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SARS: A RATIONALE LITERATURE STUDY BASED ON ETIOLOGY, PATHOGENESIS AND MANAGEMENT

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ABSTRACT
Severe acute respiratory syndrome (SARS) is a newfangled infectious disease instigated by a novel coronavirus that eventually result in deadly respiratory pathological complications. Owing to high spreading and death rate, SARS has progressed as a chief respiratory disease which may stumble upon ubiquitously around the world. The possible variability of the SARS-CoV genome may eventually give fresh SARS outbursts and several sections of the viral genomes open reading frames have been recognized which may provide to the intense harmfulness of the virus. The pathogenesis of SARS involves numerous mechanisms including both direct action on target cells as well as indirect action by means of the immune system. The utmost striking method to thwart novel epidemics of SARS is vaccination; nevertheless the expansion of vaccines is challenging owing to mislaid data on the part of immune system-virus relations and the highly probable mutability of the virus. Even though new infections are not reported currently, SARS leftovers as a foremost health hazard, as new epidemics may rise at any time. Consequently, advance experimental and clinical investigation is indispensable to halt the threat of this disease.

INTRODUCTION
Severe acute respiratory syndrome (SARS) is one of the principal novel infectious disease of this epoch. SARS has been initiated from Southern China by Dec 2002 with a huge death rate and spread. This deadly disease resulted in affecting around 8000 people and death of 800 people within a period of 6 months since it been reported.[1] The disease presented a novel risk for pulmonary medicine and signifies a threat for antiviral drug discovery and management.[2] SARS is instigated by a new, SARS- related coronavirus (SARS-CoV)[3] which has been recognized by a World Health Organization (WHO)-led international laboratory system. After information from health establishments in Hong Kong on the outburst of a novel epidemical atypical pneumonia in public hospitals, the WHO delivered a worldwide attentive on the disease. Meanwhile circumstances of SARS were also testified from China, other Asian countries as well as American and European continents during this time. Soon after the early global observant, the WHO introduced a concerted multi-center research scheme on SARS diagnosis, ran by eleven main laboratories around nine countries. [4] By means of contemporary communication skills to augment the analysis of SARS tissue samples, it was quickly revealed that a novel coronavirus is the causative agent of SARS (SARS-CoV). Analogous to the development made in the epidemiology and clinical diagnosis which has lately been established by many case reports, clinical studies and definitions,[5] experts have likewise exposed basics of the fundamental molecular mechanism of the SARS coronavirus. As it is vital for forthcoming approaches that SARS is identified in its initial stages and that therapeutic possibilities are improved, understandings into the molecular mechanism of SARS have to be utilized to advance novel therapeutic strategies and vaccines. The present overview aims to analyze and present the currently available data on epidemiology, clinical presentation and management of molecular mechanisms of SARS. Additionally, it is significant to emphasize that in the current state of not any precise drug or vaccine being accessible, small insight into molecular mechanism is also included which is vital to recognize potential treatment targets.

Etiology: Erstwhile the progress of therapeutic managements centered on molecular mechanisms of the virus, the causative agent had to be quarantined and examined. Rapidly after the quick founding of the international WHO laboratory network, speedy growth was completed in the documentation procedure of the causative agent, and it was stated that SARS is maximum probably instigated by a new strain of the family of coronaviruses.[6] These viruses are normally recognized as a reason for pulmonary and gastrointestinal illnesses of humans and domestic animals.[7] The cluster of coronaviruses is classified under the order nidovirales, which characterizes a group of enveloped positive-sense

RNA viruses comprising of coronaviridae and arteriviridae.[8] Viruses of this group are documented to make a 3' co-terminal set of subgenomic mRNAs in the infested cells.[9]

