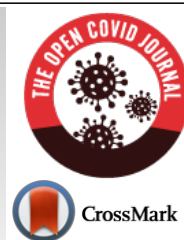




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PERSPECTIVE ARTICLE

Bacterial Quorum-sensing Signal Molecules as Potential Inhibitors of Cytokine Storms in COVID-19

Ramakrishnan Sitaraman^{1,*}

¹Department of Biotechnology, TERI School of Advanced Studies, 10 Institutional Area, Vasant Kunj, New Delhi-110070, India

Abstract:

In this perspective article, we suggest that bacterial quorum-sensing signal molecules (QSSMs) be systematically screened and evaluated for their ability to exert anti-inflammatory activity in the context of COVID-19-associated cytokine storms and other hyper-inflammatory conditions. Rapid and relevant *in vitro* screening of these and other compounds (natural or synthetic) can be accomplished by a careful choice of assay systems that are relevant to the disease context. Some lines of evidence indicating the utility of using such an approach, its potential benefits and risks during actual usage, as well as avenues for further research, are discussed.

Keywords: SARS-CoV-2, Inflammation, QSSM, Immunomodulation, Anti-inflammatory, COVID-19, Cytokine release syndrome, Pro-inflammatory.

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1. INTRODUCTION

The greater clinical severity of a proportion of COVID-19 (Coronavirus disease 2019) cases arising from infection with the SARS-CoV-2 (severe acute respiratory disease coronavirus 2) virus originating from Wuhan, China, is attributable to hyper-inflammatory responses. Hyperinflammation is characterized by the increased production of pro-inflammatory cytokines, a phenomenon that is termed “cytokine storm” or “cytokine release syndrome” (recently reviewed by Fajgenbaum and June) [1]. While different viral infections, including corona and influenza viruses, may elicit cytokine storms, a systematic review of human patient data by Olbei *et al.* (2021) determined that the precise profile of inflammatory and non-inflammatory cytokines consistently induced or repressed is dependent on the infecting virus. Specifically, general increases in the levels of the cytokines IL-18, CXCL10, and IL-6 (pro-inflammatory) and IL-1RA (anti-inflammatory) were observed. Key anti-inflammatory cytokines such as IL-10 and IL-2 exhibited mixed trends, while IL-4 exhibited no increase [2]. Therapeutic strategies proposed or tested to minimize tissue damage during COVID-19-induced cytokine storms have focused on the administration of drugs (notably steroids) that have a general anti-inflammatory effect or target specific cytokines [1, 3].

Prokaryotes (bacteria and archaea) colonising multicellular organisms (including humans) as commensals, pathogens, or mutualists have evolved various strategies to modulate the host's immune defenses, whether innate or adaptive and thereby persist for extended lengths of time within the host. One functional class of molecules secreted by prokaryotes are Quorum-Sensing Signal Molecules (QSSMs), whose concentration in the environment serves as a proxy for cell numbers for microbes of a given species or even across species. This is analogous to stipulating a ‘quorum’ wherein collective decisions require the presence and affirmation of a minimum number of individuals to be legally valid, hence the name. Microbes of the same or different species respond physiologically to concentrations of QSSMs above a certain threshold. The best-studied of these molecules are either oligopeptides (produced by Gram-positive bacteria) or acyl-homoserine lactones (produced by Gram-negative bacteria, generically termed autoinducer – 1 (AI-1)) or autoinducer – 2 (AI-2, produced by both Gram-positive and -negative bacteria). Other notable categories of molecules known to serve as QSSMs are alkyl 4-quinolones, diffusible signal factors (fatty acids), and diketopiperazines. It is notable that the sensing of microbial QSSMs and mounting physiological responses to them occur not only within and across species but also across kingdoms [4, 5].

I suggest that microbe-derived non-peptide QSSMs, particularly those derived from bacteria (or other microbes) that establish a chronic infection, be screened as potential anti-

* Address correspondence to this author at the Department of Biotechnology, TERI School of Advanced Studies, 10 Institutional Area, Vasant Kunj, New Delhi, 110070, India; Tel: 91-11-71800222; Fax: 91-11-2612874; E-mail: minraj@gmail.com

inflammatory agents. Current strategies to suppress cytokine storms have not taken this class of molecules into serious consideration. Additionally, most translational research on QSSMs focuses on controlling and eliminating bacterial (and fungal) infections by disrupting key QSSMs (“quorum quenching”) elaborated by the pathogen, as is evident from reviews of patents granted in the field [6 - 8]. However, it might be equally beneficial to examine the immunomodulatory effects of QSSMs in the context of dampening inflammatory responses and determine whether some of these molecules could supplement or substitute for currently used steroids such as dexamethasone that are often accompanied by undesirable side-effects [9].

