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INSIGHTS INTO THE IMMUNE RESPONSE TO VIRAL INFECTION OF "COVID-19"

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Insights into the Immune Response to Viral Infection of "COVID-19"

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Coronavirus infections disease 2019 (COVID-19), caused by "severe acute respiratory syndrome coronavirus type 2" (SARS-CoV-2), is currently a threat to global public health. In order to understand how the viral behavior and host response to SARS-CoV-2 infection, this article sheds the light on some topics including the cytokine and chemokine response patterns and the characterization of the transcriptional response to infection, which constitute a key role in immunity and immunopathology during viral infections; type I and III interferon, serving as antiviral protection, and dysregulation of interleukin-6 signaling, which is associated with inflammatory and progression of pathological conditions of COVID-19. Finally, a hypothetical approach for therapeutic intervention targeting COVID-19 is presented, which based on multifunctional hybrid nanoparticles conjugated with two different aptamers.

Keywords: COVID-19, Virus-induced signaling events, Interferons, Interleukin 6, Neutralizing antibodies, Multifunctional hybrid nanoparticles.

1. Introduction

The outbreak of coronavirus infections disease 2019 (COVID-19) has evoked a panic of humans because of its highly contagious among the human population around the globe and its serious development within the body leading to inflammation and pneumonia. The threat COVID-19 poses to global public health is more serious than that presented by other coronaviruses. This is related to the high case-fatality rate. Among the four common coronavirus genera (alpha, beta, gamma, and delta) this pandemic is related to betacoronavirus genus. COVID-19 is an acute infection of the respiratory tract caused by "severe acute respiratory syndrome coronavirus type 2" (SARS-CoV-2), which is a member of single-stranded positive-sense RNA coronavirus family ((+)ssRNA virus).[1] (+)ssRNA virus is a virus that uses an enveloped positive sense, single-stranded RNA as its genetic material, *i.e.* the viral capsid is enclosed within a lipid bilayer and the viral genome encodes viral protein. The positive-sense viral RNA genome can serve as messenger RNA and can be translated into protein in the host cell. Development of SARS-CoV-2 infection causes acute respiratory distress syndrome, and in more severe cases can be worsened in a short period of time leading to multiple organ failure.[2]

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This article discusses the cytokine and chemokine response patterns and the characterization of the transcriptional response to infection, which constitute a key role in immunity and immunopathology during viral infections. In this regard, both of type I and III interferon and signaling of interleukin-6 are briefly discussed. Finally, a proposed approach for therapeutic intervention targeting COVID-19 is presented, which based on multifunctional hybrid nanoparticles conjugated with two different aptamers.

2. The host response to SARS-CoV-2

In order to understand the molecular basis of COVID-19, it is important to shed the light on the viral behavior and host response following SARS-CoV-2 infection with regard to the cytokine and chemokine response pattern in different stages of the progress of this virus and the characterization of the transcriptional response to infection.

Cytokines and chemokines have been thought to play an important role in immunity and immune-pathology during viral infections.[3] Evidences have shown that cytokine-mediated inflammatory responses have been associated with pulmonary inflammation and acute lung injury in SARS-CoV-2 infection.[4] Furthermore, it has been reported that proinflammatory cytokine and chemokine production induced by the virus were observed in both of symptomatic and asymptomatic cases, and returned to normal after recovery. The data have shown abnormally elevated IP-10, IL-10, and IL-7 levels in these patients. As disease progresses, an overwhelming induction of IL-6, IL-7, IL-10, IL-18, G-CSF, M-CSF, IP-10, MCP-1, MCP-3, MIG, and MIP-1α was found to be associated with the severity of COVID-19.[5]

The differentiation of naïve CD4+ T cells into effector and memory subsets is one of the most fundamental facets of T-cell–mediated immunity.[6] Besides, the balance between the naïve and memory CD4+ T cells is crucial for maintaining an efficient immune response. Evidences have revealed that both helper T (Th) cells and suppressor T cells in patients with COVID-19 were below normal levels, with lower levels of Th cells in the severe cases.[7] The percentage of naïve Th cells increased and memory Th cells decreased in severe cases. Such a higher naïve-to-memory CD4+ T-cell ratio in severe cases indicated that the immune system in the severe infection cases was impaired more severely. Additionally, the lower levels of regulatory T cells, especially induced regulatory T cells, which have a key role in restraining allergic inflammation at mucosal surfaces, was demonstrated in the infected patients, especially in the severe cases.[7]

Defining the host response to SARS-CoV-2, there are data indicating that the virus infection drives a lower antiviral transcriptional response that is marked by low levels of type I and III interferons (IFN-I and IFN III) and elevated chemokines and high expression of IL-6 compared to other highly pathogenic coronaviruses and common respiratory viruses.[8] In addition, these data showed that neutrophils could contribute to the disease observed in COVID-19 patients.[7,8] The restricted immune response in the age population prevents the inhibition of viral spread at early stages of infection, further exacerbating the morbidity and mortality observed for the age cases.[8]

Evidences have revealed that the cell surface protein ACE2 and the protease TMPRSS2 were expressed in sustentacular cells of the olfactory epithelium but not, or much less, in most olfactory receptor neurons. Consequently, SARS-CoV-2 virus affects the function of olfactory receptor neurons through accumulation

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firstly in sustentacular cells, by interfering with their metabolism. The damage to these cells caused by the virus impairs smell sensation as the case in COVID-19 patients.[9]

In view of the low levels of type I and III interferons accompanied with high expression of interleukin 6 (IL-6) as critical components of innate immune response and the transition to effective adaptive immunity, it is important to highlight the role of these cytokines.