SARS virus genome structure and expression: The construction of the SARS viral RNA is prearranged in 13–15 open reading frames (ORF) and encompasses an overall of around 30,000 nucleotides.[10] Lately, 61 SARS-CoV sequences found from the initial, central, and dawn phases of the SARS endemic along with viral sequences of palm civets were examined.[11] Morphological distinctive of every phase were exposed, and it was established that the unbiased mutation speed of the viral genome was persistent. On the other hand, the degree of amino acid replacement of the coding sequences decelerated throughout the progression of the epidemic. The spike protein presented the sturdiest early retorts to positive selection pressures. Individual ORFs beyond fifty amino acids in translational sizes encompasses sequences responsible for structure and action of the virus which makes them interesting targets for therapeutic approaches. The assessment of the diverse SARS-CoV ORFs with those other coronaviruses discloses an accustomed design of structural gene organization with replicase and protease genes (gene\ 1a-1b) and the spike (S), envelope (E), membrane (M) and nucleocapsid (N) genes in a usual 5'- to 3' order of presence which encodes protein that may targets for novel treatment strategies.[12] Among these well-known genes, a sequence of ORFs of unidentified purpose was found: There are two ORFs located amid the spike and the envelope genes and three to five ORFs between the membrane and nucleocapsid genes. Assessment of this gene arrangement with additional known coronaviruses does not specify nearby vicinity to group II coronaviruses. Likewise, the SARS- CoV genomic sequence does not comprise a gene for hemagglutinin-esterase (HE) protein, which is existing in the majority of group II coronaviruses. 66 % of the SARS RNA is prearranged in the gene 1a-1b whose protein sequence is largely reserved amongst all coronaviruses.[13] ORFs 1a and 1b encrypt two polyproteins, pp1a and pp1ab, the later through a ribosomal frameshifting tool. These polyproteins are sorted out by virus-encoded proteinases, to give 16 distinct proteins. Maximum potential gene 1a-1b products are legitimately fine preserved amongst SARS-CoV and other coronaviruses. Numerous of their purposes are unidentified nevertheless it is recommended that they contribute to viral RNA replication, creating them probable targets for the progress of antiviral compounds. Single exclusion from the overall preservation of SARS-CoV gene 1a-1b is the shortage of a sequence coding for PL1pro, one of the binary papain-like proteinases working on cleavage spots at the N-terminus of the polyproteins. The main proteinase (Mpro), also called 3C-like protease (3CLpro), is accountable for the cleavage of all the residual proteins encoded by gene 1a-1b.[14] Sub genomic mRNAs are the source from which coronavirus genes are usually expressed. They start at various distinct sites in the genome prolonging toward the 3'-end of the virus genome sharing a mutual leader sequence at the 5'-end.[15] Certain ORFs may similarly be eccentrically translated from a single mRNA. As these rare translation mechanisms are not much effective and the gene products are scanty, these ORFs characteristically encode nonstructural proteins. While the ORFs in the midst of the structural protein genes are very assorted among the diverse coronaviruses and not vital for viral replication, current studies recommended that obliteration of non-essential ORFs might end in a augmented virulence.[16] This agrees to the fact that many of these non-essential ORFs of the novel SARS-CoV genome might be the factor behind huge SARS-CoV virulence. Up to now, five to eight subgenomic mRNAs were established in SARS-CoV-infected cells.[17] Thiel and colleagues accomplished the major thorough study on mechanisms and enzymes responsible for SARS-CoV genome expression. They found out the series of the SARSCoV isolate Frankfurt 1 and categorized the major RNA elements and protein roles behind the genome expression by describing regulatory mechanisms such as the discontinuous synthesis of eight subgenomic mRNAs, ribosomal frameshifting and post-translational proteolytic processing. Correspondingly, the actions of SARS-CoV enzymes such as the helicase or the two cysteine proteinases (PL2pro and Mpro) were depicted as they were responsible for replication, transcription or post- translational polyprotein processing. The structural proteins of the new SARS-CoV are probable objects for novel management choices. The novel SARS-CoV solitarily covers the three envelope proteins, spike (S), envelope (E), and membrane (M) but not the hemagglutinin- esterase (HE) protein, which is existing in certain coronaviruses of the additional group. The spike glycoprotein is accountable for the typical spikes of the SARS-CoV. Proteases within and outside cellular environment frequently cut the S protein into S1 and S2 domains, with the cleavage process regularly accumulating contagion of the virus. The spike proteins of coronaviruses are defined to fix to receptors of object cells and the domains accountable for receptor-binding are usually positioned in the N-terminal region of S1.[18] The spikes contains oligomeric structures, that are molded by heptad duplications of the S2 domain which also signify a union peptide sequence. This peptide is responsible for the coronavirus fusion activity. The SARS-CoV S protein appears to possess maximum of its features in conjoint with the S proteins of other coronaviruses, however it will be significant for the studying of the SARS-CoV pathogenic properties to recognize the particular circumstances of membrane merging, i.e. pH dependence and protease sensitivity, which can upsurge the contagion. The envelope and membrane proteins are integral membrane proteins and obligatory for virus assemblage.[19] An exciting property of the SARS-CoV and other coronaviruses is that it can withstand its degradation by gastrointestinal fluids regardless of the lipid enveloped structure. Molecular