2. ANTI-INFLAMMATORY EFFECTS OF QSSMs

There are relatively few reports in the literature regarding the specifically immunosuppressive effects of QSSMs, as most studies are conducted in the context of infectious diseases wherein inflammation to eliminate the pathogen is the actual and/or desired readout. Bandyopadhyaya *et al.* (2016) demonstrated that 2-acetoamino-1-phenylethan-1-one (2-AA) produced by *Pseudomonas aeruginosa* induced a tolerant state in human and murine cell lines (THP-1 monocytes and RAW264.7 macrophages, respectively) wherein pre-exposure attenuated induction of TNF- α , IL-1 β , and MCP-1. A similar effect was seen when primary human and murine macrophages were studied. This outcome was found to be mediated epigenetically via induction of histone demethylation of target genes by the histone deacetylase HDAC1, but the signalling cascade that leads to this effect is unknown. Most tellingly, pre-treatment of mice with 2-AA followed by a burn-*P. aeruginosa* infection protocol improved survival outcomes post-infection, which benefit was abrogated on the administration of the specific HDAC1 inhibitor trichostatin A [10]. Similarly, *N*-(3-oxododecanoyl) homoserine lactone (3-oxo-C12-HSL) from *P. aeruginosa* was found to reduce the production of pro-inflammatory cytokines IL-6, TNF- α and IFN- γ , while concomitantly elevating the production of the anti-inflammatory cytokines IL-10 and IL-4 in a (human-derived) mixed lymphocyte dendritic cell (MLDR) reaction [11]. TNF- α production by human peripheral blood mononuclear cells after bacterial lipopolysaccharide (LPS) stimulation was attenuated by the application of increasing concentrations of 3-oxo-C12-HSL [12]. More interestingly, 3-oxo-C12-HSL was also found to increase the production of the anti-inflammatory cytokine IL-10 in LPS-stimulated RAW264.7 cells [13]. Synthetic analogues of 3-oxo-C12-HSL have also been tested for anti-inflammatory effects on Caco-2 and RAW264.7 cell lines, with promising results showing a reduction in IL-6 and IL-8 in pre-stimulated cells [14]. Finally, Okamoto *et al.* (2012) determined using the human intestinal cell line Caco2/_{bbe} that application of the *Bacillus subtilis* QSSM competence and sporulation factor (a peptide) resulted in the induction of IL-10 (an anti-inflammatory cytokine) and reduced the release of the pro-inflammatory cytokines IL-6, CXCL-1 and IL-4 [15]. Studies in mice have also indicated that QSSMs can exert immunosuppressive effects in the context of type I diabetes [16, 17], which is an autoimmune disorder.

3. MECHANISTIC INSIGHTS INTO THE MODE OF ACTION OF QSSMs

The molecular mechanisms by which QSSMs exert the observed effects on eukaryotic cells are only beginning to be unravelled. The family of G-protein coupled bitter taste receptors (T2Rs or Tas2Rs) have been found to be involved in innate immunity in extra-oral tissues, including respiratory tissues [18, 19]. For example, acyl-homoserine lactones secreted by *Pseudomonas aeruginosa* (PA) bind to T2R38 [20, 21] which, in turn, activates a G-protein-mediated signalling cascade that activates the phospholipase C isoform β (PLC β 2), resulting in the production of the second messenger inositol 1,4,5-trisphosphate (IP3). IP3 induces Ca²⁺ release from the intracellular store, and the cascade culminates in bactericidal levels of NO production [22]. Pundir *et al.* (2019) determined that the human mast cell-specific G-protein coupled receptor MRGPRX2 could be activated by peptide QSSMs from Gram-positive bacteria, leading to mast cell degranulation and release of reactive oxygen species, TNF- α and prostaglandin D₂ [23]. Note, however, that these are instances of essentially pro-inflammatory responses.

A recent study of the cytoplasmic aryl hydrocarbon receptors (AhRs or AHRs) has indicated that they are able to sense QSSMs during bacterial infections and determine immunological outcomes. Most importantly, it was discovered that *N*-(3-oxododecanoyl)-L-homoserine lactone and 4-hydroxy-2-heptylquinoline from PA could inhibit AhR activation by 1-hydroxyphenazine (a virulence factor produced by PA) in cell lines with no appreciable loss of cell viability. More interestingly, AhR activation *in vivo* in zebrafish and mice is tuned to the growth phase of PA, with host defenses being activated only at high bacterial densities, indicating active sensing of QSSM levels [24]. AhRs belong to the superfamily of basic-helix-loop-helix/PER-ARNT-SIM (PAS) transcription factors and are expressed in various tissues, including lungs. Inactive AhR resides in the cytoplasm bound to chaperones such as Hsp90. Upon binding to a suitable ligand that could be one of several types of synthetic as well as naturally occurring molecules such as pollutants, toxins, bacterial metabolites, *etc.*, it undergoes a conformational change, dissociates from the bound chaperones, and translocates to the nucleus. Within the nucleus, it forms a complex with the AHR nuclear translocator (AHRNT); this complex can bind DNA and induce or inhibit several target genes. Among those genes induced is the pro-inflammatory cytokine IL-6 [25]. Recently, it was found that SARS-CoV-2 infection can result in increased mucus secretion (and eventually hypoxia) due to increased activation of AhR as a result of the interferon response, which is the normal innate immune response to viral infection [26]. Furthermore, murine coronavirus can directly activate AhR bypassing cellular controls [27]. Therefore, given the critical role of AhR activation in precipitating inflammatory states, downregulation of AhR has been proposed as a therapeutic strategy [28], and the potential of bacterial QSSMs to do so could be explored in greater detail.

