Therapeutic challenges in COVID-19

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Abstract

SARS-CoV2 is a novel respiratory coronavirus and, its molecular mechanisms of infection leading to developing disease symptoms are largely unknown. Understanding the molecular mechanism is a prerequisite to develop proper and effective treatment of covid-19. This positive strand RNA genome carrying virus has a protein coat with spikes (S) that attaches with the ACE2 receptor at the cell surface of human cells. Depending on the expression level of ACE2 receptor it primarily attacks lung alveolar cells and, has ability to infect other tissues. Several existing drugs are used to treat covid-19 patients and proved to be unsuccessful. Several vaccines have been approved for emergency use. Although these vaccines are unable to prevent infection but believed to reduce the viral load to prevent developing symptoms of covid-19. Major challenges of their efficacy include inability of antibody molecules to enter cells but remains effective in bloodstream to kill the virus particles. The efficacy of vaccines also depends on the length of time they stay effective in the body and, their neutralizing ability to constantly evolving new virus strains due to novel mutations and evolutionary survival dynamics of the virus. Taken together, SARS-CoV2 antibody vaccines may not be very effective and other approaches based on genetic, genomic and protein interactome could be fruitful to identify therapeutic targets to control the pandemic and reduce disease related mortalities.

Keywords: SARS-CoV2; Covid-19; Therapeutic; antibody; vaccine; challenges

Introduction

Recently novel coronavirus (virus, SARS-COV2; disease, COVID-19) infection and, its related mortalities are so widespread that WHO declared it as a pandemic. COVID-19 mortalities exceeded over 3,000,000 worldwide on April 15, 2021. Mortality rates differ in various countries, In Wuhan, China it was little more than 2% whereas it is so far more than 5% of infected people in Mexico, Peru, Brazil and USA. Disease severities varies with population as African descent and, Hispanics are severely affected with mortalities probably due to their genetic background, socio-economic conditions and, associated with other illness (co-morbidities).

Several drugs such as Hydroxychloroquine (HCQ), Remdesvir (GILEAD) and Dexamethasone were used to treat COVID-19 without much beneficial outcome in morbidities and, mortalities. Several vaccines are initiated to use, such as DNA vaccine (Inovio) or RNA vaccine (Corbett, Edwards et al. 2020, Jackson, Anderson et al. 2020) (Moderna therapeutics, Pfizer), adenovirus mediated vector carrying spike protein (Univ Of Oxford/AstraZeneca, Johnson & Johnson, Gamaleya Institute)(Caddy 2020, Corbett, Edwards et al. 2020, Knoll and Wonodi 2020, Sadoff, Le Gars et al. 2021) but their efficacy to resist SARS-CoV-2 infection is still under investigation in large population (Kim, Erdos et al. 2020) (Jackson, Anderson et al. 2020) . Antibody cocktail (Regeneron) also are being approved as treatment for Covd-19. Plasma therapy although looked promising but not effective with its limitations for wide applications (Focosi, Anderson et al. 2020, Islam, Rafiq et al. 2020). Most importantly, covid-19 patients show a wide spectrum of phenotypes, such as respiratory distress, immune activation, cardiovascular complications including stroke and myocardial infarction, blood clotting etc. (Altable and de la Serna 2020, Cappannoli, Scacciavillani et al. 2020, Chan, Lee et al. 2020, Fraser 2020, Fumagalli, Misuraca et al. 2020, Klok, Kruip et al. 2020). Identifying genetic risk groups for SARS-CoV2 infection, infection related mortalities and its prevention is important. Covid-19 related morbidities depends on the SARS-CoV2 viral load in patients with other health related conditions (Pujadas, Chaudhry et al. 2020). The symptomatic survived covid-19 patients and, the deceased patients have average viral count of ~65000/ul and ~125000/ul respectively

when measured in 15-20 days after infection from nasal swab. Thus, decreasing viral load in a patient is a key point for survival. IFIH1 mediated IFN-ß production upon SARS-CoV2 infection may be important aspect to decrease viral load to prevent disease severities as well as covid-19 related mortalities (Maiti 2020).

Thus, to control the SARS-CoV2 infection in population and develop efficient medicine to treat covid-19, it is necessary to understand the molecular mechanism of its mode of infection, functions of viral genes to evade human immune system and the evolutionary trajectories of the virus to create new mutations to survive in human host.

