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Preview

Inhaled hydrogel-based microspheres for management of COVID-19 – a new sweeper biological platform

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Abstract

The cytokine storm caused by SARS-CoV-2 infection threatens the condition of patients, even leading to death. In this issue of *Matter*, Prof. Wenguo Cui and co-workers have prepared lung sweeper-inhaled hydrogel microspheres for intratracheal neutralization of COVID-19 and calming the cytokine storm, which could be applied for antiviral tissue regeneration, drug delivery, and disease diagnosis.

Main text

Looking back to human history, it has been a fighting against viruses, such as smallpox, influenza, and more recently, COVID-19. Researchers from various fields develop different strategies to fight against COVID-19. Different from the traditional administrations, such as intravenous injection, per os, researchers from Shanghai Jiao Tong University ingeniously (Prof. Wenguo Cui's Group) prepared the inhaled microfluidic hydrogel microspheres that can significantly reduce SARS-CoV-2 infection effectiveness and neutralize proinflammatory cytokines.[1]

In the battle between humans and viruses, both sides developed various strategies for winning.[2,3] The propagation mode, replication period, viruses' mutation makes the pandemic of the viruses.[4] From the human side, the standard defense methods are anti-viral drugs, vaccinations, and hormonal drugs.[5,6] However, these defense methods have limitations, such as side effects, limited effectiveness, long research period, and expensive research-development cost. Therefore, humans have to discover various strategies in fighting against the viruses.

By masterfully mimicking some natural phenomena, we have creatively made various achievements in fighting against viruses. In this regard, and in the field of bioengineering, Prof. Wenguo Cui's Group mimicked the sweeper. They construct inhaled microfluidic hydrogel microspheres to eliminate cytokine storms, viruses and protect the body system (**Figure 1**).

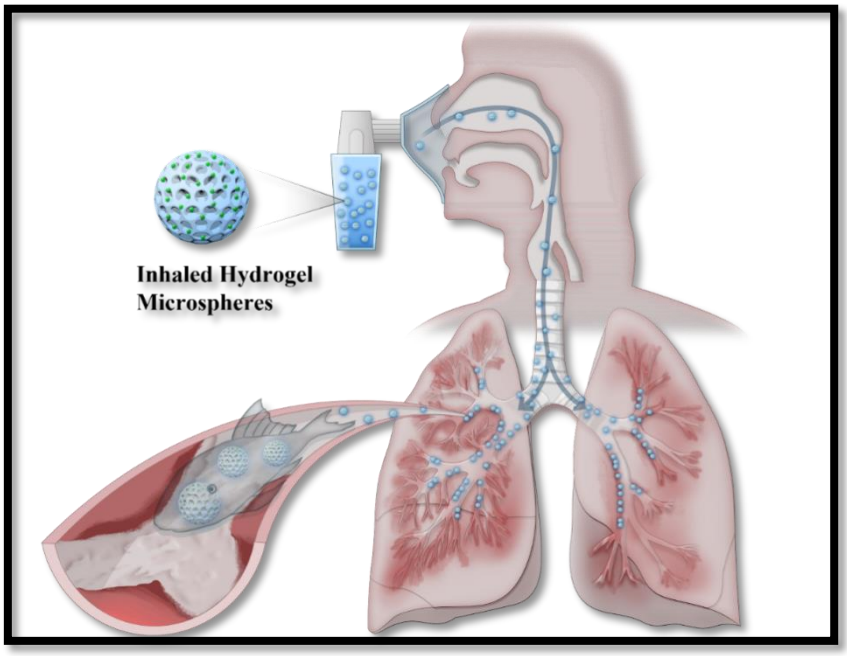

Figure 1. "Lung sweeper" calming down the cytokines storm and eliminating the virus. The schematic illustration of the inhaled microfluidic hydrogel microspheres to eliminate cytokine storms, virus, and protect the body system.

For the construction of such 'sweeper', inspired by SARS-CoV-2 infecting alveolar epithelial cells through ACE2 receptors, the authors genetically modify HEK293 cells with the overexpressing ACE2-receptor and isolate the ACE2-engineered cell membranes.[7] After that, they fused this cell membrane with the cell membrane of pro-inflammatory macrophages, aiming to neutralize pro-inflammatory cytokines and alleviate hyper inflammation of lymph nodes and spleen. Although the fused cell membranes have their unique biological properties, these membranes exhibit limited capability in accumulating on the respiratory system. Therefore, inspired by the habit of sweeper in the aquarium that these fishes usually attach to rocks and glass to stabilize the body, the authors have attached these cell membranes on inhaled microfluidic

hydrogel microspheres to improve their accumulation in the respiratory system. Since the deposition site of microspheres is determined by their aerodynamic diameter (Dare) in the respiratory system,[8] for the 'sweeper' system to work, the authors have precisely controlled the Dare of microspheres at 7.89, 6.63, and 4.21 μm. In this way, these microspheres accumulated in the oropharynx, upper airway, and lower airway of the lung lobes, leading to the protection of the whole respiratory tract against the virus and potentially reducing the viral transmission in humans.

The primary food sources of sweepers are excrement, algae, which means that sweepers hardly harm other fishes and purify the water quality. According to the origin of "excrement," it can be divided into two parts: cellular origin and the sweeper itself. For lung sweepers, the inhaled microfluidic hydrogel microspheres are able to eliminate the "cellular excrement" by neutralizing inflammatory cytokines (such as IL-1β, IL-6, and TNF-α) in the serum, and inhibiting apoptosis induced by cytokines in alveolar epithelial cells. Additionally, as for the microspheres themselves, cilia can effectively capture the microspheres in the upper respiratory tract. This capture method makes microspheres to be excreted mechanically via the actions of cilia and coughing, leading to reduce upper respiratory viral loads, and potential reducing the spread of the virus among the population. The remained microspheres inside alveoli and the microspheres themselves can be decomposed by enzymatic hydrolysis.

Interestingly, such 'sweeper' system can also be the security guard for other fishes. Accordingly, the lung 'sweeper' has a similar behavior in the body. Different from the commercial vaccination and neutralizing antibody administration suppress alveolar

viral loads and lung damage with robust infection in the upper respiratory tract, especially nasal turbinates.[9] The authors demonstrated that microspheres protected the upper respiratory tract against SARS-CoV-2 infection for 3 days, indicating that microspheres' inhalation could potentially reduce the viral load in patients in the mild-to-moderate early stages of the infection. However, the level of the reduction is still limited, and whether it reduces the risk of transmission in human, needs to be further studied.

Beyond its contribution to the prevention and treatment of COVID-19, the inhaled hydrogel microspheres provide an advanced inhalation carrier with easily modified chemical structure, controlled aerodynamic diameter, favorable biocompatibility and clearance from a point of view of both bioengineering and pharmaceutical fields. In the future, this innovative technology is expected to pave the way to fabricate a wide range of inhaled hydrogel microspheres for various applications, such as tissue regeneration, drug delivery, and disease diagnosis.

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