mechanism behind the withstanding of the lipid virus envelope in stomach and gastrointestinal environment is uncertain and invites additional research in this extent which is significant for the regulation of upcoming SARS outbreaks.

Clinical presentation: Though human coronaviruses are typically instigating self-limiting tiny diseases, the query of possible long-lasting SARS contagions is of main prominence for a forthcoming disease governance. If the SARS-CoV reason for an enduring tenacious infection, chronic carriers may function as causes for novel SARS outbreaks. But, the detection of SARS- CoV in stool of patients for lengthier times than 6 weeks afterward hospital discharge has not been informed up to now. In distinction to usual human coronavirus infections with small lengths, greatest animal coronaviruses results in tenacious infections. As an instance, the feline coronavirus FIPV which affects animals endure to produce virus for episodes up to seven months post infection deprived of any disease indications.[20] Even though the SARS-CoV has hopped to humans it may still possess chronic infection capability.

The average incubation period of SARS was assessed to be 6.4 days. The average informed time from the start of clinical indications to the hospital admittance differ within three and five days.

[21] Main quantifiable features of the disease are in the early dated usual symptoms like chronic fever, myalgia, chills, dry cough, faintness, and headache. Additional, though fewer symptoms are sore throat, sputum production, coryza, vomiting or nausea, and diarrhea.[22] The clinical path of the disease appears to trail a bi- or triphasic array. In the initial phase viral replication and a cumulative viral load, fever, myalgia, and other systemic symptoms are seen. These indications usually recover within some days. In the next phase demonstrating an immunopathology inequity, main clinical results are oxygen desaturation, a reappearance of fever, and clinical and radiological development of severe pneumonia. This second phase is associated with a reduction in the viral burden. A mainstream of patients is ransomed in this second phase to treatment. But around 20% of patients may show advancement to the further dangerous phase. This phase is categorized by the growth of acute respiratory distress syndrome (ARDS) usually requiring mechanical ventilation.

Fast development has been completed in accepting the clinical performance of SARS in adults and children. [23] In contrast to adults, SARS appears to be fewer violent in younger children.[24] while in adults, systemic infection as well as respiratory infection may be the decree. SARS is ample slighter with non-specific cold-like signs in children younger than 12 years.[25] This may be presumably due to changes in developmental stage of the immune system. The progression of the disease in teenagers more prospective looks like adults in regarding clinical presentation and disease development. SARS may also grow unembellished illness needful intensive care and aided ventilation youngsters. Though, high-resolution computed chest tomography in clinically supposed cases may show to be an initial diagnostic assistance when first chest radiographs seemed ordinary. While fast analysis with the first-generation RT-PCR assay was not satisfactory, better RT-PCR assays may aid to identify SARS in initial stages. In this admiration, a sensitivity imminent 80% in the first 3 days of illness when achieved on nasopharyngeal aspirates may be attained. Though, it is vital to highlight that continued checking for long-term problems due to the illness is of main significance.[26]

