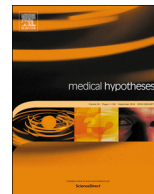




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Deceiving SARS-CoV-2 molecular-tropism clues – A combinational contemporary strategy

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ABSTRACT

Several attempts to control the dreadfulness of SARS-CoV-2 are still underway. Based on the literature evidences we have speculated a prospective contemporary remedy, which was categorized into Specificity, Remedy, and a Conveyor. In which, pros and cons were discussed and inferred the possible alternatives. (a) Specificity: Implicit to express the ACE2 receptors in conveyor cells to deceive SARS-CoV-2 from prepone targets. (b) Remedy: As depletion of pulmonary surfactants causes strong acute respiratory distress syndrome, we propose an entity of a cost-effective artificial surfactant system as a remedy to pulmonary complications. (c) Conveyor: We propose red blood cells (RBCs) as a conveyor with embedded artificial surfactant and protruding ACE2 receptors for the target-specific delivery. Overall we postulate focused insights by employing a combinational contemporary strategy to steer towards a prospective direction on combating SARS-CoV-2.

Introduction

In December 2019, a cluster of patients were dreadfully affected by pneumonia-like infection in Wuhan City, Hubei Province, China. The causative agent was found to be a novel strain of coronavirus isolated from the bronchoalveolar lavage of the patients, later named as SARS-CoV-2. SARS-CoV-2 causing COVID-19 was declared as a global pandemic as it deprived several numbers of lives across the globe and cruising human life and economy on menace [1]. The initial stage of infection evinces highly varied symptoms among the patients such as cough, fever, and sore throat. However, later stage exhibits strong acute respiratory distress syndrome (ARDS) with breathing difficulties and kindles multi-organ dysfunction [2]. The disease complexity incited from the mark of pulmonary attack, which prompted us to look at the molecular clues and to speculate a prospective contemporary remedy against SARS-CoV-2. We have convened three compelling processes i.e. Specificity, Remedy, and a Conveyor to deploy combinational contemporary strategy.

Specificity

Viruses are typically parasites, which pounce the host cell, hijacks cellular processes to develop several copies of viral progenies. The

molecular cascades progress upon viral entry into the host is complex and makes it much more complicated to develop drugs at the time of pandemic or endemic situation to comprehend the novel viruses [3]. Hopes on deploying quick vaccination as a safeguard measure were also down as recurrent of viral antigenic shift is higher. Restricting the SARS-CoV-2 attachment to the host cell shall be a simple and effectual means to avoid infection. In general, sialic acid, a small sugar moiety attached to the several proteins of the host cell serves as a receptor for viral attachment. However specific receptor domain of the host becomes the first point of viral contact, a recent report has elucidated the SARS-CoV-2 possesses a similar binding domain to that of SARS-CoV [4]. In closer prospective viral spike glycoprotein present in SARS-CoV-2 exhibit tropism towards ACE2 receptors in the host cells with 10–20-fold higher affinity than SARS-CoV [5]. The interaction studies on SARS-CoV-2 have interpolated a precise interaction with ACE2, which are largely displayed by the oral tissues and, oesophagus tract paving the viral entry points [6]. In specific, SARS-CoV-2 causes a devastating effect on type II alveolar cells which are highly rich in the ACE2 receptor [7]. Due to this, a post-infection outbreaks cascade of immune response events such as ‘Cytokine storm’, vasodilatation and, congregating heap of cells leading to dilution of pulmonary surfactants. Eventually causing decreased bloodstream gas exchange, and attributing to ARDS [8]. As to counter to this, drugs like tocilizumab were

