteins, replication of the virus would be hindered as well as proliferation of infection can also be restricted, thereby providing adequate time for the natural defenses to instigate effectual antiviral reactions. PERK pathway attenuates viral infections by eIF2α kinases, thereby PKR results in Interferon-triggering reaction and precise identification of viral RNAs, plays a crucially significant task in triggering attenuation of translation in infected viral cells [32]. The novel viruses brilliantly have developed diverse methods to thwart PKR. Nevertheless, the non-structural 5A (NS5A) protein of Human corona virus unswervingly interacted with the active site of PKR, thus blocks PKR activation [33-37]. During the enhancement of virus infection, amass assembly of viral proteins can overwhelm blocks that have folding capacities for ER.

Earlier the S protein in SARS-CoV also has shown to activate ERK phosphorylation and revealed to augment IL8 release [38-45]. Furthermore, viral proteins of SARS-CoV have displayed in ERK triggering reaction. SARS-CoV Papain Like protease as well as SARS-CoV 3b expression proteins have shown significantly to enhance ERK1 ubiquitin-arbitrated disintegration to repress IFN-triggered reactions [46-49]. Although, SARS-CoV, MERS-CoV infection and now novel COVID-19 is also combined in triggering ERK phosphorylation setup. Nevertheless the ERK phosphorylation was not substantially influenced by HCoV-229E infection, since this mutated form is resistant to phosphorylated ERK but can be instigated by the use of Hydroxychloroquine a known antimalarial agent which was found to be effective against viruses [50]. Hence, profound comprehension on ERK pathway triggering method could reveal to be substantial competence in the period of HCoV infection [51].

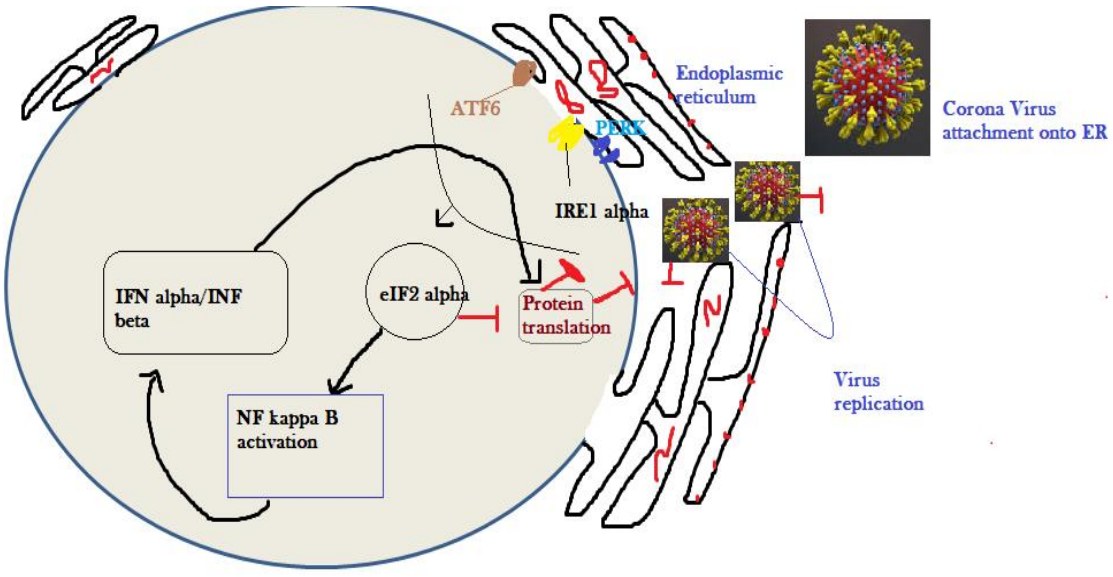

Figure-3: Attenuation of Corona virus infection reduces translation of proteins by PERK pathway

5. Emerging COVID-19 reports from Wuhan city in China including various countries

WHO reports of March 10, 2020, approximately 113,702 validated cases internationally, and 4012 mortalities have been recorded; approximately 75% of all authenicated cases (80,924) and 80% of overall demises are associated with COVID-19. Amongst,(3140) cases began from China and

its territories. Regardless, the beginning of this virus cases came to notice from Wuhan city in China. Furthermore, WHO has formally announced China as a "Red alert zone" region for COVID-19 [52-54].

