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Hypothesis

The Role of Surface in the Pathogenesis and Treatment of COVID-19

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Abstract: Recently, an inverse relationship between incidence of COVID-19 and seasonal aerosolization of mold spores was demonstrated. Analyses of that relationship suggested mold spores compete with SARS-CoV-2 virions for a receptor on the pulmonary epithelial surface. By inference, the operative receptor was proposed to be Toll-like receptor 4, with surface-localized virions being responsible for symptomatology. In this report, the pathogenesis of COVID-19 is further developed, with a focus on a role for surfactant protein D in the process. This developed proposal provides both mechanistic understanding and suggested treatments of COVID-19.

Keywords: COVID-19; SARS-CoV-2; surface; toll-like receptor 4 (TLR4); surfactant protein D (SP-D); fibrin(ogen); COVID-19 therapy

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1. Background, Introduction, and Rationale

The SARS-CoV-2 pandemic has produced a broad spectrum of clinical presentations, from asymptomatic to fatally ill [1]. According to the model espoused here, symptomatic illness is a consequence of the complexation of virions with Toll-like receptor 4 (TLR4), a notion congruent with the findings that: (1) aerosolized mold spores, with which sharply seasonal respiratory viruses appear to compete, have, as their likely receptor, TLR4 [2], (2) TLR4-mediated signaling is upregulated in COVID-19 patients [3], (3) the SARS-CoV-2 spike protein induces pro-inflammatory responses in human leukocytes via TLR4 activation [4], (4) activated TLR4 may increase the expression of angiotensin-converting enzyme 2 (ACE2) [5], a membrane protein generally held responsible for SARS-CoV-2 entry [6], and (5) TLR4 activation is a determinant for viral entry and tropism in other seasonal respiratory viruses [7]. However, if the complexation of SARS-CoV-2 with TLR4 is responsible for symptomatic COVID-19, then, given the existence of so many asymptomatic persons, there must be an immune defense operating to prevent such complexation. And because humans are naïve to the SARS-CoV-2 virus [8], that defense must be innate.

TLR4 is expressed abundantly on the pneumocytes and alveolar macrophages that constitute the pulmonary epithelial surface [9,10]. That surface serves not only as a nidus of SARS-CoV-2 infection, but also—by means of cough—as a platform for viral transmission. In this regard, TLR4 potentiates the activity of transient receptor potential V1 (TRPV1) [11], a receptor implicated in the genesis of cough [12]. Because some seasonal respiratory viruses upregulate TRPV1 in the airways of diseased hosts [13], it seems likely that TLR4 activation benefits them by triggering cough, thereby maximizing the dissemination of viral progeny.

2. Hypothesis

Because: (1) engagement of epithelial TLR4 yields the systemic inflammation characteristic of SARS-CoV-2 infection [3], (2) TRPV1 activation can occur at the level of the pulmonary epithelium [12], and (3) the life cycle of SARS-CoV-2 necessitates persistence of

the virus on the environmental face of the pulmonary tree, it appears that the pulmonary epithelial surface is central to COVID-19 pathogenesis. This notion is further supported by the targeting of ACE2, which is expressed primarily on ciliated cells of the respiratory tract [14]. Inasmuch as mucociliary clearance is responsible for removal of virions from the epithelial surface [15], its disruption ensures accumulation and—again by means of cough—maximal aerosolization and the transmission of infectious materials. Although the virus demonstrates tissue tropism for some organs [16], early reports suggested that most hospitalized patients did not have detectable levels of viral materials in their sera [17]. Although a more recent report has demonstrated viral materials in 50–60% of sera of moderate-to-critically ill patients, no association has yet been shown between serum detection and the development of multiorgan dysfunction syndrome, either prior to admission or during the first 24 h of intensive care [18]. Overall, the evidence suggests that viremia is not a requirement for either symptomatology or severe disease.

Observations made early in the pandemic indicate that COVID-19 severity is a function of viral dose [19], an indication supported by an animal model [20] and elaborated upon by others [21]. Given both the dose dependence and the certain existence of an innate defense, symptomatic SARS-CoV-2 infection must be a consequence of a viral dose that exceeds temporally the capacity of the innate defense. Because available evidence suggests that symptomatic COVID-19 involves the engagement of TLR4 on pulmonary epithelium, the innate defense operating to prevent engagement likely involves an effector native to the pulmonary epithelial surface.