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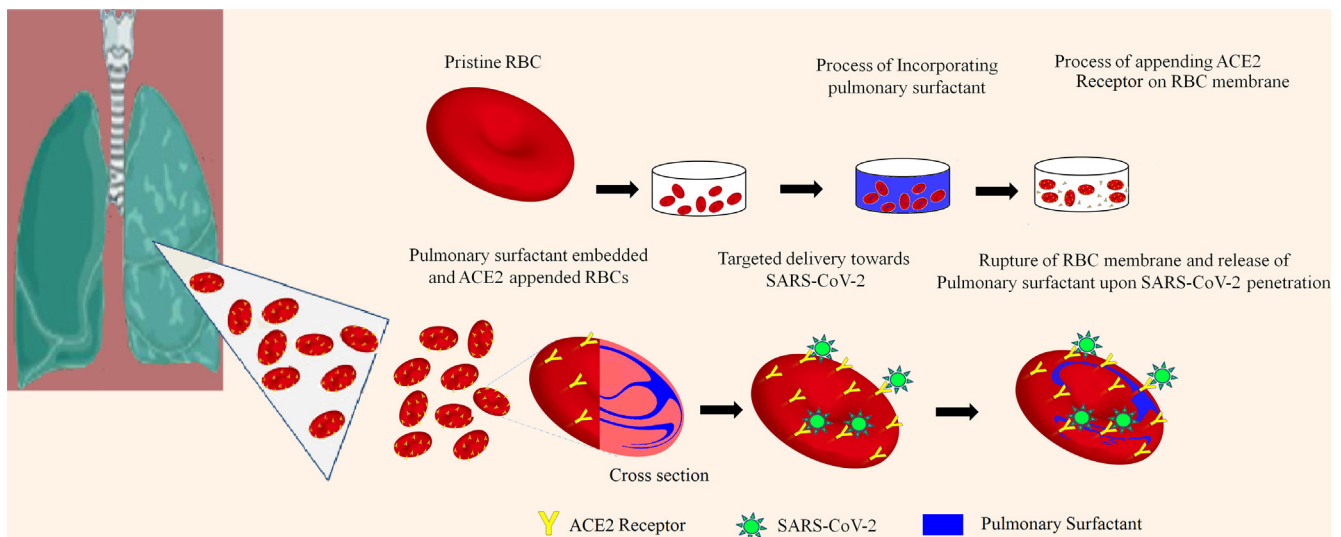


Fig. 1. . Schematic representation of fabricating artificial surfactant loaded RBCs with protruding ACE2 receptors for SARS-CoV-2 specific binding.

projected to block the IL-6 activity thereby restricting the immunological events. However, this is not an ideal solution, as these drugs restrict other immunological events causing further illness, a primitive message learned not to target host cells [9]. Moreover, viruses undergo antigenic shifts by mutation in order to evade from the antibody therapies. Also, it devastates the agonist or antagonist efforts on viral membrane receptors. Aforementioned thumps a ray of hope only on the virus receptor specificity, implicit to express the ACE2 receptors in conveyer cells, to deceive the virus from prepon targets.

Remedy

A remedy to shade away from the catastrophic events of COVID-19 is to protect alveolar collapsing by restoring the pulmonary surfactant. Pulmonary surfactant is a lipoprotein mixture, secreted into the alveolar space, to maintain the air-liquid interface. The lipoprotein mixture comprises majorly of phospholipids, in which zwitterionic saturated phosphatidylcholines are primarily responsible for decreasing the surface tension to near-zero. While, negatively charged phosphatidylglycerol, unsaturated phospholipids, hydrophobic proteins SP-B and SP-C plays a major role in re-spreading, flexibility and to maintain the surfactant film [10,11]. Several attempts were made to synthesize artificial surfactant, Dwivedi MV et al [12] have developed a reproducible model system consisting of zwitterionic 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine, negatively charged 1,2-dipalmitoyl-*sn*-glycero-3-phosphoglycerol and surfactant-specific protein SP-C to mimic the natural ones. On a commercial note, Surfacten® prepared from the extracts of the bovine lungs were used to treat ARDS in the Newborn Infants. However, the drawbacks of unknown antigenicity have restricted its usage. Further development of Surfaxin®, a protein or peptide-based surfactant consisting majorly of phospholipids dipalmitoyl-phosphatidylcholine, aliphatic acid, synthetic peptide KL4, and phosphatidylglycerol have shown promising results [13]. Nevertheless, owing to the expensiveness they could not serve the pandemic or epidemic situations to treat large population.

