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Title Page

Title- COVID-19 : Immunological lessons from bats, pangolins and old coronaviruses; and how we can possibly apply them in a timely way for a better outcome.

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Abstract

Introduction**-** The COVID-19 pandemic is a global crisis, the number of cases and deaths are on a steep incline. This article reviews the possible immunological mechanisms which underlie the disease pathogenesis by looking at the behaviour of previous coronaviruses not only in humans but also other mammals which possibly act as reservoir hosts.

Observations**-** A key aspect of this coronavirus as well as the previous SARS CoV seems to be the importance of host immune response in the pathology and clinical severity of illness caused by them. A hyperactive innate immune state in combination with an exhausted adaptive immune response are possible determinants of severe illness.

Conclusion**-** There is a possibility that the current SARS CoV 2 has immune evasive tactics similar to SARS CoV in its repertoire, since they share a 76% homology. These might have been learnt behaviour from long periods of persistence in their reservoir hosts and they may be the reason behind the dysregulated immune response evoked in humans. That in turn is highly likely to be one of the factors which govern disease severity. With this in mind we want to bring the medical community's attention to a '*hit early, hit hard*' intervention as a possible strategy to modify the course of the disease and bring down the numbers of severe sufferers.

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Introduction

COIVD-19 is a global pandemic caused by the SARS CoV 2, a novel betacoronavirus[1]. The human immune system is entirely naive to this organism; there hasn't been any report yet of cross protection afforded against this illness in people who have previously suffered from other coronavirus infections. Even if that were the case, the overwhelming

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population of the world would still be naive to this virus as prior to this illness as there have been only been limited clusters of coronavirus outbreaks in humans[2,3,4]. In such viral illnesses it is the innate system of immunity which forms the backbone of a body's defence. Therefore, it is crucial that we look at the evolution of this virus in immunological terms; we need to understand how it has learnt to adapt itself to the defences deployed by the innate immune system. A look into the immune system of likely reservoir hosts, bats and pangolins, gives us some important clues. We also look at the behaviour of other coronaviruses like SARS CoV and the Ebola virus to gain insights into possible mechanisms which are driving the immuno-pathogenesis of this illness. With this immunological information in mind we review possible treatment strategies which can be effective in shaping in a favourable outcome.

A quick review of the innate immune system

The innate immune system is an ancient, evolutionarily conserved defence mechanism, human beings share it with other living organisms including plants and insects[5]. The closer one species is to another in terms of phylogeny, the more remarkable the similarity[6]. Which means that if a virus has adapted itself for survival in a closely related mammalian reservoir host then that virus can, potentially, be pre-equipped to fight back against the human immune system. COVID-19 is a sobering example of this. The discovery of SARS C0V 2 like viruses in bats and pangolins has suggested that either of the two could have served as the original reservoir host[7-11]. As more insights are gained into the immune systems of these mammals, especially bats, a very disturbing picture emerges. Bats, many researchers postulate, may be an ideal reservoir for these viruses[12,13,14,15]. There is a possibility that they allow these viruses to persist in their bodies for a long time, therefore giving them ample opportunity to learn from and adapt themselves to the innate immune defence mechanisms of mammals[13]. The enemy may already be in possession of our battle plans.

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Bats as a reservoir for viruses

Bats account for 20% of the mammal population in the world. They have been found to harbour viruses which have been implicated in human illnesses. In some cases the viruses aren't the same but share homology suggesting a common ancestor; in others they are the same and direct spillover from bats to humans is implicated. The table below exemplifies the scope of these mammals in viral disease causation though it is by no means exhaustive :

Table 1

Virus	Family	Disease	Reservoir Host
Hendra Virus (HeV)[16,17]	Paramyxoviridiae	HeV Infection	Genus Pteropus (fruit bats)
Nipah Virus[16]	Paramyxoviridiae	Nipah virus disease	Genus Pteropus (fruit bats)
Ebola Virus[18,19]	Flivoviridiae	Ebola virus disease	Genus Pteropus (fruit bats)
Marburg Virus[20]	Flivoviridiae	Warburg virus disease	Rousettus aegypticus (African fruit bat)
SARS CoV[7-9,21]	Coronaviridiae	SARS	Genus Rhinolophus (Horseshoe bats)
MERS-CoV[22-24]	Coronaviridiae	MERS	Possibly Neoromicia capensis (unconfirmed)