Mechanism of SARS-CoV2 infection

Understanding the mechanism of SARS-CoV2 infection and, invasion is a prerequisite for developing therapy. SARS-COV2 has a protein coat with spikes and a positive ~30kb (29,903 base) RNA genome (Ren, Wang et al. 2020). The principle mode of transmission of SARS-COV2 is air-droplet-borne although evidences are accumulating that it could be air-borne (Greenhalgh, Jimenez et al. 2021). Eventually the virus enters lung alveolar cells through the upper respiratory tract. SARS-CoV2 with its key entry-point residues in RBD (Receptor Binding Domain) domain in S (spike) protein attaches with human ACE2 receptor (Hoffmann, Kleine-Weber et al. 2020). ACE2 is highly expressed in pneumocytes in lung, endocytes in gut and nasal goblet cells but also expresses in almost all tissues in the human body with a moderate level (Ziegler, Allon et al. 2020). Although lung cells are primary site of infection, SARS-CoV2 has ability to invade multiple organs through bloodstream (by entering into blood vessels as endothelial cells of blood vessels also express ACE2 receptor) and, faces constant challenges from tissue specific immune surveillance with multiple niches of internal environmental conditions. After attaching to the host cells with its spikes it uses TMPRSS2 enzyme to enter into host cells and, uses its host machinery to replicate its RNA genome to thousands of copies (Hoffmann, Kleine-Weber et al. 2020). It also uses host protein synthesis system to synthesize its coat proteins to pack its RNA genetic material to become a new full-fledged virus and bursts the host cells to come out to infect other cells. Lung cells damaged

or destroyed by infection cannot carry out their function of supplying oxygen to the blood (Chan, Yuan et al. 2020).

Mechanism of coronavirus induced host immune responses.

The first line of response of host defense system against viral attack is to sense the pathogen via pattern recognition receptors (PRR). One major PRR that first senses the presence of viral RNA is IFIH1 (InterFeron Induced Helicase 1; MDA5) (Barral, Sarkar et al. 2009). Along with RIG1, IFIH1 is a viral RNA sensor protein but mechanistically differs from RIG-1 as it mainly senses coronavirus, picornavirus, and rhinovirus whereas RIG1 senses influenza B and Dengue virus (Loo, Fornek et al. 2008, Chistiakov 2010). Upon viral infection, IFIH1 induces Type 1 interferon (IFNα, IFNß, IFN-Γ) production in the host body and they are received by a receptor, IFNAR2 in the cell membrane (Novick, Cohen et al. 1994). After entering into cells IFN triggers immune responses of cell mediated immunity involving neutrophil and macrophages, humoral immunity (antibody generation; dendritic cells to B cells) and activates MAVs (Mitochondrial Antiviral System) (Belgnaoui, Paz et al. 2011). Dendritic cells are considered as a guardian of the body that captures virus and digests foreign particles (virus etc.) through autophagous lysosomes. Lysosomal undigested portion is represented in the cell surface to present as a message as antigen exposition. This message is captured by B cells that produces antibody against this antigen. However, it is demonstrated that SARS-CoV2 adopts a different pathway for lysosomal degradation over viral induced classical lysosomal pathway (Ghosh, Dellibovi-Ragheb et al. 2020). These consequences presumed that antibody generation in the human body by SARS-CoV2 virus is seriously compromised by defective antigen representation by the dendritic cells. In fact, it is observed that antibody that is raised against natural SARS-CoV2 virus is weak in nature and unable to neutralize the virus itself and creating symptoms with mortalities.