6. Chinese continent and surrounding areas

In China and its region of Hubei, involves Wuhan. Nevertheless, recently has been reported the largest authenticated COVID-19 positive cases and mortalities in areas of China (67,760 cases and 3,024 deaths). Amongst several regions in China has shown to cross the thousands mark especially in Guangdong, Henan, Zhejiang, and Hunan each have 1,353, 1,272, 1,215, and 1,018 cases, respectively during March beginning (Table -1). Later greater number of demises was registered in Guangdong with more than 22 cases [55-58].

Table-1: Epidemiology of COVID-19 in Main land china (March 20th)

Places	Confirmed cases	Deaths
Hubei	67,801	3160
Beijing	554	8
Liaoning	127	2
Anhui	990	6
Chongqing	578	6
Shaanxi	248	3
Tianjin	141	3
Fujian	318	1
Hunan	1018	4
Sichuan	545	3
Gansu	136	2
Heilongjiang	484	13
Jiangxi	936	1
Guangdong	1428	8
Shanghai	414	4
Yunnan	176	2
Zhejiang	1240	1

Table-2: COVID-19 reports of other countries

Country	Overall cases	Latest cases	Overall deaths	Latest deaths	Overall recovered	Positive cases	Danger state	Entire cases
Italy	63,927	-	6,077	-	7,432	50,418	3,204	1,057
USA	46,145	+2411	582	+29	295	45,268	1,040	139
Spain	35,136	-	2,311	-	3,355	29,470	2,355	751
Germany	29,056	-	123	-	453	28,480	23	347
Iran	23,049	-	1,812	-	8,376	12,861	-	274
France	19,856	-	860	-	2,200	16,796	2,082	304
South Korea	9,037	+76	120	+9	3,507	5,410	59	176
Switzerland	8,795	-	120	-	131	8,544	141	1,016
UK	6,650	-	335	-	135	6,180	20	98
Netherlands	4,749	-	213	-	2	4,534	435	277
Austria	4,477	+3	21	-	9	4,477	16	497
Belgium	3,743		88	-	401	3,254	322	323
Norway	2,625	-	10	-	6	2,609	41	484
Australia	2,136	+249	8	+1	118	2,010	11	84
Canada	2,091	-	24	-	320	1,747	1	55
Portugal	2,060	-	23	-	14	2,023	47	202
Sweden	2,046	-	27	-	16	2,003	104	203
Brazil	1.924	-	34	-	2	1,888	18	9

7. Emerging COVID-19 cases in India

In India there are 30 states and Union territories which went under lock down as HCoV cases in India spiked to 471 on Monday 23/03/2020 as shown in (Table-3). Various places throughout India imposed curfew in their own states. All domestic flights from midnight have been cancelled to refrain the virus spread, stepping up a nationwide lockdown. Even though the virus continues to spread worldwide, with the total number of infected cases reaching 378,741 and 16,502 death.

Table-3: COVID Data upto date

Name of State/UT	Confirmed cases (Indian)	Confirmed cases (Foreigners)	Deaths
Andhra Pradesh	7	0	0
Bihar	2	0	1
Chattisgarh	1	0	0
Delhi	30	1	1
Gujarat	29	0	1
Haryana	12	14	0
Himachal Pradesh	3	0	1
Karnataka	37	0	1
Kerala	87	8	0
Madhya Pradesh	7	0	0
Maharastra	84	3	2
Odisha	2	0	0
Puducherry	1	0	0
Punjab	21	0	1
Rajasthan	31	2	0
Tamil Nadu	10	2	0
Telangana	22	10	0
Union territory of Chandigarh	6	0	0
Union territory of J&K	4	0	0
Union territory of Ladakh	13	0	0
Uttar Pradesh	32	1	0
Uttarakhand	3	0	0
West Bengal	7	0	1
Total	**451**	**41**	**9**
Grand Total	**492**		