3. Type I and III interferon (IFN)

During viral infection, type I and III IFN proteins are induced in order to confer antiviral protection on the target cells. Type I IFN is encoded by a single IFN-β gene, a dozen IFN-α, and various related genes and pseudogenes depending on species. Whereas type III IFN comprises of three genes (IFN-λ1, λ2, and λ3), and is encoded on a different chromosome, and is related in structure and sequence to the cytokine interleukin 10 (IL-10). The level of control of IFN production depends mainly on transcriptional control. In the absence of stimulus, IFN gene expression is maintained at near silent levels. Gene repression is provided through both a repressed chromatin configuration involving occluding nucleosome and the recruitment of gene-specific transcriptional repressors.[10,11] A number of transcriptional repressors have been implicated in negative regulation, including IRF2, a factor that binds to one of the positive regulatory elements in the IFN-α and –β promoters. Following stimulation, IRF2 is replaced by an activating IRF protein such as IRF3 or IRF7. BLIMP or PRDI-BFI is another negatively acting transcriptional repressor associated with the INF-β promoter, and acts as a post-induction repressor to attenuate IFN-β gene expression.

The induction of type I IFN gene requires recruitment of sequence-specific transcription factors that are activated by phosphorylation in response to signaling cascades stimulated during viral infection. The IFN-β promotor contains four positive regulatory domains (PRD I-IV), which are occupied by overlapping transcription factor complexes.[10,12] The binding of each of these components in the correct orientation and location as well as in orchestrated temporal sequences leads to activation of the INF-β promoter in response to viral infection.[10,13] A higher order assembly of multiple transcription factor components for effective transcription of the INF-β gene triggers its expression in a stochastic fashion in minority of virus-infected cells.[14] Notably, in virus-induced activation of IFN-β promoter, NF-κB, IRF3 and IRF7 are considered as vital transcription factors that play essential and non-overlapping roles.[10] The IFN-α genes show a similar regulatory architecture. The IFN-λ genes display IRF and NF-κB binding sites at their promoters, which subtle changes in their expression or function can lead to profound effect on viral infection.

3.1. Virus-induce signaling pathways

Sensing microbial pathogens is the first step required to initiate and modulate the IFN-dependent innate immune response. In fact, cellular sensors responsible for pathogen recognition can be classified into four groups.[10] In this regard, both of cytoplasmic RIG-like receptors (RLR) and membrane bound Toll-like receptors (TLR) are briefly further highlighted.

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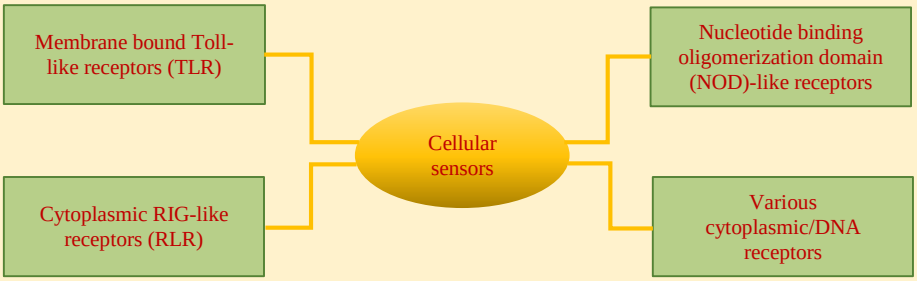

Cytoplasmic RLR signaling pathway

Sensors of RNA virus infection are activated by the RLR proteins, which are a group of three cytosolic RNA helicases, namely, retinoic acid inducible gen (RIG-1); melanoma differentiation-associated gen 5 (MDA5); and LGP2. RIG-1 and MDA5 recognize the presence of primarily 5`-phosphorylated RNA and long double-stranded RNA, respectively, whereas LGP2 play an assistant role in RNA recognition.[10,15] They possess an N-terminal caspase activation and recruitment (CARD) domain (a central DExD/H-box helicase domain), and C-terminal RNA-binding domain (CTD). During viral infection, the CTD of RIG-1/MDA5 binds to viral RNA, leading to activation of CARD domains followed by RIG-1 promoting the formation of large prion-like MAVS (mitochondrial antiviral signaling) that aggregates on the mitochondrial membrane, which trigger downstream signaling.[10,16,17] This auto-propagatory conformational switch may be considered as a remarkable hallmark for high sensitivity and amplification to antiviral responses.