CONCLUSION

Given the foregoing account, it is evident that suitable mammalian/human immune primary cells and cell lines can be experimentally stimulated to produce cytokines such as IL-6

[29], IL-18 [30], and CXCL10 [31] that seem to be elevated in SARS-CoV-2 infections [2]. *In vitro* cytokine assays can be used to evaluate the ability of QSSMs to lower levels of pro-inflammatory cytokines and/or elevate levels of anti-inflammatory cytokines. Such assays could also be used to test QSSMs for the ability to render cells refractory to immune hyper-stimulation upon subsequent exposure to pyrogenic molecules such as bacterial lipopolysaccharide (LPS). This screening method may be used to test QSSMs for their immunosuppressive capabilities in COVID-19 as well as other inflammatory diseases if enough *a priori* information on the relevant cytokines and cell/tissue types to be targeted is available [31].

To sum up, receptors for bacterial QSSMs exist on human cells that can, in principle, be modulated by QSSMs to induce pro- or anti-inflammatory states. More specifically, QSSMs could be screened for their ability to target AhR (see the previous section) and exert an antagonistic anti-inflammatory during COVID-19, which could then form the basis of future therapeutic strategies. As a receptor class that binds to diverse types of compounds ranging from xenobiotics to bacterial metabolites, AhR is a suitable target for anti-inflammatory intervention. The availability of databases of both non-peptide [32] and peptide [33] QSSMs can inform efforts to systematically screen QSSMs for specific physiological effects, including, but not limited to, the inhibition of inflammatory processes. One advantage of using non-peptide QSSMs would be that similar molecules are produced by the resident microbiota, potentially minimizing the chances of adverse side-effects or of developing allergies. A collateral benefit of using non-peptide QSSMs to mitigate cytokine storms is that their likely low antigenicity considerably reduces the risk of adverse immune reactions after subsequent administrations of the same molecule. It is notable that the *P. aeruginosa* QSSM *N*-(3-oxododecanoyl)-L-homoserine lactone conjugated to bovine serum albumin was found to elicit protective antibodies in one study on mice [34]. But the requirement for conjugation to a protein underscores its intrinsically low antigenicity. It has also been suggested that the ability of probiotics to alleviate COVID-19 symptoms by reducing inflammation could be examined [35]. However, introducing large numbers of live organisms into patients already suffering extreme immune dysfunction exemplified by cytokine storms raises serious safety concerns. Furthermore, probiotics can serve as a reservoir of antibiotic resistance determinants and can occasionally result in opportunistic infections [36]. The strategy of testing QSSMs proposed here can be extended to screen any molecule, whether natural or synthetic, for anti-inflammatory activity in a variety of disease contexts, provided an appropriate assay system is available. This would facilitate the identification and isolation of specific immunomodulatory molecules elaborated by probiotics and would obviate the need to administer live organisms.

All the same, it must be borne in mind that the same QSSM can have different effects on different host cell types [37, 38]. A therapeutic strategy would need to consider the key cell types influencing clinical outcomes in the organ(s) most affected. Furthermore, the presence of lactonases among the resident microbiota and the production of paraoxonases by the human (mammalian) host might limit the persistence time of such molecules within the system, complicating the determination of an appropriate dosing regimen. Strategies to

deliver the QSSMs to the affected site would also have to be devised depending on the site location. A concomitant concern would be the effect of such microbial signaling molecules on the resident microbiota and whether such administration could trigger a problematic dysbiosis or an increase in opportunistic bacterial infections. In conclusion, QSSMs (or their synthetic derivatives) in isolation or combination with more conventional anti-inflammatory agents could potentially help reduce or eliminate unpleasant side effects associated with current therapies.

LIST OF ABBREVIATIONS

COVID-19	= Coronavirus Disease 2019
SARS-CoV-2	= Severe Acute Respiratory Syndrome Coronavirus 2
QSSM	= Quorum-Sensing Signal Molecule
LPS	= Lipopolysaccharide
AhR/AHR	= Aryl hydrocarbon receptor

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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