The drugs that are used to treat covid-19 and their inefficacy

SARs-CoV2 is a novel virus and has many aspects that are not earlier observed in other virus. Thus, once infected, drugs those were effective for other viruses are not effective for SARs-CoV2 [**Table 1**]. Hydroxychloroquine (HCQ) that facilitates oxygen carrier Heam binding (Nimgampalle, Devanathan et al. 2020) which is reduced by SARS-CoV2 infection could not prevent other organ failures and has severe side effects (Horby, Mafham et al. 2020, Rughiniş, Dima et al. 2020). Dexamethasone, a steroid and an autoimmune disease drug although effective

Table 1: Drugs that are used for treating Covid-19

Drugs	Manufacturer	History	Functions	Reason to use for SARS-CoV2	Responses	References
Hydroxychloroquine (HCQ)	Generic	Drug for Malaria	facilitate heam binding with O_2	O2 is not carried by RBC	Failed in large clinical trial	Rosenberg et al (2020)JAMA,323,249
Remdesvir (inosine analogue)	GILEAD	Developed to block reverse transcrition of Hepatitis C and ebola virus	Introduction of Inosine into RNA to stop reverse transcription	SARS-CoV2 is also an RNA virus	Failed in large clinical trial	Pan et al, 2021, NEJ 384,497-511
Dexomethazone (corticosteroid)	Generic	Steroid for autoimmune diseases, such as lupus and Rheumatoid arthritis	immunosuppressor	Effective for reducing mortalities. Limitations to use for everybody with severe illness	Reduced mortalities	Sterne et al, 2020, JAMA 324, 1334
Ivermectin	generic	Use to treat helminthiasis and scrabies	blocks spike protein attachment	Kills SARS-CoV2 in cell culture	Extremely high dose needed to suppress SARS-CoV2	Ahmed et al (2020),J.infec.dis. 103,214-226
Ritonevir	Generic	Antiretroviral	potent inhibitor of cytochrome 450	SARS-CoV2 is also a retrovirus	Effective when treated with interferon beta	Hung et al (2020) Lancet, 395,1695
Ribafirin	Generic	Antiretroviral to treat hepatitis C	nucleoside analogue	SARS-CoV2 is also a retrovirus	Effective when treated with interferon beta	Hung et al (2020) Lancet, 395,1696
Monoclonal antibodies	Custom					
Bamlanivimab and etesevimab (LY-CoV555)	Eli-lily	Monoclonal antibody specifically designed against sars-CoV2 spike protein	Monoclonal antibody	developed against SARS-CoV2	Absence of large data	NA/Not published
Casirivimab and imdevimab (REGN-COV2)	Regeneron	spike protein antibody cocktail	Monoclonal antibody	developed against SARS-CoV2	No clinical trial published yet	NA/Not published

for reducing inflammatory "cytokine storm" in lung induced by SARs-CoV2 has limited abilities to reduce

inflammation in heart or other tissues. Although it helps severely affected patients from developing covid-19 related complications and reduced mortalities (Sterne, Murthy et al. 2020), but not considered as very effective drug to reduce covid-19 mortalities (Theoharides and Conti 2020). Remdesvir (GILEAD) that was initially projected as an effective treatment for covid-19 is unfruitful and withdrawn by WHO. It is actually developed against Hepatitis C and then Ebola virus to block reverse transcription (RNA dependent RNA polymerase, RDRP mediated) of these virus by providing a nucleoside analogue, inosine (Warren, Jordan et al. 2016). This drug failed to stop Hepatitis C, Ebola and also to SARS-CoV2 (Pan, Peto et al. 2021) . This is probably because these viruses possess strong proof-reading and editing activities that removes inosine from the RNA during reverse transcription. Not only that, Ebola and SARS-CoV2 RDRP protein do not have any significant similarities (data not shown) in amino acid sequences and there was no basis that it would work for SARS-CoV2.

Challenges to antibody therapy

Vaccines are generally antigens from which antibodies are raised against the whole virus or part of a crucial protein that are needed for viral attachment. Whatever the way antibodies are produced, the principal mechanism of antibody production by host B cells remains same. The whole virus, part or whole of a crucial viral protein, RNA or DNA (that codes for a crucial viral protein) is administered into host body that are initially captured by dendritic cells. The RNA or DNA is delivered by a vehicle, in most cases, LNP (Lipid NanoParticles) that facilitates them to enter into these cells. RNAs or DNAs by general molecular biology principle are transcribed (DNA) and translated to its corresponding protein by the cellular machinery. These proteins are presented by Antigen Producing Cells (APC dendritic cells) as antigens and induce B cells to produce antibodies against them in the blood.