Post the 2002 SARS epidemic numerous studies have shown the presence of SARS like Coronaviruses (SL-CoV) in bats leading researchers to speculate that bats[7-9] may be the ancestral host or natural reservoir for these viruses. SARS CoV 2 has been found to share 96% resemblance with RaTG13[10], a bat coronavirus, which is more than the homology between it and the old SARS CoV (79%) and MERS-CoV (50%)[25]. Another candidate ancestor is the Pangolin-CoV, found in dead Malaysian pangolins with which it shares 91% homology[11]. At present neither has been definitely proven to be the original host but the likelihood of one or the other being so is high.

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A comparison between the innate immune system of bats and humans

Micro-organism associated molecular patterns (MAMPs) are recognised by various immune sensors present on or within the sentinel cells of innate immunity i.e. the macrophages, the dendritic cells etc[5]. This allows for a quick recognition of danger and a suitable response to be mounted. Viral RNA is recognised by signalling sensors TLRs (Toll like receptors)[26,27] and cytosolic sensors like RIG-I (Retinoic acid inducible gene I) and MDA-5 (Myeloma differentiation associated gene 5)[28,29]. These sensors (especially RLRs like RIG-1 and MDA-5) trigger Type 1 Interferon production which is the cornerstone of antiviral immune response of our body. The IFN in turn causes up regulation of certain genes whose products help fight the virus. They are referred to as ISG - Interferon Signalled Genes, and cells which have unregulated expression of them are referred to as bearing the IFN signature, i.e. conclusive evidence of exposure to type I IFN[30,31]. Transcriptional analysis has found 10 functional TLRs in the bat species *Pteropus alecto*[32]. RIG-I is the most potent of RNA sensors and it's function appears to be conserved between man and bat[33]. In bats interferon induction machinery includes IRF-3 (Interferon regulatory element) and IRF7, which is also similar to humans, although the sequence of IRF-3 in bats is evolutionarily distinct[34,35,36]. Many bat species respond to Poly (I:C) treatment with increased type I IFN and up regulation of ISGs which shows that the mechanisms for sensing dsRNA and responding to them are similar to those observed in humans[33,37,38].

More interesting than the similarities however, are the points of divergence. Like the fact that the genome locus which encodes type I IFN is contracted in bats, containing only ten IFN loci[39]. The mRNA for IRF-7 is constitutively expressed in a wide distribution of cells in bats whereas in humans it is inducible[36]. *Pteropus alecto* has been found to have *constitutive* expression of the three IFNa genes (not seen in all bat species)[39]. Bats also

possess machinery which can limit the pro-inflammatory responses to coronavirus infection, something which humans lack. For instance, c-Rel in bats can restrict TNF production[40]. They also have lower levels of NLP3 activation and IL-1β secretion in response to viral stimulation as compared to humans[41].The ISG expression kinetics in *P.alecto* cells treated with IFNα revealed an *early rise* followed by an *early fall*[42]. This cap on inflammation is believed to be one of the reasons why bats might have persistence of virus in their systems without developing signs of overt disease[43]. By contrast the typical IFN response observed in humans to coronavirus infection is a *late rise* and a *prolonged persistence* of ISG signature in cells[42]. A crucial reason for the lateness of IFN response in humans is believed to be the development of immune evasive mechanisms by coronaviruses. The research into SARS CoV has revealed that it has many such mechanisms in it's armamentarium, we briefly mention a few of them. Viral replication in membrane bound organelles called viroplasm-like structures (VLS) can ostensibly protect them from sensors like RIG-I and even TLRs[44-46]. SARS CoV protein Nsp16 (Nonstructural protein) helps to mask a viral MAMP, the unmethylated 5' tri-/diphosphate ends of dsRNA[47,48]. SARS CoV expresses papain like protease (PLP) domains within Nsp 3 which can inhibit STING (Stimulator of IFN genes)[49]. There is also evidence that SARS CoV dampens NF-kB signal[50,51]. SARS CoV is capable of targeting STAT1 in order to suppress IFN signalling[52,53]. The exact role these mechanisms played in the pathogenesis of SARS remains to be elucidated. It also remains to be seen how many of these mechanisms have been adopted by the SARS CoV 2 and what role they play in the immuno-pathogenesis of COVID-19.