Signaling pathway of TLRs

The immune receptors, toll-like receptors (TLRs) are key receptors in innate immune cells such as dentritic cells. They act as the primary viral sensors for IFN production in plasmacytoid dentritic cells (pDC) (cells that are capable of producing very high levels of IFN and are critical for antiviral defense).[18] In the presence of viral RNA, it is recognized by TLRs that are expressed on the membranes of leukocytes. Upon activation, TLRs recruit adaptor proteins (proteins that mediate other protein-protein interactions) within the cytosol of the immune cell in order to propagate the antigen-induced signal transduction pathway. The adaptor proteins are responsible for the subsequent activation of other downstream proteins such as protein kinases that further amplify the signal and ultimately result in the upregulation or suppression of genes that orchestrate inflammatory response and other transcriptional events.

3.2. The antiviral response

Type I (IFN-α and β) and Type III (IFN-λ) IFNs are secreted by infected cells or stimulated pDCs, which bind distinct receptors on target cells. Such binding to their respective receptors results in activation of the

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transcriptional interferon-stimulated gene factor 3 (ISGF3) (composed of STAT1*, STAT2, and IRF9), and the transcriptional activation of a common set of interferon stimulated genes (ISGs). It is the proteins encoded by ISCs that mediate the antiviral, immunestimulatory, and antiproliferative effects of these cytokines.[18]

The most prominent difference between IFN-α/β and IFN-λ action is related to receptor distribution. The IFN-α/β receptor is present on all cells, and all nucleated cells can produce and respond to it. Whereas expression of IFNLR chain of the IFN-λ receptor is limited to epithelial cells. Indeed, organs with a high epithelial content such as intestine, skin or lungs are the most responsive to IFN-λ and expressed the higher amounts of IFN-λ receptor.[19] In addition, several studies have demonstrated that IFN-λ is preferentially induced by viral infections in epithelial cells of both respiratory and gastrointestinal tracts, and it has potent antiviral activity in epithelial tissues.[20-21] For example, evidences have shown that IFN-λ is preferentially induced by influenza A virus infection, and that it has potent antiviral activity in lung epithelium.[22] These evidences have revealed that the diversity of IFN types play a critical role in the antimicrobial host defense enabling their enhanced production and prolonged action in the anatomic compartments that are open to the outside of the body and therefore act as main portals for pathogen entry.

4. Signaling of Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is an important cytokine with various physiological functions such as immune cell proliferation and differentiation, and tissue homeostasis. However, dysregulation of IL-6 signaling is associated with inflammatory and progression of certain pathological conditions, such as rheumatoid arthritis, and cancer.[23,24] IL-6 is produced by anti-presenting cells (APCs) and non-hematopoietic cells following external stimuli, serving as an important mediator of the inflammatory response and the major regulator of hepatic production of acute phase proteins, such as fibrinogen and hepcidin (a master regulator of iron metabolism).[25-27] In addition, IL-6 is a potent growth factor for B cells and inducer of plasma cell differentiation, and antibody production.[26] Excess IL-6 causes a decrease in circulating triglycerides.[28]

IL-6 binds to its α-receptor (IL-6R) that leads to the recruitment of glycoprotein 130 (gp130), which is the signal-transducing β-receptor.[29] Such binding is followed by an association with gp130 expressed on the surface of the cell. Consequently, IL-6 is secreted from various activated immune cells, including dendritic cells and macrophages after engagement with toll-like receptors (TLRs) and non-immune cells. For example, the binding of IL-6 to IL-6R expressed on dendritic cells induces intracellular signaling from gp130 expressed on $CD4^+$ T cells to generate pathogenic T helper 17 (Th17) cells.[30]

In fact, there are four signaling pathways that can be induced by IL-6 and subsequent STAT3 phosphorylation: i) classic signaling refers to cells expressing the IL-6R together with gp130; ii) trans-signaling depends on proteolytic release of the IL-6R which in complex with IL-6 can bind and stimulate

*The effects of signal transducer and activator of transcription (STAT) activation: STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers that translocate to the cell nucleus where they act as transcription activators. Stat 1 activation is pro-inflammatory and pro-apoptotic, Stat 3 activation antagonizes transcriptional activation by Stat 1, both Stat 3 and Stat 5 activation promote cell proliferation, whereas Stat 4 activation is anti-apoptotic and essential for Th1 differentiation.[10] Stat 2 activation forms a complex with stat 1 and IFN regulating factor proteins (IRF9), which acts as transactivator, but lacks the ability to bind DNA directly.

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gp130 on cells lacking the IL-6R; iii) trans-presentation, which can act on the same or neighboring cells and even between distinct tissues and organs[31]; and iv) joint reconstituted signaling (JRS), which depends on full-length membrane-bound IL-6R released via extracellular vesicles (EVs), that can fuse with distant cells, and thus, enables long term signaling on cells that do not express the IL-6R.[32]

NF-kB plays an important role in the induction of IL-6 transcription, and NF-kB-activating factors efficiently induce IL-6 transcription.[33] There is a synergistic effect of NF-κB and STAT3 on IL-6 transcription in non-immune cells, which promote pro-inflammatory mediators from these cells in the presence of a IL-6 signal.[34] This synergism is known as the "inflammation amplifier".