The main drawback of this procedure is that antibody is a big protein molecule that circulate in the blood but has no capacity to enter into a cell. Depending upon the nature of virus habitat, antibodies always are not very effective. As for example, HIV virus remains within CD4/CD8 cells and unable to be destroyed by its antibody in the blood (Gray, Laher et al. 2016). SARs-CoV2 is a novel virus whose mechanism of transmission is not clearly known although it primarily enters through nasal passage to the lung alveolar cells (also may be through goblet cells to nerve and brain cells) and destroy them. In some cases, it is transmitted to other tissues through blood. It has been reported that only in 40% cases, SARS-CoV2 enters into bloodstream (Zheng, Fan et al. 2020). As expected, antibody vaccine can destroy the virus in those patients whom it enters into bloodstream through endothelial cells of the blood vessel [**Figure 1**].

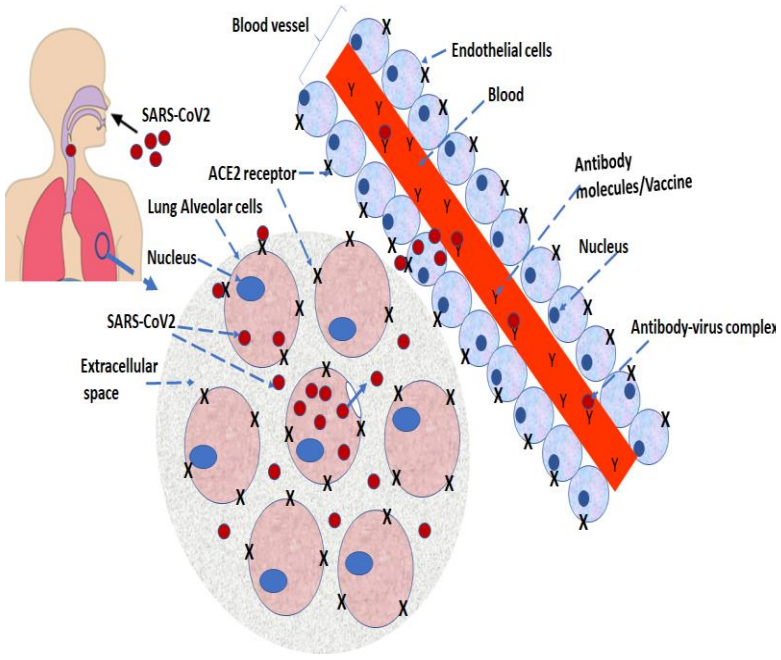

Figure 1. The mechanism of SARS-CoV2 infection and antibody actions. The virus enters into lung cells through nasal passage, attaches to ACE2 receptor of cell surface, amplify using cellular machineries and destroy the lung cells to come out to extracellular space. Some of the virus, not all, enter from extracellular space to endothelial cells through ACE2 receptor and enters blood vessels. As antibody/vaccine molecules circulates in the blood but cannot cross the endothelial cell barrier to enter the cell, it only kills the virus when they come into blood and reduce the viral load in some people to prevent developing symptoms.

Thus, antibody vaccine may not be as effective for those people (60%) whom the SARS-CoV2 does not come to blood but may continue to destroy cells in tissues where it primarily entered.

SARs-CoV2 generates new mutations to evade its own antibody responses

An emerging virus like SARS-CoV2 that has a highly dynamic evolutionary trajectories with new mutations (Maiti 2020) threatens vaccine development. Treatment with convalescent plasma of Covid-19 patient carries antibody of this naturally occurring virus are largely unsuccessful (Focosi, Anderson et al. 2020, Islam, Rafiq et al. 2020). It is also demonstrated that upon convalescent plasma treatment, SARS-CoV2 generates new mutations with the emergence of a dominant viral strain bearing D796H in S2 region and **Δ**H69/**Δ**V70 in the S1 N-terminal domain NTD of the Spike protein (Kemp, Collier et al. 2020). The new strain bearing **Δ**H69/**Δ**V70 and D796H conferred decreased sensitivity to convalescent plasma, whilst maintaining infectivity similar to wild type. Thus, it appears that SARS-CoV2 develops resistance to its own antibodies raised against it in the human body by generating and selecting mutations for its own survival.

