Intracellular Co-Delivery of Carbon Monoxide and Nitric Oxide Induces Mitochondrial Apoptosis for Cancer Therapy

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Understanding the interplay between gasotransmitters is essential for unlocking their therapeutic potential. However, achieving spatiotemporally controlled co-delivery to target cells remains a significant challenge[1, 2]. Herein, we propose an innovative strategy for the intracellular co-delivery of carbon monoxide (CO) and nitric oxide (NO) gasotransmitters under clinically relevant wavelengths[3]. This approach rationally couples aerobic photooxidative and anaerobic photocatalytic reactions within a polymeric micelle platform, using palladium (II) tetraphenyltetrabenzoporphyrin (PdTPTBP) as both photosensitizer and photocatalyst. Notably, the photooxidation-mediated release of CO generates a local hypoxic microenvironment, which facilitates the photoredox catalyzed release of NO. This self-adaptive micelle platform enables efficient uptake by tumor cells and intracellular co-delivery of CO and NO under 630 nm light irradiation, demonstrating potent anti-tumor activity in a 4T1 tumor-bearing mouse model via the synergistic induction of mitochondrial apoptosis.

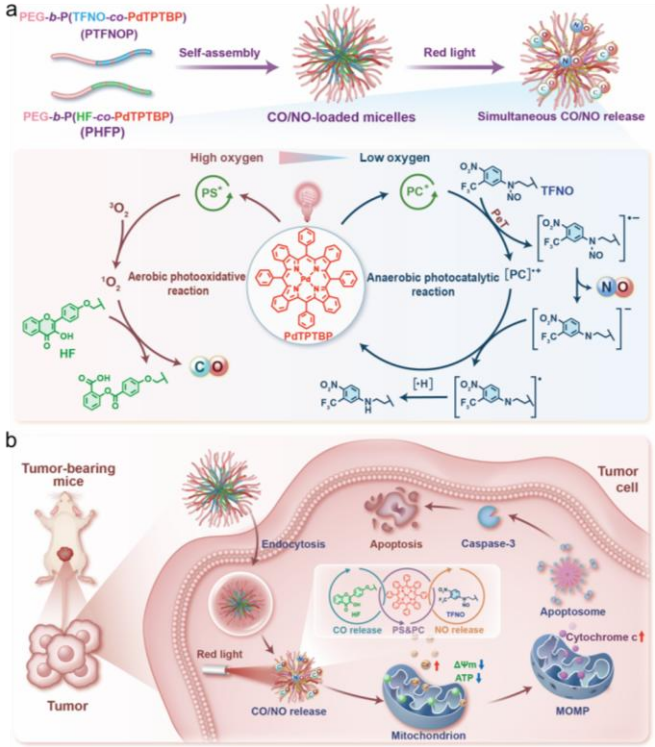

Figure 1: (a) Schematic illustration of the construction of CO/NO-releasing micelles through the co-assembly of PHFP and PTFNOP copolymers. Upon 630 nm light irradiation, CO and NO are simultaneously released from the micelle core. The proposed mechanism involves PdTPTBP serving as both a PS and a PC. The release of CO scavenges $^1O_2$, creating a localized hypoxic microenvironment. This hypoxia facilitates the photoredoxcatalyzed release of NO, achieving the synchronized release of CO and NO. (b) The co-release of CO and NO under 630 nm light irradiation induces mitochondrial dysfunction, leading to enhanced tumor cell apoptosis.

References:

[1] Z. Q. Shen; J. M. Hu; et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 20452-20460.
[2] Z. Q. Shen; J. M. Hu; et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202219153.
[3] Z. Q. Shen; J. M. Hu; et al. *Angew. Chem. Int. Ed.* **2025**, *64*, e202419939.