5. Proposed approach for therapeutic intervention targeting COVID-19

Based on the aforementioned discussion, it appears that neutralizing or even blockade of IL-6 in combination with enhancing type III IFN (IFN-λ) may be a viable therapeutic intervention for COVID-19. I speculate that neutralizing of IL-6 may lead to its ablation in dendritic or macrophage cell lineage, which, in turn, may suppress lung inflammation. Furthermore, substantial studies have revealed that the high epithelial content of lungs makes this organ the most responsive to IFN-λ, and the viral lung infection is dramatically suppressed by IFN-λ.[19-22] For instance, evidences have revealed that the IFN-λ–mediated innate immune response is crucial for the clearance of influenza A virus from the respiratory tract, and the absence of IFN-λ resulted in the dysregulation of IFN-stimulated genes (ISGs) transcription and an inefficient innate immune response, which aggravated acute influenza A virus lung infection *in vivo*.[35] Consequently, it is proposed that the antiviral activity of IFN-λ is superior as a therapeutic candidate to control acute influenza viral lung infection.[35]

In view of this conclusion, it should adapt appropriate monoclonal antibodies or small molecules that aim to realize a dual function to neutralize IL-6 or IL-6R and to enhance IFN-λ. Surveys of available approved drugs are, therefore, of importance in that they can help to underscore the scope and generality of immunomodulating properties of the desired therapy. At this juncture, it would be tantalizingly close to the target therapy and need only to formulate the final agent and then to adjust its administration.

Screening some of the approved drugs point out that, there are monoclonal antibodies directed at the IL-6 neutralization such as siltuximab (for the treatment of the autoimmune castleman diease),[24] targeting IL-6R such as tocilizumab (for treatment of different forms of arthritis),[23] or sarilumab (which binds to both soluble and membrane bound IL-6R and blocks IL-6 signaling, and used as therapeutic agent for rheumatoid arthritis)[36]. As a small molecule, pomalidomide **1** acts as upregulation of IFN-λ, IL-2 and IL-10, as well as downregulation of IL-6, and used as a treatment for relapsed and refractory multiple myeloma (Figure 1).[37] Besides, LMT-28 **2** is IL-6 inhibitor that functions through direct binding to gp130 (a circulating form of receptor subunit for IL-6 cytokine family, and has proved to play a crucial role in several pathogens).[38] LMT-28 shows low toxicity and selectively inhibits IL-6 induced phosphorylation of STAT3, JAK2, and gp130 (Figure 1).[39]

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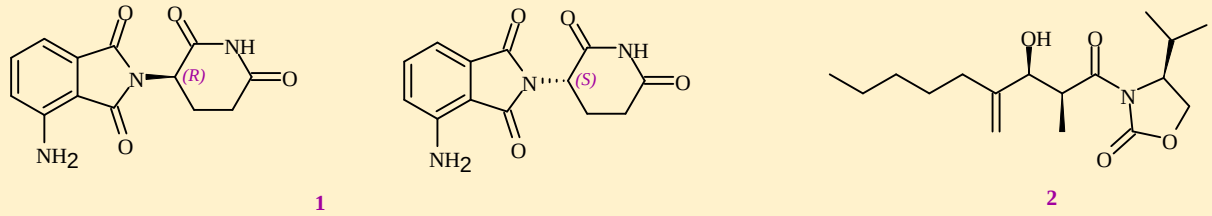

Figure 1. The structures of pomalidomide **1**, and LMT-28 **2**.

Paving the way for more ambitious and challenging therapeutic agents that aim to neutralize of IL-6 juxtaposed with enhancing IFN-λ, I propose an approach based on multifunctional hybrid nanoparticles. In fact, the features of hybrid nanoparticles include distinct enhanced properties compared to their individual components, multipurpose uses, and high surface area that can carry more than one functional group, e.g. small molecules, aptamers[**], antibodies, without significant interferences between them due to the presence of different discrete domains. In addition, they can easily be prepared in different shapes.

5.1. Au@MnO nanoflower-shaped nanocomposite matrix

In this regard, I propose a novel Au@MnO nanoflower-shaped nanocomposite matrix, which can be functionalized with two different aptamers. Such a nanocomposite made up of gold (Au) and manganese oxide (MnO) domains may provide two functional surfaces for the attachment of different molecules, hence, increasing the therapeutic potential. On the other hand, aptamers have the ability to bind with high affinity to target proteins, which, in turn, inhibit the binding to their receptors, similar to therapeutic neutralizing antibodies, but in a preferred manner (e.g. showed low immunogenicity).[40] Furthermore, aptamers are so small that they are able to recognize epitops that antibodies cannot access,[41] and efficiently penetrate into biological compartments.[40] Aptamers have emerged as optimal compounds for affinity tailoring of nanoparticle surfaces with enhanced recognition capabilities, and their immobilization is quite easy and efficient compared to antibody immobilization.

As a hypothetical approach, the aptamer-functionalized Au@MnO nanoflowers may serve as a therapeutic option for CVID-19. In this proposed approach, the Au@MnO nanoflowers may functionalize with two different aptamers: the RNA aptamer 17M-382 conjugated at the 5´ end with symmetrical branching molecule 2-cyanoethyl-*N*,*N*-diisopropyl (CED) phosphoramidite PEGylation (sbC-PEGylation)[42] anchored to the metal oxide petals to target IL-6, and a thiol-terminal RNA aptamer modified with IFN-λ molecule anchored to the gold core. The RNA aptamer 17M-382 functionalized with sbC-PEGylation was chosen as a model target molecule for IL-6 for some reasons. First, it was shown to inhibit the IL-6 production induced by IL-17A (a cytokine that is produced by T helper 17 cells and plays a pathogenic role in systemic inflammation disease) in a concentration-dependent manner in animal-models. Second, it was markedly improved the *in vivo*

[**]Aptamers are short, single-stranded DNA or RNA (ssDNA or ssRNA) molecules that can bind non-covalently to a specific target, e.g. protein, peptide, carbohydrate, or small molecule, with high selectively and specificity. They are selected from a complex library of random RNA sequences of typically 10^{14} different molecules by an *in vitro* iterative process known as SELEX (systematic evolution of ligands by exponential enrichment).