Adverse effect caused by the current vaccine strategies

The safety of a vaccine is not beyond questionable especially when novel methods are introduced for urgency of treatment. After vaccination long period of incubation is necessary to observe the proper side-effect of a vaccine. Vaccines are generally vulnerable to immunocompromised patients and it has also been observed for SARS-CoV2 vaccine (Gresham, Marzario et al. 2021). Astra-Zeneca SARS-CoV2 vaccine is linked to blood clots in the patient (Greinacher, Thiele et al. 2021). In case of RNA vaccines against spike protein that are being introduced in the human body for SARS-CoV2 (Pfizer, Moderna therapeutics), the amount of RNA (~100ug) is enormously high (1 ug RNA of 300bases=6.24 $x10^{12}$ copies) These RNAs are supposed to be translated in the host cell (dendritic) machinery to spike protein (part of) and is presented as antigen in the cell surface to develop antibody against these protein in B cells. As we discussed earlier SARS-CoV2 adopts a different lysosomal pathway than

other RNA virus, it is not known whether spike protein of the virus (made by external RNA) is undergoing classical lysosomal pathway or natural SARS-CoV2 adopted alternative pathway. As the consequences are not studied, the effect and the side effect of RNA vaccines cannot be predicted until long time.

Furthermore, SARS-CoV2 bears LTR (Long Terminal Repeat) sequences (G-Quadruplex) structures(Maiti 2021) like HIV that helps HIV to integrate into human genome (Ohmori and Tsuruyama 2012, Ruggiero, Tassinari et al. 2019). It is indeed observed that SARS-COV2 genome may integrate into human genome (Zhang, Richards et al. 2020). If it does, it is unknown whether it would integrate at random sites or at specific sites in the genome disrupting major genes. Thus, it is also unknown whether external spike protein RNA (RNA or DNA vaccines) that is administered into cells can also integrate to human genome and disrupts the function of the important genes developing severe other illnesses.

Furthermore, the vehicle used for RNA vaccine is LNP particle that facilitates RNA to enter cells. However, although the fate of LNP particle is known as it is reported to be degraded moderately inside the cell in mice model (Christensen, Litherland et al. 2014), but it is unknown whether similar mechanism of LNP degradation occurs in human cells or very high amount of these LNP particles are a burden to a cell to create other effects or, damage the cells where it enters.

Finally, the surveillance of antibody vaccine in the bloodstream would destroy virus as they come from cells and keep the viral count low to develop symptoms. But the remnant virus or whom they don't enter into bloodstream may continuously destroy cells posing a serious threat to the tissues to develop other illness.

Moreover, adenovirus (Ad5) vector carrying vaccines earlier showed a series of complications when used HIV genes (HIV vaccines) as antigen. The possibilities of replicating these complications for SARS-CoV2 has not been ruled out (Buchbinder, McElrath et al. 2020).

Genetic mutations cause to emerge new SARS-CoV2 strains that challenges vaccine development

Effective vaccines or medicines development and, testing them in animals, it is necessary to know the origin of this virus and, how it is behaving in the human population by changing their genetic profile with evolutionary dynamics. The creation of new mutations with evolutionary trajectories driving these pandemic could be replicated *in vitro* that could predict the reversion of vaccine effect and, its virulency as shown in other RNA virus (Stern, Yeh et al. 2017).

SARS-CoV2 virus is believed to be originated from a closely related bat Coronavirus RaTG13 lineage after gaining insertions of RBD of spike (S) protein by exchanged recombination with pangolin virus (Li, Giorgi et al. 2020). RaTG13 has 96.3% identity with SARS-CoV2 genome implying that it substituted ~1106nt to evolute as present-day virus (Ren, Wang et al. 2020, Zhou, Yang et al. 2020). Temporal analysis of SARS-CoV2 sequences revealed that its nucleotide substitution rate is 2.22nt/month with an evolutionary rate of $9x10^{-4}$/site/year, which is a little less than other retrovirus (10^{-4} to 10^{-6}/site/year) (Maiti 2020). Genetic codon analysis indicates that SARS-CoV2 evolution from RaTG13 strictly follows neutral evolution with strong purifying selection whereas its propagation in human disobeys neutral evolution and, proceeding towards divergent selection predictably for its infection power to evade multiple organs (Maiti 2021). Invasion of SARS-CoV2 into various human organs is predictably increasing the nonsynonymous mutation over synonymous mutations that are persisted over the deleterious mutation and, increases its selection fitness (Maiti 2021). This property of SARS-CoV2 is enabling it to generate mutations that would help it to survive aggressively. Thus, there is a possibility that it can evolute to new strains frequently to become virulent and escape antibody vaccine response.

