轉譯開發 NORM 應用於細胞療法、再生醫學及癌症治療

Translational development and application of NORM on cell therapy, regenerative medicine, and cancer treatment

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In this interdisciplinary research project, we aim to translate the physiological function of NO into therapeutic approaches via the development of novel nitric oxide-release molecules and materials (NORMs). Derived from encapsulation of dinitrosyl iron complex (DNIC) into a PLGA nanosphere, NanoNO features therapeutic effect against HCA-1 orthotopic tumour in mice. In addition, normalization of tumour vessel by low-dose NanoNO improves the delivery and effectiveness of small-molecule chemotherapy (DOX), macromolecular therapeutic agents (recombinant TRAIL protein), and cancer vaccine immunotherapy in both primary tumours and metastases (Fig. 1a, ***Nat. Nanotechnol.*** 2019, *14*, 1160-1169). To conquer pancreatic ductal adenocarcinoma (PDAC) with stromal barriers, a DNIC-loaded nanogel featuring NO-delivery and stroma-targeted nature was explored to remodel the fibrotic tumor microenvironment of desmoplastic PDAC, to overcome the drug resistance toward the loaded anti-cancer TRAIL, and consequently, to sensitize the PDAC tumors to cancer therapy (Fig. 1b, ***Gut*** under revision.). Near-infrared (NIR) light was also adopted as a physical trigger to control the burst release of NO from a injectable hydrogel consisted of NO-delivery DNIC, photothermal hollow Ag-Au nanocages (HGN), and silk fibroin, which displays synergistic NO-release and photothermal effects against cancer (Fig. 1c, in preparation). On the other hand, through the conjugation of DNIC with MOF-derived Fe_3O_4 followed by encapsulation in PLGA microsphere, the assembled magnetic-responsive NO-release material (MagNORM) can serve as an approach for bacteria-infected cutaneous wound relying on its bactericidal and wound healing effects (Fig. 1d, ***ACS Appl. Mater. Interfaces*** under revision). In terms of application of NORM on regenerative medicine, NO-delivery DNICs were also investigated to treat neurodegenerative disease. Relying on the reversible binding nature of DNIC toward Cysteine-containing proteins, DNIC can serve as a vehicle for oral delivery of NO into brain, which further activates the hippocampal neurogenesis and ameliorates the metabolic syndrome-impaired cognitive ability (Fig. 1e, ***JACS Au*** 2021, *1*, 998-1013). Through the combination of DNIC and MOF, the assembled DNIC@MOF microrod exhibits enhanced oral NO delivery and therapeutic effect against hypertension (Fig. 1f, submitted). Based on the preliminary *in vitro* and *in vivo* results, mesenchymal stem cell (MSC) primed with the treatment of DNIC display elevated survival rate due to the activation of hemeoxygenase-1-mediated cytoprotective signaling pathways (Fig. 1g, in preparation). In the near future, study of post-engrafted cell viability and therapeutic efficacy to ischemic stroke will be continued to explore DNICs as novel adjuvants for cell therapy.