Pangolins as possible original hosts

Recently a study has identified a virus, named Pangolin-CoV in Malaysian Pangolins and this virus has 90% homology with the human SARS CoV 2[11]. In addition the segment of SARS CoV 2 genome which encodes the receptor binding motif (RBM) which is the

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transcript for the receptor binding domain (RBD) was found to be more similar to Pangolin CoV (90.5%) than RaTG13[11]. This puts forward Pangolins as an alternative host for the current coronavirus. It is relevant to mention that the SARS CoV 2 has a unique PRRA (Pro-Arg-Arg-Ala) segment which has not been found in any of the other viruses, the origin of this insertion remains unclear at present.

Pangolin genome has not been examined as widely as that of bats, but there is some information available. Like bats, they too have a highly contracted IFN genome. The number of IFNA genes is lower as compared with humans and IFNE gene is pseudogenized in them[54]. How this impacts virus infection and evolution is a subject which needs further research.

The immunological consequences in humans

There is evidence to suggest that the pathology of severe disease due to SARS CoV 2 is linked with excessive inflammation, the 'cytokine storm' as it is called[55,56]. Predictors of severe disease include elevated IL-6, ferritin, lymphopaenia, an elevated neutrophil to lymphocyte ratio and elevated D-Dimers[55-58]; all of which suggest an unregulated inflammatory response. At this point it is worth reiterating that the SARS CoV infection had a similar pathogenic outcome. It has been suggested that a critical switch from hyperactive innate immunity to adaptive immunity failed to happen in those with severe SARS[59]. Roughly these illnesses in their severe avatar seem to follow three stages, a) immune evasion and suppression of antiviral IFN response which allows the virus to replicate with ease, b) the eventual cytokine storm and c) severe systemic manifestations due to the unregulated inflammation. By contrast the immunological profile of a patient with mild disease demonstrated a robust adaptive immune response by day 7 of illness. A large spike in IgG and Ig M antibodies with persistent rise from day 7 till 20 was noticed in this patient who had mild symptoms and recovered quickly. In addition she also had increased titres of follicular helper T cells, activated CD4+ T cells and CD8+ T cells[60].

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It is clear that not all patients develop this dreaded complication, in fact only a small proportion of population is susceptible to it. One risk factor which has emerged clearly as a cause for severe illness in SARS CoV 2 is age[61,62]. There are few studies regarding sepsis associated macrophage activation like syndrome and none has looked at the age wise incidence of this complication. But theoretical knowledge does lend some support to the hypothesis that older individuals might be at higher risk for this complication. The senescence of immune system is a well documented phenomenon with lymphopaenia, especially reduced regulatory T-Cell population and recused effectiveness of immune cells including macrophages and dendritic cells[63]. But the newborn infant also has a deficient innate immune system yet the severity of illness is much less in them so this cannot be fully explained by reduced lymphocyte responsiveness alone[63]. The one major difference between infants and elderly is the increased pro inflammatory cytokine milieu comprising of IL-1β, IL-6, IL-18, TNFα etc. in the latter which results in persistent low grade inflammation[63]. It should be remembered that the relevance of these findings is by no means certain.

The key point to bear in mind is the possible importance of early recognition of this state as it may allow for timely institution of available anti-viral therapy. Such a course of action may modify the disease course and lessen the severity of this illness. Which brings us to the next important question, how do we identify it early enough?