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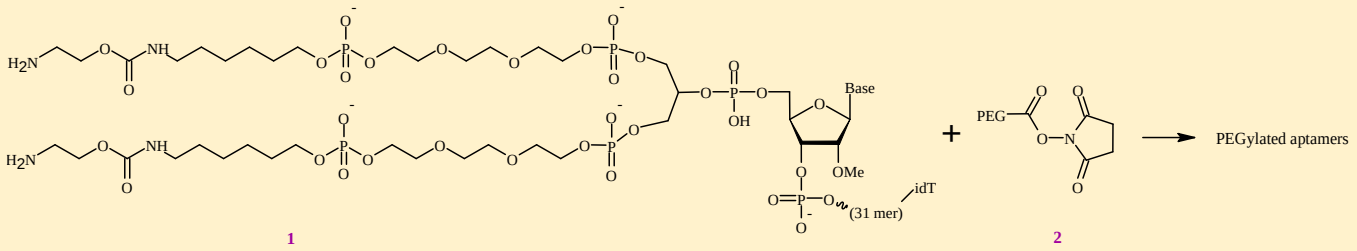
pharmacokinetic properties, which exhibited the ability to inhibit the enzyme degradation and renal clearance of drugs and, hence, to improve their stability *in vivo*.[42] In scheme 1, the final synthetic step of sbC-PEGylated aptamers is illustrated, in which the PEGylation precursor **1** was reacted with an activated PEG **2** followed by purification to give the desired purified PEGylated aptamer.[42]



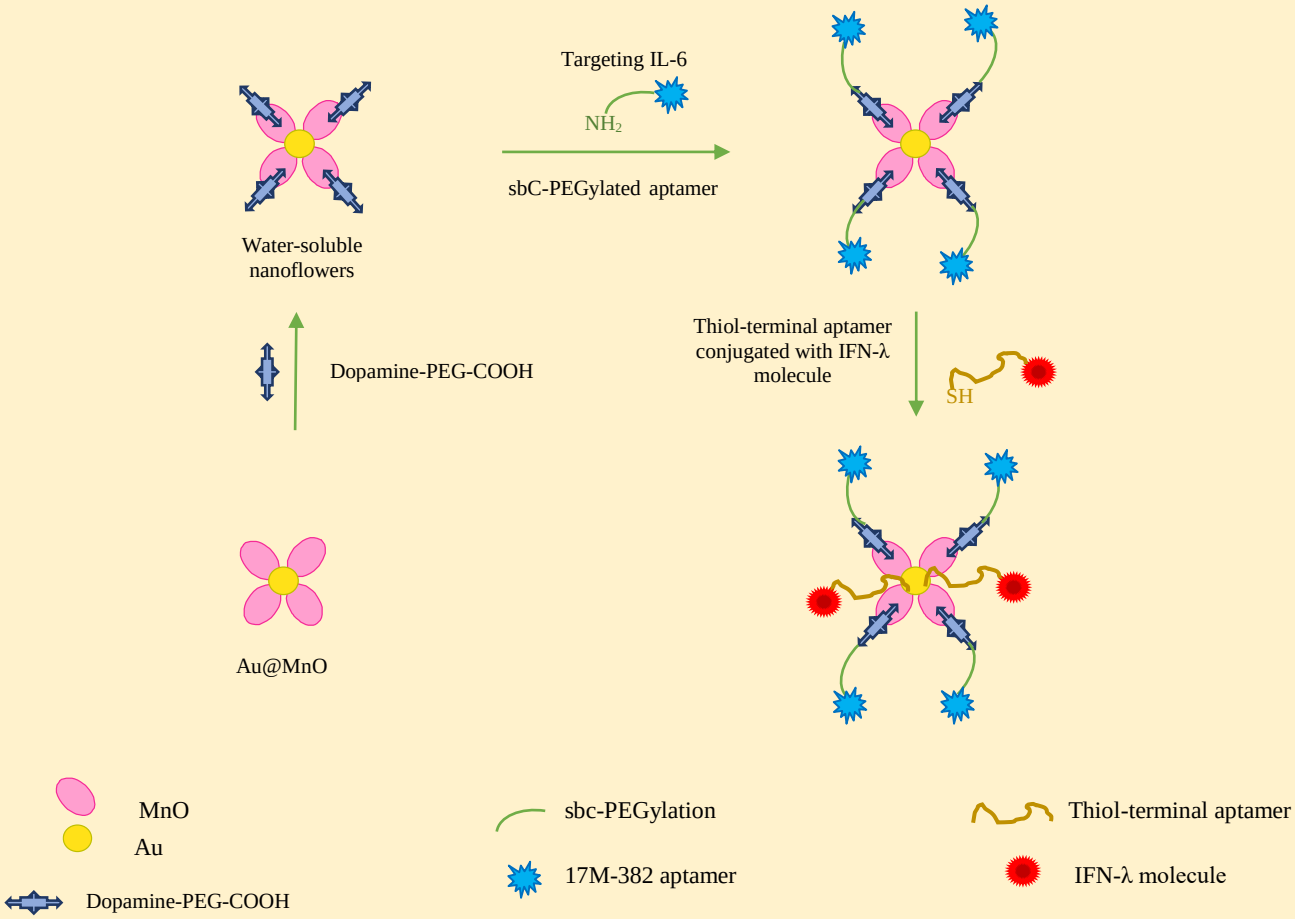
Scheme 1. The final preparation step of sbC-PEGylated aptamers.