Molecular mechanisms of SARS virus pathogenesis

Cytocidal mechanisms: Cytopathic effects such as cellular lysis or apoptosis are obvious from invitro cell line studies due to corona infections.[27] Likewise, the virus can effect in cellular fusion progressing to the establishment of syncytia. These cytopathic effects are triggered by phases of the viral replication such as the deployment of vesicles to result in viral replication complex,[28] which progress to the disturbance of Golgi complexes.[29] Similar to outcomes on other coronaviruses, SARS-CoV has been uncovered to aim in cytopathic effects in Vero cells and the creation of syncytia in lung tissues. As molecular mechanism for this fibrosis which has been stated for contagions with the coronavirus MHV, the N protein has been recognized to persuade promoter activity of the prothrombinase gene that associates with fibrin deposition.[30] **Immune-mediated mechanisms:** Following to cytocidal effects, also immune-mediated mechanisms of together the innate and adaptive immune system appear to donate to the pathogenesis of SARS-CoV infections. In this reverence, it has been revealed that in MHV infection, T cells and cytokines show a significant part in growth of the disease.[31] Also, humoral antibodies have been described to be vital in infections produced by coronaviruses such as FIPV. Here, antibodies contrary to the spike protein were exposed to be connected with the initiation of peritonitis.[32] For SARS-CoV infections, it has been stated that there appears to be an inflammatory cell influx comprising in particular of macrophages in the airways, and a huge discharge of cytokines throughout the uttermost of the infection.[33] It is therefore precarious that these immune mechanisms are auxiliarily examined on the molecular basis which gives an idea about anti-inflammatory managements that can be evaluated along with antiviral drugs for the clnical symptoms of anticipated SARS cases**.** The therapy for SARS with anti-inflammatory steroids is contentious and largely circumstantial.[34]

Mechanisms of target cell specificity: Spike (S) protein gene is the most prevalent gene, that is a game changer of SARS pathomechanisms. An individual mutation in the S gene of MHV has prominent outcome on the viral virulence and tissue tropism.[35] Likewise, mutations in

the S gene progress to the occurrence of the slightly virulent PRCV from the virulent enteric species.

[36] Additionally probably significant genes are the 'non-essential' ORFs which portrays an important difference between SARS-CoV and other coronaviruses. Likewise, further viral gene products such as the M or E proteins might have an influence on the pathogenesis of the illness because of induced interferon production.[37]

Molecular targets for antiviral treatment: Respiratory epithelial cells are the chief target cells of SARS-CoV infection along with gastrointestinal epithelial cells. Besides this, it is also located in macrophages and many other cells in blood, liver, kidney and urine. . Additionally indications of a systemic vasculitis were seen in which swelling, local fibrinoid necrosis, and penetration of blood cells out into the blood vessel membrane. Cell death and distruction of parenchymal cells of several visceral organs constitute systemic toxic changes along with disease complication.

Target cell receptors: Spike protein affinity to cellular receptors determines the target cell specificity. It is already well established that group I coronaviruses bind to aminopeptidase receptors in target cells, [38] whereas group II coronavirus such as MHV utilize carcinoembryonic antigen (CEA) receptor.[39] Lately, it was reported that a metallopeptidase, angiotensin-converting enzyme 2 (ACE2), proficiently fixes the S1 domain of the SARS-CoV S protein making it a functional receptor for SARS-CoV[40] which was likewise recognized by an additional investigation.[41] Lately, the C-type lectin CD209L was found out to be an additional human cellular glycoprotein which can act as an another receptor for SARS-CoV.[42] The disruption of virus-receptor communications might be a probable goal for anticipated therapeutic strategies.

Virus entry: The next molecular path of interesting may be the development of anti-SARS drugs is the entry of virus inside the cells. Along with plasma membrane fusion mediated entry acidic environment dependent endocytosis is also utilized by SARS-CoV.[43] Fusion peptide is anticipated to have good probability as a drug candidate in this stage.

Intracellular replication: The central dogma gene coding processes like transcription, translation and protein synthesis may be further probable target for drug development. In this regard, the RNA polymerases (SARS-CoV RdRp) might be a good target for anticipated anti- SARS therapy. A recent study[44] reported that a good anti-SARS-CoV RdRp nucleotide-analog inhibitor may show a hydrogen bonding interaction for the 2' and 3' groups of the sugar ring and C3' endo sugar puckering. Protease activity which is vital for SARS-CoV RNA replication and protein processing can be inhibited to immediately halt viral RNA synthesis. [45] Absence of the PL1pro protein is taken over by the PL2pro. Additionally SUD protein which is proposed to express in the life cycle of SARS-CoV may create an smart target for therapeutic involvement. The hexapeptidyl chloromethylketone inhibitor reported by Anand et al. in their crystallographic investigation of the TGEV Mpro was hired by Yang et al. to designate the communication of the SARS-CoV enzyme with substrate. On the foundation of their crystallographic effort, Anand et al. reported that the binding style of their hexapeptidyl chloromethylketone inhibitor to the TGEV Mpro look like that of AG7088 in complex with the 3C proteinase of human rhinovirus.[47] AG7088 is in phase II/III clinical studies as an inhalation management for the usual cold was proposed by Anand et al. to be a good starting point for the development of anti-SARS drugs