The relevance of lymphopaenia

There have been many studies which have utilised different combinations of inflammatory markers to identify macrophage activation syndrome or macrophage activation-like syndrome. The Hscore has been recommended but many find it to be insensitive in sepsis especially in the early phase[56]. Macrophage activation-like syndrome has been used as a term to describe the hyper-inflamed state seen in sepsis which does not fulfil the criteria for secondary hemophagocytic lymphohistiocytosis[64].The same group

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proposed the use of Ferritin levels of greater than 4000 ng/mL as a sensitive and specific marker for identifying this state but the SARS CoV 2 infection non survivors were found to have a median ferritin level of 1297.6 ng/mL in one case series making the utility of this parameter doubtful[65]. All these highlight the need for finding a more sensitive marker to identify the accompanying inflammatory state in this illness. One possibility is using a combination of DIC (disseminated intravascular coagulation) and HBD (hepatobiliary dysfunction) as an indicator of the hyperimmune state[64]. However, the lack of widespread consensus on the cut-offs to denote hepato-biliary dysfunction in this condition and unavailability of tests in many resource poor situations is a drawback. We would like to draw attention to lymphopaenia as a possible early marker which may be used to institute early effective therapy.

Two case-series of COVID-19 have demonstrated that relative lymphopaenia i.e. lymphocyte count <20% of total white cell count, predicts severe disease[61,62,65,66]. A recent article has proposed the use of a Time-LYM% (time from symptom onset-lymphocyte percentage) model in order to classify disease severity[67]. This is by no means the first viral illness where the importance of lymphopaenia in predicting disease severity has been highlighted. In 2018, a study reported the disabling of lymphocyte immune response by the Ebola virus (EBOV)[68]. Lymphopaenia was found to be a marker of fatality in EBOV infections and the authors proposed that it might be a sign of an underlying 'cytokine storm' initiated by the virus. In view of past and current medical experience this lab parameter might fulfil the need we have for a simple, easily available medical test which can help predict outcome. Even those who do not meet the case definition and are not eligible for RT-PCR testing due to limited test kit availability can undergo serial lab measures of lymphocyte count. This might allow for timely recognition of those who would benefit from early testing and treatment.

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A note on treatment strategies which are aimed at immune modulation

The use of convalescent plasma from recovering patients is a strategy which is targeting the apparent exhaustion of adaptive immunity in those with severe disease. A case series is ongoing to test for treatment efficacy[69].

Interferon Alfa-2B is also a proposed treatment, to be used in the early days of illness when our body is failing to mount an adequate anti-viral response. Rapid control of viral replication at this stage can possibly mitigate severe illness. The exact timing of administration and withdrawal need further research.

Baricitinib has been proposed as a possible treatment option in combination with antiviral therapy. An AI (artificial intelligence) derived knowledge graph helped identify member of numb associated kinase (NAK) family as potentially beneficial[70].

One problem is that these strategies are unlikely to be available on a large scale soon enough and in the mean time mortalities are mounting. A possible solution is treatment with available anti-viral drugs *early* in disease course, especially in a high risk case. Decreasing viral replication early enough may prevent a cytokine storm from setting in later.

Conclusion

This article reviews the available literature regarding the immunology of previous viral infections, the inter-species differences in immune mechanisms of the reservoir host and humans and previous experience in sepsis induced cytokine storm with a view to shed light on the possible immune-pathogenesis of SARS CoV 2. Although there are inherent dangers in generalising and extrapolating information to apply in a different set of circumstances, this pandemic has given us a very limited window of time in which to respond. In this case it would be prudent that we use all the theoretical knowledge at our disposal to devise potentially effective treatment strategies. Early institution of treatment, utilising simple laboratory markers for identifying potentially severe cases can all help in

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modifying the disease course and reduce the burden of severe disease. It might be more prudent to treat early on a wider scale and then retrospectively analyse the benefits of such a strategy rather than waiting for a prospective trial to prove it's benefits.

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