3. Discussion

Innate effectors active on pulmonary epithelium especially feature pulmonary surfactant, a lipoprotein complex comprised of 90% lipid and 10% protein. Although the biophysical function of pulmonary surfactant in preventing alveolar collapse is well-understood, the immunological function of it remains actively investigated. Essential to the operation of pulmonary surfactant are surfactant proteins A (SP-A) and D (SP-D), collagen-containing C-type lectins, or collectins, expressed constitutively by pneumocytes [22]. They are involved in the clearance of sharply seasonal respiratory viruses [23,24], ones proposed to elicit disease by engaging TLR4 [2]. More specifically, SP-A and -D have affinities for viral fusion proteins [25], e.g., the SARS-CoV-2 spike proteins [26,27].

Although both SP-A and SP-D have roles in defense against respiratory viruses, available evidence prioritizes SP-D in the defense against coronaviruses [28–30]. As examples of that priority, SP-D binds the SARS-CoV-1 spike protein with higher affinity than does SP-A [28]. That binding, in turn, promotes the recognition of SARS-CoV-1 by dendritic cells [28]. SP-D also binds the spike protein of SARS-CoV-2, preventing cellular entry and replication [29,30]. Importantly, SP-D binds TLR4 [31] and can alter its interaction with pathogen-derived ligands [32], including, perhaps, the SARS-CoV-2 spike protein [33]. Consistent with these findings, SP-D directs TLR4-mediated inflammation [34]. Finally, SP-D regulates the expression of pulmonary surfactant phospholipid [35], anionic species of which modulate interactions between pathogen-derived ligands and TLR4 [36]. Given the roles of SP-D in modulating pathogen-directed TLR4 signaling and the role, proposed here, of TLR4 activation in COVID-19, it comes as no surprise that lung biopsies of COVID-19 patients show hypertrophy and hyperplasia of type II pneumocytes [37], cells responsible for SP-D production and recycling.

Because SP-D is such a key player, it is reasonable to propose COVID-19 severity depends on SP-D availability relative to the load of SARS-CoV-2: a low dose of virion is readily neutralized, yielding the asymptomatic state, whilst a high dose of virion—one in excess of SP-D availability—is not neutralized, yielding the symptomatic state. Persons with low ambient levels of SP-D, i.e., smokers [38], the obese [39], or the pregnant [40], should be most susceptible to severe COVID-19 [41–43]. Moreover, because youths have larger intracellular and alveolar surfactant pools, as well as a much higher rate of SP-D

recycling compared to the elderly [44], advanced age, too, should be a risk factor for disease severity [45].

Regarding SP-D availability, the use of steroids to treat COVID-19 [46] is also noteworthy: the critically ill benefit most, with a trend toward harm in those less sick [47]. Interestingly, steroids upregulate SP-D production [48]. Even as corticosteroid increases SP-D levels, insulin reduces them [48], providing rationale for diabetes as a risk factor for severe COVID-19 [49].

One can imagine that, under homeostatic conditions, the ambient level of SP-D accommodates both respiration and innate immune function. However, if, for example, a SARS-CoV-2 'dose' is a large one, the availability of SP-D increases commensurately to accommodate the viral threat. The physiological response, then, is a function of both viral burden—exogenous and endogenous—and surfactant availability, Figure 1.