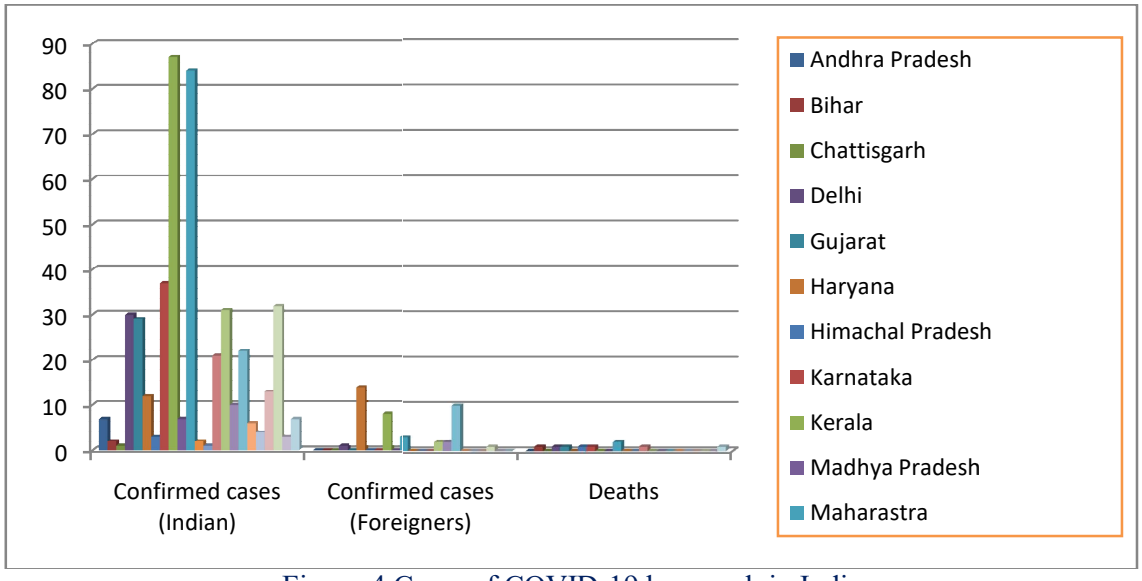

Figure-4 Cases of COVID-19 bar graph in India

8. Clinical signs and symptoms of COVID-19

The symptoms might be symptomatic or symptomless infections which have been described [59-63], but number of their frequency occurrence is unknown. As in cases with asymptomatic infection on chest computed tomography (CT), greater than 60 percent had displayed prototypical ground-glass opacities or speckled darkening imaging

abnormalities [64]. In few cases arised low-levels of ailments, with or without other representative manifestations, are following few days on diagnosis.

9. Clinical manifestations

The preliminary clinical manifestation of the disease enhancement was pneumonia which happens to be the utmost regular staid materialization of infection, considered predominantly with ailment, tussis, hyperpnea and bilateral infiltrates on chest imaging [65-66]. At present stage of existence allow no particular clinical features that can comprehensibly and authenticately differentiate COVID-19 from other viral respiratory diseases. At present scenario of Wuhan, where outbreak of COVID-19 occurred described that 138 patients suffered from viral pneumonia in Wuhan, the majority of recurrent clinical aspects at the outset of ailment were [67-69], along with that Fever at low level not above 100.4°F/38°C in 99 percent cases. In several patients other common features were fatigue, dry cough, anorexia, dyspnea etc [70-72]. However, the fact has to be understood that fever might not be a universal finding.

10. Outline and Guidance

Recently December 2019, a unique/mutant virus, identified as SARS-CoV-2, basically recognized as the significant reason for onset of acute respiratory disease first at Wuhan, a province of China. Nevertheless all began from there; reports have revealed the outbreak of first COVID-19 disease which has expanded widely greater than eighty thousand cases in China itself and thereby increasing cases worldwide. Hence WHO has declared a general well being extremity recently in January 2020. Later it has been characterized as a epidemic in March 2020. The symptoms of COVID-19 displayed fever and persistent dry cough in patients or respiratory tract symptoms. Those infected asymptomatic patients who have had recent close contact also confirmed with COVID-19. Since these asymptomatic patients travelled to areas where community transmission has been reported (eg, China, South Korea, most of Europe [including Italy], Iran, Japan and several other parts of the world including India. Every clinician has to be conscious about the threat of COVID-19 in cases with severe respiratory diseases and take effective precautionary measures while treating those patients. Any suspects of COVID-19 infection have to be notified through helpline and promptly control measures have to be implemented. The best precautionary, measure to decrease the menace for transference of infection to community by cleaning hands daily, follow personal hygiene (eg, cover mouth while cough), and keep away from mass gatherings as well as avoid local association with infective persons. Social distancing from each individual is counselled, especially in areas which already been community transmitted.

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