Recently several new strains of SARS-CoV2 are emerged as B.1.1.7 (UK), P.1 and P.2 (Brazil), (B.1.351) (South Africa), A23.1 (Uganda), Double mutant (India), B.1.526, B1.525 (USA) etc. that are poising threat to the ongoing pandemic. B.1.1.7 has 9 mutations in spike protein including N501Y at the RBD domain and has higher infectivity with increasing mortalities (Davies, Abbott et al. 2021). N501 is an extremely important residue for attaching ACE2 receptor and almost gave a passport to the virus to enter into human host from bat RATG13

(Maiti 2020). When *in vitro* monoclonal antibody was tested for B.1.1.7 strain, reduced neutralizing efficacy is observed with the escape of antibody effect (Planas, Bruel et al. 2021, Supasa and al 2021). The South African virulent strain (B.1.351) showed nine fold less effective for neutralizing the virus efficiently for RNA vaccine (Pfizer) and threatens the efficacy of the vaccine (Tada, Dcosta et al. 2021). The new wave of infection extended the pandemic due to emergence of Delta variant (B1.6.1.7.2) This variant is not only more infective, it is also resistant to most of the vaccines that are available now (Deng, Garcia-Knight et al. 2021). Thus, in future when a flux of virulent SARS-CoV2 strain will continue to generate, it will be difficult to generate antibody vaccines with the same pace to withstand the widespread effect of this virus.

Many companies are in a race to generate vaccines for these new and aggressive variant strains. Although they neutralize these new strains in lab conditions, it would be extremely difficult to implement in large population. For example, to develop combined antibodies for as many new strains, spike RNA (DNA) of each strain is needed to administer into human body that will increase to enormous amount of total RNA to raise effective antibodies for each strain. In contrast, keeping the RNA amount same (e.g.,100ug), each spike RNA amount may not be sufficient to be effective to generate enough antibodies responsive for each strain. In addition, separate clinical trials would be needed in large population. By the time another new mutant strain will emerge! Taken together, SARS-CoV2 antibody vaccines could not be very effective to control the pandemic.

Drugs are being currently developed

Upon viral attack immune system of the host body undergoes series of changes to withstand the virus. In response to host immune system virus modifies itself to survive and multiply. Human immune system response comprises cell mediated immunity, humoral immunity and Mitochondrial anti-viral systems (MAVs). Thus, except only antibody responses other responses and their pathways inhibiting molecules could serve as drugs for SARS-CoV2 virus.

Cell mediated immunity- Neutrophil and macrophages are known to phagocytose virus and destroy. IFIH1 protein that are expressed in these cells senses the coronavirus RNA genome although its role for SARS-CoV2 is not known and could be further studied. Upon viral sensing, IFIH1 induce interferon type 1 (α, ß, Γ) secretion that circulates in the blood and enters to the cell by interferon type 1 receptor, IFNAR2 (Novick, Cohen et al. 1994). After entering into cells interferon, especially IFN-ß induces a series of genes/proteins to activate the host immune systems. Coincidentally, IFNAR2, a receptor for type 1 interferon, is one of the strongest associated ($p< 5.8 \times 10^{-23}$) gene in human in covid-19 patients in worldwide population in a GWAS (Genome Wide Association Studies) study by COVID-19 HGI (Covid-19 Human Genome Initiative (Gana, Liao et al. , Gaziano, Giambartolomei et al. 2021). Thus, indirect evidence suggests that Interferon pathway is one of the important pathways to manipulate macrophages and neutrophil activities to engulf the SARS-CoV2 virus and, prevent infection and multiplication to reduce the viral load to reduce covid-19 mediated morbidities and mortalities.

Humoral immunity-Dendritic cells are the guardian of the body that first senses the RNA genome of the virus through IFIH1(Barral, Sarkar et al. 2009) or RIG1(Loo, Fornek et al. 2008) and digests through lysosomes. Lysosomal end product is presented in the cell surface and, that signals are captured by B cells which produces antibody against the antigen. However, as we discussed earlier that SARS-CoV2 adopts a different lysosomal pathway (Ghosh, Dellibovi-Ragheb et al. 2020), enabling defective/malfunctional antigen presentation leading to weak antibody response which could also be true for external vaccine. However, the novel pathway adopted by SARS-CoV2 could be studied extensively for identifying therapeutic target to enhance effective antibody response.