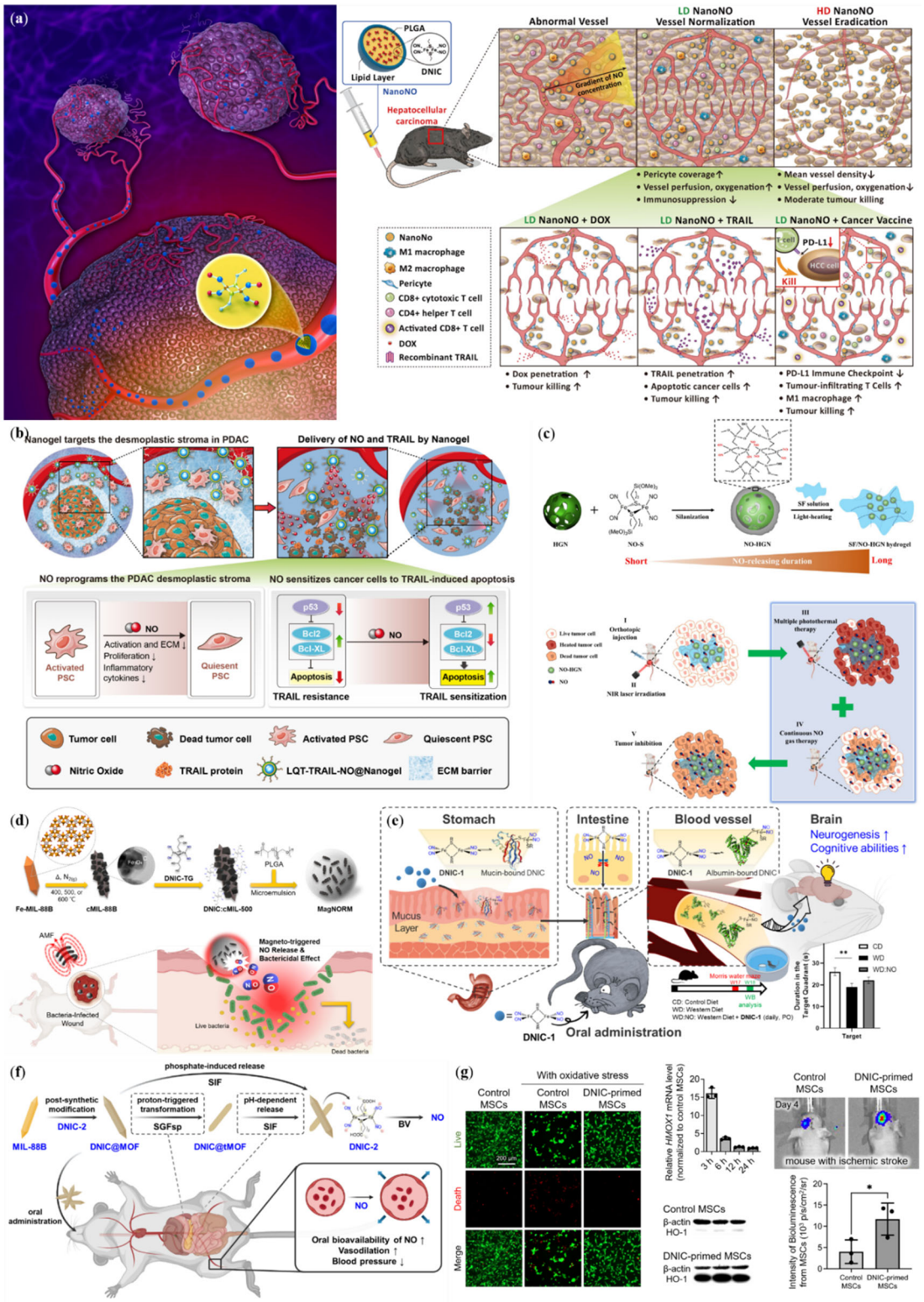

Figure 1. (**a**) Delivery of nitric oxide with a nanocarrier promotes tumour vessel normalization and potentiates anti-cancer therapies. (**b**) Reversal of pancreatic desmoplasia by a tumor stroma-targeted nitric oxide nanogel overcomes TRAIL resistance in pancreatic tumors. (**c**) A silk composite hydrogel system combined long-term NO release and photothermal therapy for cancer treatment. (**d**) Magnetic-responsive release of nitric oxide from a MOF-derived Fe_3O_4@PLGA microsphere for the treatment of bacteria-infected cutaneous wound. (**e**) Endogenous conjugation of biomimetic dinitrosyl iron complex with protein vehicles for oral delivery of nitric oxide to brain and activation of hippocampal neurogenesis. (**f**) Enhanced oral NO delivery through bioinorganic engineering of acid-sensitive prodrug into a transformer-like DNIC@MOF microrod. (**g**) DNIC treatment protects MSCs against oxidative stress by modulating HO-1-mediated antioxidant response.