5.2. The proposed synthetic procedure of functionalized Au@MnO nanoflowers

Scheme 2 depicts a proposed synthetic procedure of functionalized Au@MnO nanoflowers. The nanoflowers can be synthesized by decomposition of manganese acetylacetonate [$Mn(acac)_2$] in diphenyl ether in the presence of preformed gold nanoparticles (Au NPs) ("seeds"), with oleic acid and oleylamine as surfactants.[43,44] The gold "seeds" can be generated in situ by decomposition of gold acetate [$Au(OAc)_3$] at low temperature, which could be traced by a color change to deep red. The formation of MnO petals can be achieved by epitaxial growth on the surface of the Au NPs at higher temperatures. The size and morphology of the nanoflowers can be varied by changing the molar ratio of the precursors, while the number and size of the MnO petals can be increase with increasing [$Mn(acac)_2$]/[$Au(OAc)_3$] ratio.[44]

These Au@MnO nanoflowers should be water-soluble using dopamine-PEG-COOH biopolymer. Synthesis of this heterobifunctional ligand, dopamine-PEG-COOH, can be carried out with the three following steps: (i) synthesis of 3,4-dihydroxyhydrocinnamic acid pentafluorophenol ester, (ii) synthesis of NH_2-PEG-COOH, and (iii) synthesis of dopamine-PEG-COOH.[45]

The preparation of surface functionalized Au@MnO nanoflowers can be carried out as follow. First, the dopamine side of the biopolymer has two hydroxyl groups that can react with the MnO component of the nanoflowers through strong catechol reactions to transfer nanoflowers to an aqueous environment for bioapplications. To activate the carboxyl group of the biopolymer, EDC/NHS chemistry should be applied to the dopamine-PEG-COOH biopolymer-attached nanoflowers.[45] The amine (-NH2)-group-terminated sbC-PEGylated aptamers can be introduced into the activated dopamine-PEG-COOH nanoflower solution followed by incubation. Second, the thiol-terminal RNA aptamers modified with IFN-λ molecule can be immobilized on the surface of the Au domain of nanoflowers through thiol-gold surface conjugation. Such thiol-gold conjugation can be accomplished through direct interaction between thiol-terminal aptamers and Au, or non-functionalized thiol aptamers using a bifunctional linker to react with Au, *e.g.* 4-aminothiophenol.



Scheme 2. Schematic illustration of surface functionalized of Au@MnO nanoflowers with two different aptamers.

5.3. The predicted results of this hypothetical approach

The predicted results can be derived from these facts. First, conjugating the negatively charged aptamers/ aptamers modified with IFN-λ molecules to the surface of Au@MnO nanocomposite may result in the formation of a negatively charged complex, which, in turn, may lead to increasing the electrostatic interaction between the nanocomposite and the single-stranded positive-sense RNA SARS-CoV-2. Such electrostatic interaction may strengthen the target binding ability. Second, the presence of sbC-PEGylation aptamers may confer the nanocomposite a high lipophilic character, which may compete with the strong hydrophobic protein-protein interaction between the host receptor of the angiotensin converting enzyme 2 (ACE2) and SARS-CoV-2. It has been reported that the affinity constant for the receptor binding domain (RBD) of SARS-CoV-2 to ACE2 is greater than that of SARS-CoV by as much as a factor of 10 to 15, which contributes to the efficiency of virus transmission.[46] Furthermore, both electrostatic complementarity and hydrophobic

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interactions are critical to enhancing receptor binding and escaping antibody recognition by the RBD of SARS-CoV-2.[46]

6. Conclusions

This article discussed the immunity response of the host to SARS-CoV-2 infection and came to the conclusion that dysregulation of IL-6 signaling is associated with inflammatory and progression of pathological conditions of COVID-19. Furthermore, IFN-λ plays an important role in antiviral protection. Based on this explanation, which may provide clues for developing intervention strategies against SARS-CoV-2, a novel hypothetical approach was presented. This approach is based on multifunctional hybrid nanoparticles aiming to neutralizing IL-6 juxtaposed with enhancing IFN-λ. Au@MnO nanoflower-shaped nanocomposite matrix is functionalized with the RNA aptamer 17M-382 conjugated with symmetrical branching molecule PEGylation anchored to the metal oxide petals to target IL-6, and a thiol-terminal RNA aptamer modified with IFN-λ molecule anchored to the gold core. The predicted results of this approach can be derived from two main facts, namely, the formation of negatively charged complex and its high lipophilic character. The formation of a negatively charged complex may increase the electrostatic interaction between the nanocomposite and the single-stranded positive-sense RNA SARS-CoV-2 resulting in reinforcing the target binding ability. The high lipophilic character may compete with the strong hydrophobic protein-protein interaction between the host receptor of ACE2 and SARS-CoV-2. On the basis of these demonstration, I believe that future work can benefit from the rational design of engineering aptamers and nanocomposites for biomedical studies, and could aid the development of therapeutic agents for COVID-19.