Vaccines against the SARS virus

The possible vaccine development for SARS disease was obvious as utmost patients advance an immunity counter to the SARS-CoV and endure the infection.[48]

Live-attenuated vaccines: Live-attenuated coronavirus vaccines can be produced by obliterations in "group-specific genes". The removals of these genes do not alter replication properties but weaken the virus.[49] Examples are live attenuated IBV vaccines utilized in broiler chickens.[50] However, recombination of the vaccine strain with wild type strain the great threat remains that a vaccine strain might result in reversion of a live-attenuated SARS-CoV to virulence strain.

Whole killed vaccines: This is probably safer and easy method of vaccination. In this regard, an inactivated canine coronavirus vaccine.[51] as well as SARS coronavirus (SARS-CoV) strain F69 with formaldehyde and mixed with $Al(OH)_{(3)}$[52] has been reported. Though, killed vaccines are developed for the purpose, they are not efficiently safe counter to diverse strains of coronaviruses.

Recombinant subunit vaccines: Recent studies shown that genetic engineering techniques can be used to create recombinant vaccines against SARS. [53] Library screening of eight recombinant human single- chain variable region fragments (scFvs) counter to the S1 domain of spike (S) protein of the SARS-CoV from two nonimmune human antibody libraries professionally counteracted SARS-CoV and subdued syncytia development between cells expressing the S protein and those expressing the SARS-CoV ACE2 receptor. A current reported that a specific SARS-CoV spike protein receptor binding domain aa 318–510 caused initiation of actual defusing antibodies. [54] Recombinant subunit vaccines may have a restricted capability to safeguard against SARS-CoV infections in assessment of the disparities which may ascend in the viral genome in forthcoming outbursts. Therefore it demands vaccines focusing on cell mediated immunity as good supplementary approach along with this method.

Recombinant vectored vaccines: A method by means of recombinant vaccines with DNA or a viral vector might be a hopeful target. The DNA prime or adenovirus or MVA boost tactic presently examined for a possible usage in the growth of HIV vaccines provide an efficient approach to stop SARS infections. In this reverence, a multi-valent methodology which brings together humoral and T cell-mediated host reactions appears to be the greatest striking approach. A DNA vaccine was established which covers the nucleocapsid protein gene of porcine transmissible gastroenteritis virus (PTGV which initiate mutually humoral and cellmediated immune host responses.[55] Of late, three murine studies verified that DNA vaccines coding diverse SARS-CoV antigens are proficient of producing humoral and cellular immunity and may possibly be valuable for regulation of contagion with SARS-CoV.[56] But, there also further reports in which immunization with altered vaccinia virus Ankara-based recombinant vaccine in counter to SARS was connected with augmented hepatitis in ferrets.[57]

Epitope-based vaccines: A further policy is founded on the usage of epitopes which can be carried by viral or DNA vectors. The epitope-based approach for coronavirus vaccination has now been described.[58] and the chief benefit is the deterrence of a likely vaccine relapse to virulence. Additionally prospective abolition of any areas of the viral genomic fragment that is related with possible autoimmune effects is another advantage of this strategy. Possible mutations of epitope sequence and the probable inability of this system to combat with such disparities is the possible disadvantage. Further if the SARS-CoV progresses as a highly variable virus, it will be vital to recognize extremely well-kept-up epitopes of the virus. Thus noteworthy expansion of SARS vaccines can be advanced using numerous methods which should preferably include the initiation of both humoral and cell-mediated mechanisms.

CONCLUSION

In summary, the start of the SARS epidemic in diverse continents has progressed to the creation of a fruitful laboratory network to recognize the molecular mechanisms fundamental to the SARS infection. Besides expansion of initial diagnostic examinations and good clinical management approaches, important thrust should be given to research that can provide vaccines and antiviral agents, as there is lack of a well-known therapy till date. Though the circumstances shows only a scarce minority cases, SARS leftovers a main worldwide healthiness threat which may come back anytime in a new form.

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