A prevailing measure is to develop a low-cost pulmonary surfactant mixture from less expensive sources such as egg yolk lecithin or soy lecithin (as a 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine substitute), palmitic or stearic acid (as a higher aliphatic acid substitute), triacylglycerol or cholesterol (as a neutral lipid substitute) and Hel 13-5, P24, Hel 7-11-P24, KL4 (as a peptide substitute) [14]. Further, K Yukitate et al [15] have postulated Hel 13-5 (amphipathic helical peptide), consisting a low hydrophilic and a highly hydrophobic portion enables them to stay on the membrane surface,

while stearyl group of hydrogenated soy lecithin execute a similar function of palmitoyl group in 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine, thereby convincingly exerting equivalency to the commercial ones. Besides, the introduction of D-amino acids into Hel 13-5 could improve the potency [15]. In conclusion, an entity of a cost-effective artificial surfactant system could ease the acute respiratory distress, and propound to be an effectual remedy.

Conveyor

As the target precision and the remedy were depicted, an envoy is required to do the task. We propose RBCs as an effective conveyor to sever the present essence. As they pose biocompatibility, a higher half-life period, profusely present at the site of infection, biodegradable with no harmful by-products. Most importantly RBCs are largely involved in the lung alveolar region membrane interaction for the respiration process. In addition to the candidacy of RBCs they are enucleated, cannot be prey for virus proliferation. Several attempts were made to incorporate the drugs into RBCs by employing osmosis-based methods, electroporation, Drug-induced endocytosis [16]. However, most of them propounded to create pores by disrupting the RBC membrane, which may hamper the delivery efficiency. In contrast, He H et al. [17] have developed a non-invasive encapsulation procedure by utilizing low molecular weight protamine, as a cell-penetrating peptide without causing any perturbation on the cell membrane. The above-mentioned method would be effectual and felicitous to incorporate pulmonary surfactant on to the RBCs.

On the other hand, RBCs should fulfill the feasibility of target-specific delivery. As aforementioned ACE2 as a specific receptor for the SARS-CoV-2 attachment, RBCs protruding these receptors on membranes warrant specificity. Several methods portrayed appending protein complexes or peptides on to the RBC cell wall by using chemical cross-linkers, complement fragments and, glycosylphosphatidylinositol as an anchor or biotinylation [18]. Asher DR et al [19] have reported a pinnacle approach of expressing viral receptors on RBCs, to utilize them as a viral trap against coxsackie virus. The above-mentioned methodology presents the effective way of deceiving the viruses' infectivity from the vulnerable tissues. An execution of antagonist activity to prohibit pathogenicity. In addition, RBCs displays complement receptor type 1 (CR 1 - CD35) which binds with immune components and executes antibody-mediated opsonization.

Conclusion

Herein we postulate the ideology of utilizing RBCs as a conveyor, impregnated with artificial surfactants (of a cost-effective source which may include hydrogenated soy lecithin, a higher aliphatic acid substitute, triacylglycerol or cholesterol and Hel 13–5 with D-amino acids) to restore the pulmonary surfactant concentration in the alveolar region. Further, RBCs expressing the ACE2 receptor on the cell membrane optimistically yields the target specificity towards the SARS-CoV-2. We anticipate at the site of infection SARS-CoV-2 binds and penetrates on to RBCs via protruding ACE2 receptors and releases the pulmonary surfactant (Fig. 1), Eventually executing antagonistic effect on the virus (as RBCs are enucleated) and deceived them from binding to preponderant targets (i.e. type II alveolar cells). Comprehensively, we have presented focused insights to steer towards a novel direction to control the SARS-CoV-2 infection by deploying combinational contemporary strategy. We believe our hypothesis shall throw lights to head researchers towards our perspectives with or without certain modifications in order to combat SARS-CoV-2.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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