References

1) J. Cui, F. Li, Z-L. Shi, *Nat. Rev. Microbiol.* **2019**, *17*, 181-192.
2) N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, *Lancet*, **2020**, *395*, 507-5013.
3) R. Channappanavar, S. Perlman, *Semin. Immunopathol.*, **2017**, *39*, 529–539.
4) C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, *Lancet*, **2020**, *395*, 497–506.
5) Y. Chi, Y. Ge, B. Wu, W. Zhang, T. Wu, T. Wen, J. Liu, X. Guo, C. Huang, Y. Jiao, F. Zhu, B. Zhu, L. Cui, https://doi.org/10.1093/infdis/jiaa363.
6) M. A. Moro-García, R. Alonso-Arias, C. López-Larrea, *Front. Immunol.*, **2013**, *4*, 107.
7) C. Qin, L. Zhou, Z. Hu, S. Zhang, S. Yang, Y. Tao, C. Xie, K. Ma, K. Shang, W. Wang, D.-S. Tian, https://doi.org/10.1093/cid/ciaa248.
8) D. Blanco-Melo, B. E. Nilsson-Payant, W.-C. Liu, S. Uhl, D. Hoagland, R. Møller, T. X. Jordan, K. Oishi, M. Panis, D. Sachs, T. T. Wang, R. E. Schwartz, J. K. Lim, R. A. Albrecht, B. R. tenOever, *Cell*, **2020**, *181*, 1–10.
9) K. Bilinska, P. Jakubowska, C. S. Von Bartheld, R. Butowt, *ACS Chem. Neurosci.*, **2020**, *11*, 1555−1562.
10) D. E. Levy, I. J. Marié, J. E. Durbin, *Curr. Opin. Virol.*, **2011**, *1*, 476–486.
11) E. Ford, D. Thanos, *Biochim. Biophys. Acta.*, **2010**, *1799*, 328–336.
12) S. Goodbourn, *Semin. Cancer. Biol.*, **1990**, *1*, 89– 95.
13) R. Lin, A. Mustafa, H. Nguyen, D. Gewert, J. Hiscott, *J. Biol. Chem.*, **1994**, *269*, 17542–17549.