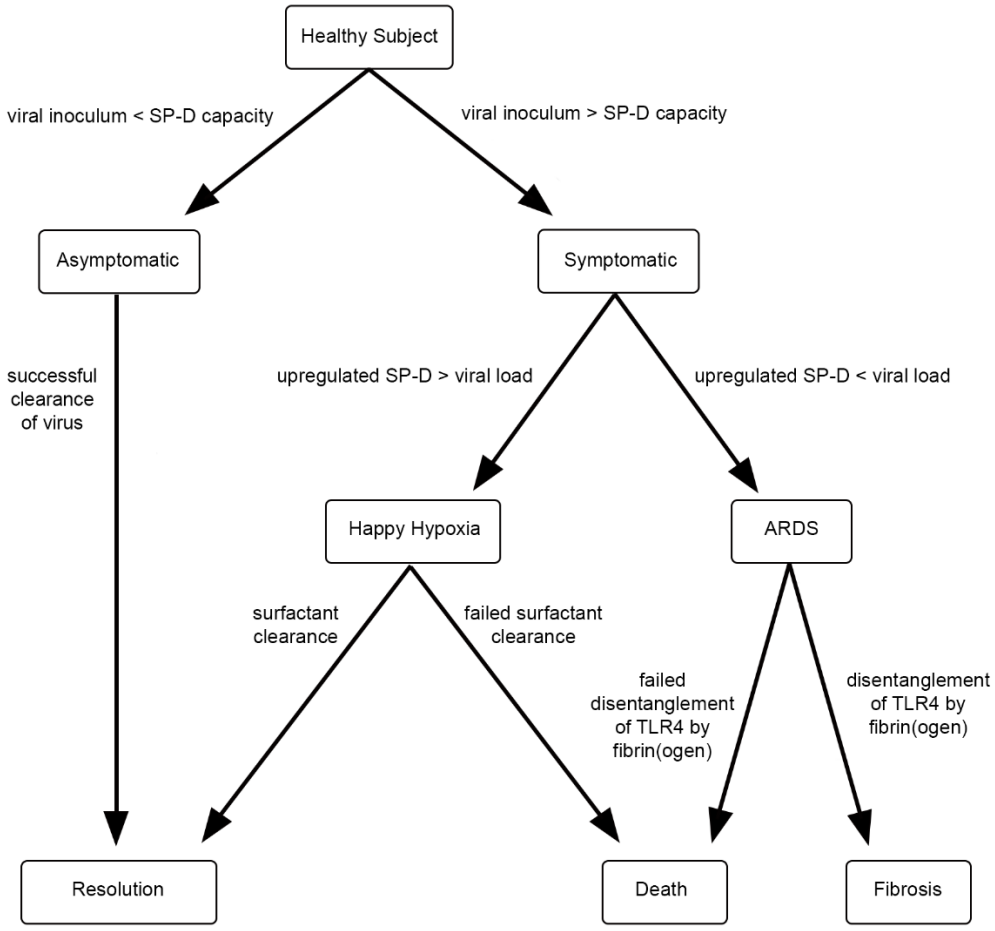

Figure 1. Proposed progression of COVID-19 pulmonary disease.

An abrupt increase of pulmonary surfactant within alveoli affects oxygenation, so symptomatic individuals tend toward 'happy hypoxia' if the compensatory response is overexuberant. In contrast, if the surfactant response is inadequate, viral activation of TLR4 continues unabated, resulting in cytokine storm and, ultimately, acute respiratory distress syndrome (ARDS). Interestingly, SARS-CoV-2-induced ARDS is attended by increased vascular permeability, with deposition of fibrin in alveolar spaces [50]. It is tempting to speculate that fibrin(ogen), a ligand of TLR4 [51], competes with virions for that receptor, thereby mitigating viral infectivity. However, because many SARS-CoV-2 patients in ARDS progress to pulmonary fibrosis [52,53], such a measure, if operative, is costly.

Not only serologic, but also radiographic, findings implicate abnormal levels of pulmonary surfactant in severe COVID-19. The rare entity, pulmonary alveolar proteinosis (PAP), involves the impaired clearance of surfactant from pulmonary epithelium [54]. A characteristic feature is the computed tomographic finding of interlobular septal thickening in a 'crazy paving' pattern [54]. This finding is also characteristic of COVID-19 [55]. Although the mechanisms responsible may be different, the net result in both cases is the increased deposition of surfactant on pulmonary epithelium. That increased deposition, in turn, affects surface tension, the consequences of which are consolidation and decreased oxygenation, manifesting as dyspnea and hypoxia.

4. Closing

Just as does treatment of PAP, treatment of severe COVID-19 should address disease pathology where it occurs, on the environmental-facing surface of pulmonary epithelium. Symptomatic COVID-19 due to unmitigated TLR4 activation might be best treated using nebulized materials, e.g., recombinant surfactant proteins or, perhaps, TLR4 antagonists or even the C-terminus of the fibrinogen γ-chain [56–59]. Because severe hypoxia associated with COVID-19 may be derived from either of two mechanisms, therapy should be tailored accordingly. For the non-inflammatory hypoxic state, due to upregulated surfactant production and the accumulation of virion–surfactant protein aggregates, serial whole lung lavage might prove therapeutic. Although such therapy has not yet been standardized for PAP, various protocols are well-tolerated and routine treatment for the condition [54]. Because critically ill COVID-19 patients might not tolerate whole lung lavage, their therapy could proceed incrementally, via the sequential decontamination of individual lobes. Those whose pulmonary function has already been circumvented by extracorporeal membrane oxygenation might be suited for more aggressive lavage therapy. For the inflammatory hypoxic state involving unmitigated TLR4 activation and ARDS, lavage fluid could be supplemented with viral binding agents or TLR4 antagonists. Differentiating between the two states should be possible by quantifying downstream markers of TLR4 activation, such as IL-6 [60], the plasma levels of which have prognostic value [61]. Because the pathophysiology of other sharply seasonal viruses relates to TLR4 engagement, their therapies might exploit similar approaches.

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