The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with emerging variants has infected more than 265 million people globally. Severe inflammation and cytokine storms causing acute lung injury (ALI) may lead to a high mortality rate. The current therapies of ALI are inefficient to control the inflammatory response in the lung tissue and result in a poor prognosis.

In this issue of ACS Central Science, Yu Yang and co-workers describe a promising nanozymatic solution to ALI by coordinating Fe\textsuperscript{3+} with an anti-inflammation drug curcumin to form nanozyme drugs (Fe-Cur NPs). The authors demonstrated two key features of Fe-Cur NPs, ROS scavenging and anti-inflammation, both in vitro and in vivo. Three typical colorimetric assays (DPPH, ABTS, and MB method) were then used to demonstrate the capability of Fe-Cur NPs in scavenging ROS in buffers. To further probe the antioxidant capability of Fe-Cur NPs inside cells, the authors treated the J774A.1 macrophage cells with lipopolysaccharide (LPS)/adenosine triphosphate (ATP) to increase the ROS level. A fluorescent indicator named DCFH\textsubscript{2}-DA was then used to probe the intracellular ROS. Interestingly, the anti-inflammation drug curcumin even further elevated the intracellular ROS level. In contrast, the nanozyme Fe-Cur NPs was able to decrease the ROS to a normal level in the sub-micromolar range (Figure 1a), showing its superior nanozymatic properties compared to the free drug curcumin.

While it is not uncommon for nanozymes to show ROS scavenging capabilities and anti-inflammation properties in therapeutic applications, the detailed mechanisms are still not well-studied. The authors revealed that Fe-Cur NPs can better suppress the inflammation response by down-regulating inflammation cytokines, suppressing the activity of inflammasomes, and decreasing intracellular Ca\textsuperscript{2+}. First, stimulated macrophage cells tend to release small proteins called inflammatory cytokines to promote inflammation. Probing the cytosine level after treating cells with nanozymes could tell us the efficacy of the nanozyme drug. Tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and interleukin-6 (IL-6) were evaluated by Western blotting and immunofluorescence assays. Indeed, Fe-Cur NPs showed an even higher
activity in decreasing the cytokines to normal levels (e.g., TNF-α in Figure 1b).

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Further, the authors examined the activity of inflammasomes, which are intracellular multiprotein complexes activated upon infection. After LPS/ATP stimulation, the NLRP3 inflammasome activation was triggered with over-expressed cleaved caspase-1 and mature IL-1β. At the same time, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription factor was activated. Using ELISA kits, the authors showed that both curcumin and Fe-Cur NPs could inhibit the inflammasome activity, downregulate the cytokine level, and mediate the signaling pathway. Notably, the nanozyme drug behaved more efficiently in the inhibition process. Taken together, Fe-Cur NPs eliminated inflammation mainly through inhibiting the secretion of TNF-α and IL-6 and suppressing the NLRP3 inflammasome and NF-κB pathway.

After testing the Fe-Cur nanozymes in vitro, the authors took a step forward and examined the effectiveness of the nanozyme drug in vivo using mice as a model. The accumulation of drugs in the targeted site is an important step for appropriate functions in vivo. To investigate the biodistributions of Fe-Cur NPs in mice, two different injection methods, intratracheal injection (i.t.) and intravenous injection (i.v.), were used. UPLC-MS/MS results indicated that Fe-Cur NPs could better target the lung tissue by both injection methods.

The authors then carefully examined the efficacy of the free drug and the nanozyme drug in vivo. One typical experiment is to test the lung function of ALI mice after drug injection. An AniRes2005 lung function test system was used to collect the information regarding the resistance of lung (RL), the resistance of expiration (Re), and respiratory lung compliance (Cdyn) levels in mice. Compared to the free drug, Fe-Cur nanozyme, as expected, showed a higher activity in recovering the lung function, which was ascribed to its better ROS scavenging ability in vivo. Notably, intratracheal administration of Fe-Cur NPs can directly target the lung tissue for ALI treatment (Figure 1c) and demonstrates enhanced therapeutic efficacy and low side effects.

The successful application of Fe-Cur NPs in treating ALI both in vitro and in vivo paves the way for nanozymes in biomedicine. Despite the gap between nanozymes and natural enzymes in selectivity and structure, the Fe-Cur nanozyme highlights the promise of nanozymes in providing new functionalities for specific applications. Looking forward, more work needs to be performed to move the nanozyme drugs forward into clinical settings. For example, more rational principles should be developed to guide the design of nanozyme drugs. Also, understanding the bio-nanointeraction both in vitro and in vivo would further help
us to elucidate the action mechanisms of nanozymes at the molecular level.

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