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14) S. Chen, J. A. Short, D. F. Young, M. J. Killip, M. Schneider, S. Goodbourn, R. E. Randall, *Virology.*, **2010**, *407*, 247–255.
15) T. Satoh, H. Kato, Y. Kumagai, M. Yoneyama, S. Sato, K. Matsushita, T. Tsujimura, T. Fujita, S. Akira, O. Takeuchi, *Proc. Natl. Acad. Sci. U S A.*, **2010**, *107*, 1512–1517.
16) F. Hou, L. Sun, H. Zeng, B. Skaug, Q. X. Jiang, Z. J. Chen, *Cell*, **2011**, *146*, 448–461.
17) Y. M. Loo, M. Jr. Gale, *Immunity*, **2011,** *34*, 680-692.
18) C. Schindler, D. E. Levy, T. Decker T, *J. Biol. Chem*., **2007**, *282*, 20059–20063.
19) C. Sommereyns, S. Paul, P. Staeheli, T. Michiels, *PLoS Pathog.*, **2008**, *4*, e1000017.
20) M. Mordstein, E. Neugebauer, V. Ditt, B. Jessen, T. Rieger, V. Falcone, F. Sorgeloos, S. Ehl, D. Mayer, G. Kochs, M. Schwemmle, S. Günther, C. Drosten, T. Michiels, P. Staeheli, *J. Virol.*, **2010**, *84*, 5670–5677.
21) J. Pott, T. Mahlakoiv, M. Mordstein, C. U. Duerr, T. Michiels, S. Stockinger, P. Staeheli, M. W. Hornef, *Proc. Natl. Acad. Sci. U S A.*, **2011**, *108*, 7944–7949.
22) N. A. Jewell, T. Cline, S. E. Mertz, S. V. Smirnov, E. Flano, C. Schindler, J. L. Grieves, R. K. Durbin, S. V. Kotenko, J. E. Durbin, *J. Virol.* **2010**, *84*, 11515–11522.
23) C. Luxembourger, A. Ruyssen-Witrand, C. Ladhari, C. Rittore, Y. Degboé, J.-F. Maillefert, P. Gaudin, H. Marotte, D. Wendling, C. Jorgensen, A. Cantagrel, A. Constantin, D. Nigon, I. Touitou, J.-E. Gottenberg, Y.-M. Pers, *Pharmacogenomics J.*, **2019**, *19*, 368–374.
24) D. E. Morra, S. K. Pierson, D. Shilling, S, Nemat, C. Appiani, M. Guilfoyle, C. Tendler, F. Van Rhee, D. C. Fajgenbaum, *Br. J. Haematol.* **2019**, *184*, 232–241.
25) L. Y. F. Wong, R. Y. H. Leung, K. L. Ong, B. M. Y. Cheung, *J. Human Hypertension*, **2007**, *21*, 875–882.
26) O. Dienz, S. M. Eaton, J. P. Bond, W. Neveu, D. Moquin, R. Noubade, E. M. Briso, C. Charland, W. J. Leonard, G. Ciliberto, C. Teuscher, L. Haynes, M. Rincon, *J. Experimental Medicine*, **2009**, *206*, 69–78.
27) G. D'Angelo, *Blood Res*., **2013**, *48*, 10–15.
28) J. M. Fernandez-Real, M. Broch, J. Vendrell, C. Richart, W. Ricart, *J. Clin. Endocrinol. and Metabol*., **2000**, *85*, 1334–1339.
29) M. Murakami, D. Kamimura, T. Hirano, *Immunology*, **2019**, *50*, 812–831.
30) S. Heink, N. Yogev, C. Garbers, M. Herwerth, L. Aly, C. Gasperi, V. Husterer, A. L. Croxford, K. Möller-Hackbarth, H. S. Bartsch, K. Sotlar, S. Krebs, T. Regan, H. Blum, B. Hemmer, T. Misgeld, T. F. Wunderlich, J. Hidalgo, M. Oukka, S. Rose-John, M. Schmidt-Supprian, A. Waisman, T. Korn, *Nat. Immunol.*, **2017**, *18*, 74-85.
31) C. Garbers, S. Heink, T. Korn, S. Rose-John, *Nat. Rev. Drug Discov.* **2018**, *17*, 395–412.
32) P. Arnold, W. Lückstädt, W. Li, I. Boll, J. Lokau, C. Garbers, R. Lucius, S. Rose-John, C. Becker-Pauly, *Cells*, **2020**, *9*, 1307.
33) J. Wolf, S. Rose-John, C. Garbers, *Cytokine*, **2014**, *70*, 11-20.
34) H. Ogura, M. Murakami,Y. Okuyama, M. Tsuruoka, C. Kitabayashi, M. Kanamoto, M. Nishihara, Y. Iwakura, T. Hirano, *Immunity*, **2008**, *29*, 628-636.
35) S. Kim, M.-J. Kim, C.-H. Kim, J. W. Kang, H. K. Shin, D.-Y. Kim, T.-B. Won, D. H. Han, C. S. Rhee, J.-H. Yoon, H. J. Kim, *Am. J. Resp. Cell Mol. Biol*., **2017**, *56*, 202-212.
36) H. Kameda, K. Wada, Y. Takahashi, O. Hagino, H. Van Hoogstraten, N. Graham, Y. Tanaka, *Mod. Rheumatol*. **201**9, *30*, 239–248.
37) R. J. D'Amato, S. Lentzsch, K. C. Anderson, M. S. Rogers, *Seminars in Oncology*, **2001**, *28*, 597–601.
38) Y. Cao, H. Zhang, H. Liu, C. Lin, R. Li, S. Wu, H. He, H. Li, J. Xu, *Sci. Rep.*, **2016**, *6*, 38364.
39) S.-S. Hong, J. H. Choi, S. Y. Lee, Y.-H. Park, K.-Y. Park, J. Y. Lee, J. Kim, V. Gajulapati, J.-I. Goo, S. Singh, K. Lee, Y.-K. Kim, S. H. Im, S.-H. Ahn, S. Rose-John, T.-H. Heo, Y. Choi, *J. Immunol*., **2015**, *194*: 000–000.
40) H. Sun, Y Zu, *Molecules*, **2015**, *20*,11959– 11980.
41) J. F. Lee, G. M. Stovall, A. D. Ellington, *Curr. Opin. Chem. Biol*., **2006**, *10*, 282–289.
42) K. Haruta, N. Otaki, M. Nagamine, T. Kayo, A. Sasaki, S. Hiramoto, M. Takahashi, K. Hota, H. Sato, H. Yamazaki, *Nucleic Acid Ther*., **2017**, *27*, 36-44.
43) H. Yu, M. Chen, P. M. Rice, S. X. Wang, R. L. White, S. Sun, *Nano Lett.*, **2005**, *5*, 379 – 382.
44) T. D. Schladt, M. I. Shukoor, K. Schneider, M. N. Tahir, F. Natalio, I. Ament, J. Becker, F. D. Jochum, S. Weber, O. Köhler, P. Theato, L. M. Schreiber, C. Sönnichsen, H. C. Schrder, W. E. G. Müller, W. Tremel, *Angew. Chem. Int. Ed.*, **2010**, *49*, 3976 – 3980.
45) I. Ocsoy, B. Gulbakan, M. I. Shukoor, X. Xiong, T. Chen, D. H. Powell, W. Tan, *ACS Nano*, 2013, *7*, 417–427.
46) Y. Wanga, M. Liu, J. Gao, *PNAS*, **2020**, *117*, 13967-13974.