MAVS (Mitochondrial Antiviral Systems)- Upon viral sensing IFIH1 or RIG1 protein activates host mitochondrial antiviral systems (Belgnaoui, Paz et al. 2011) to activate MX1 and IFIT1. MX1 is especially important as it has been demonstrated that SARS-CoV2 super virulent strain (B.1.1.7) carries one of the mutation in spike protein D614G that is more vulnerable to the people having a SNP (rs35074065, Del C) in cis eQTL with MX1 and

TMPRSS2 gene (Maiti 2020, Rambaut, Loman et al. 2020). Zhang et al (2020) showed that D614G mutated protein reduces S1 shedding and increase infectivity (Zhang, Jackson et al. 2020) and Long et al (2020) convincingly showed the widespread infectivity of a strain carrying only D614G in southern USA population (Long, Olsen et al. 2020). Thus, D614G appears to be contributing to increase the infection power of superinfective strain, B.1.1.7. However, apart from IFIH1, it is demonstrated that SARS-CoV2 also senses through RIG1 and, the SARS-CoV2 protein ORF9b suppresses the RIG1-MAVs system (Wu, Shi et al. 2021). IFIH1 sensing of SARS-CoV2 is yet to be investigated and it is extremely important to study these pathways of SARS-CoV2 sensing to find the target to develop suitable drugs that would be effective against SARS-Cov2.

Interferon administration

Interferon production is a first line of defense in the immune system to resist corona viral infection. IFN-ß supplement could be tested to resist infection(Maiti 2020). IFN-ß may not need more characterization as it is already available and being used as a drug for Multiple Sclerosis (MS)(Trinschek, Luessi et al. 2015). From Hongkong, a phase 2 clinical trial with interferon beta-1b and proteases, lopinavir-ritonavir and ribavirin has been reported and they showed that all mild and moderately affected Covid-19 patients are cured (n=86, with 100% success rate) with shortening the duration of viral shedding. They also concluded that this triple drug treatment has superior effect in curing COVID-19 patients than lopinavir-ritonavir or ribavirin alone (Hung, Lung et al. 2020). However, they did not treat or mention severely affected patients. This could be due to that Hongkong had too few available severely affected patients for a clinical trial or moderately affected patients after this treatment did not reach to severe stage. Thus, the immediate clinical trials of IFN-ß supplement could be an effective treatment for COVID-19 also in other parts of the world to reduce ongoing devastating consequences.

More effective strategy is taken by a company (Synaqirgen, UK) to treat covid-19 patients with interferon nasal inhaler (SNG001). This study in the 2nd phase of clinical trial showed 85% efficacy and final phases of clinical

trial (https://www.clinicaltrials.gov/ct2/show/NCT04385095) are currently being in progress. These treatments are believed to decrease the mortalities in Covid-19.

Conclusion

Developing suitable medicine for a virus is extremely difficult for its mechanism of action until establishing exact pathways and without understanding the evolutionary trajectories with mutations. It was not possible to develop suitable drug for HIV1 because of two facts that it resides in CD4/CD8 cells where antibody cannot enter to destroy the virus and, it integrates into genome and stay long time as a latent virus. Similar properties are observed by SARS-CoV2 as there is indication that it resides inside the lung alveolar and other organ cells where antibody cannot enter. Other fact is that it is predictably integrates into the human genome although further information about its whereabouts after integration is unknown. Antibody vaccines although apparently expected to control the pandemic but could be overestimation for its various limitations. Drug development against SARS-CoV2 to control the pandemic mainly will depend upon manipulating SARS-CoV2 induced human host functional molecular and genetic pathways. Other approaches should be used by manipulating the host system genes that are associated with SARS-CoV2 infection and, hospitalized Covid-19 patients (severely affected). Nevertheless, it would be difficult to reduce the SARS-CoV2 mediated morbidities where the other organs are already damaged or partially defective (co-morbidities) due various illness.

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