Enhanced Cancer Starvation Therapy via Autophagy Inhibition With a Functional Dendritic Mesoporous Organosilicon Nanoagent

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Research

Keywords: mesoporous nanoagent, organosilicon glucose, autophagy inhibition, starvation therapy

Posted Date: February 10th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-211148/v1

Abstract

Glucose oxidase (GOx) can effectively catalyze glucose intogluconic acid and hydrogen peroxide (H2O2) in the presence of O2, which is considered as an attractive starvation strategy for cancer therapy. However, the autophagy phenomenon protects tumor cells from starvation therapy, limiting the therapy effect, thus autophagy inhibition could be used as a troubleshooting method to enhance tumor starvation therapy. Herein, biodegradable dendritic mesoporous organosilicon nanoagent (DMON) was used as the nanocarrier to deliver GOx and 3-MA (an autophagy

inhibition agent), designed as DMON@GOx/3-MA. T his formulation could have a synergetic effect on autophagy inhibition and starvation therapy. All in vitro and in vivo results demonstrated that autophagy inhibition obviously enhanced the efficacy of starvation therapy, leading to tumor growth suppression. Our strategy will provide a new way to enhance the efficacy of starvation cancer therapy.

Full Text

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Figures

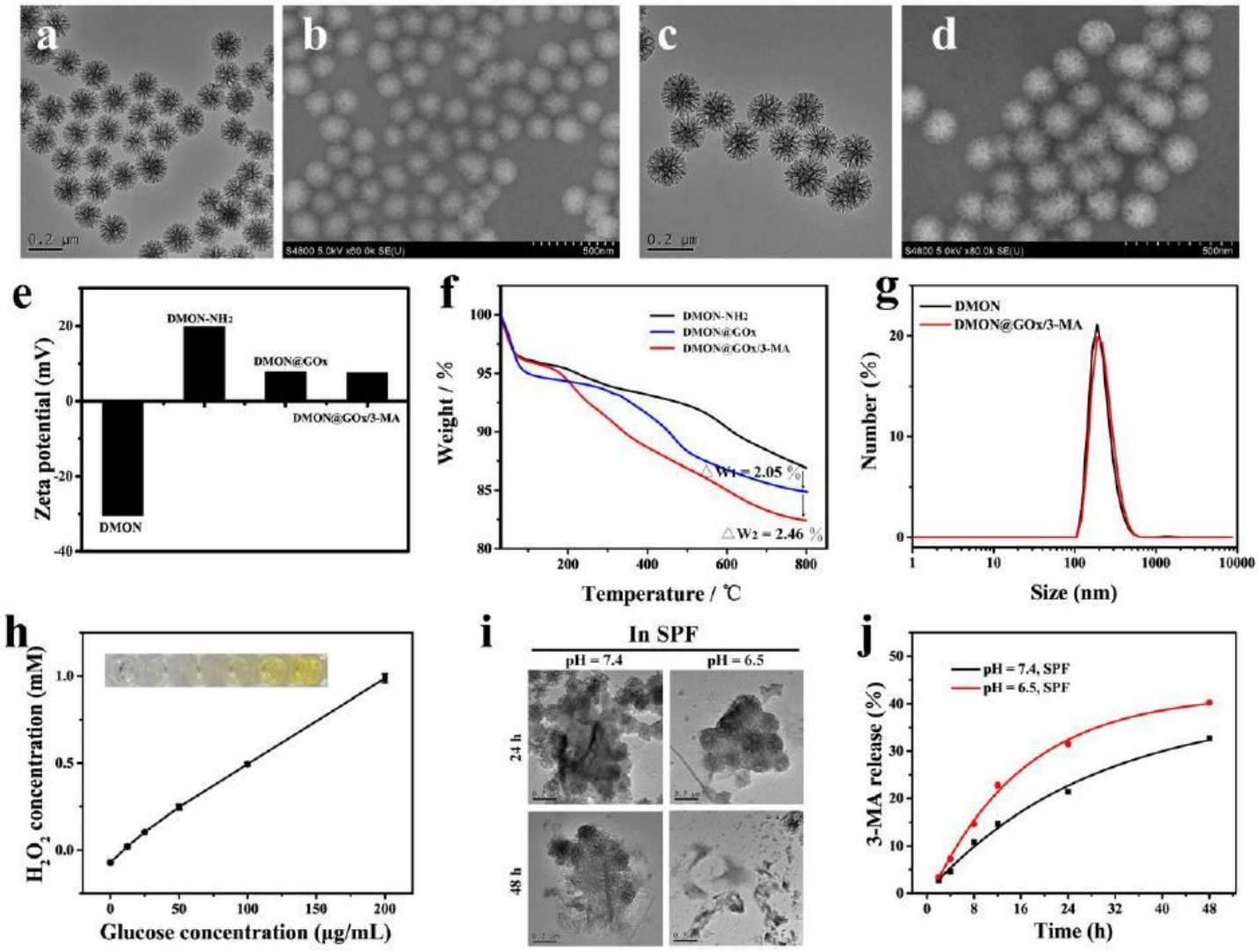

Figure 1

TEM (a) and SEM (b) images of DMON nanoparticles. TEM (c) and SEM (d) images of DMON@GOx/3-MA nanoparticles. (e) Zeta potential of different nanoparticles during the synthetic process. (f) TG curves of DMON-NH2, DMON@GO, and DMON@GOx/3-MA nanoparticles. (g) DLS data of DMON and DMON@GOx/3-MA nanoparticles. (h) The generated H2O2 concentration after co-incubation DMON/GOx nanoparticles at different concentrations of glucose for 2 h. (i) TEM images of DMON@GOx/3-MA nanoparticles after dispersed in different SBF buffer (pH = 7.4 and 6.5) for 24 and 48 h (Scale bar = 200 nm). (j) Release kinetics of 3-MA from DMON@GOx/3-MA.

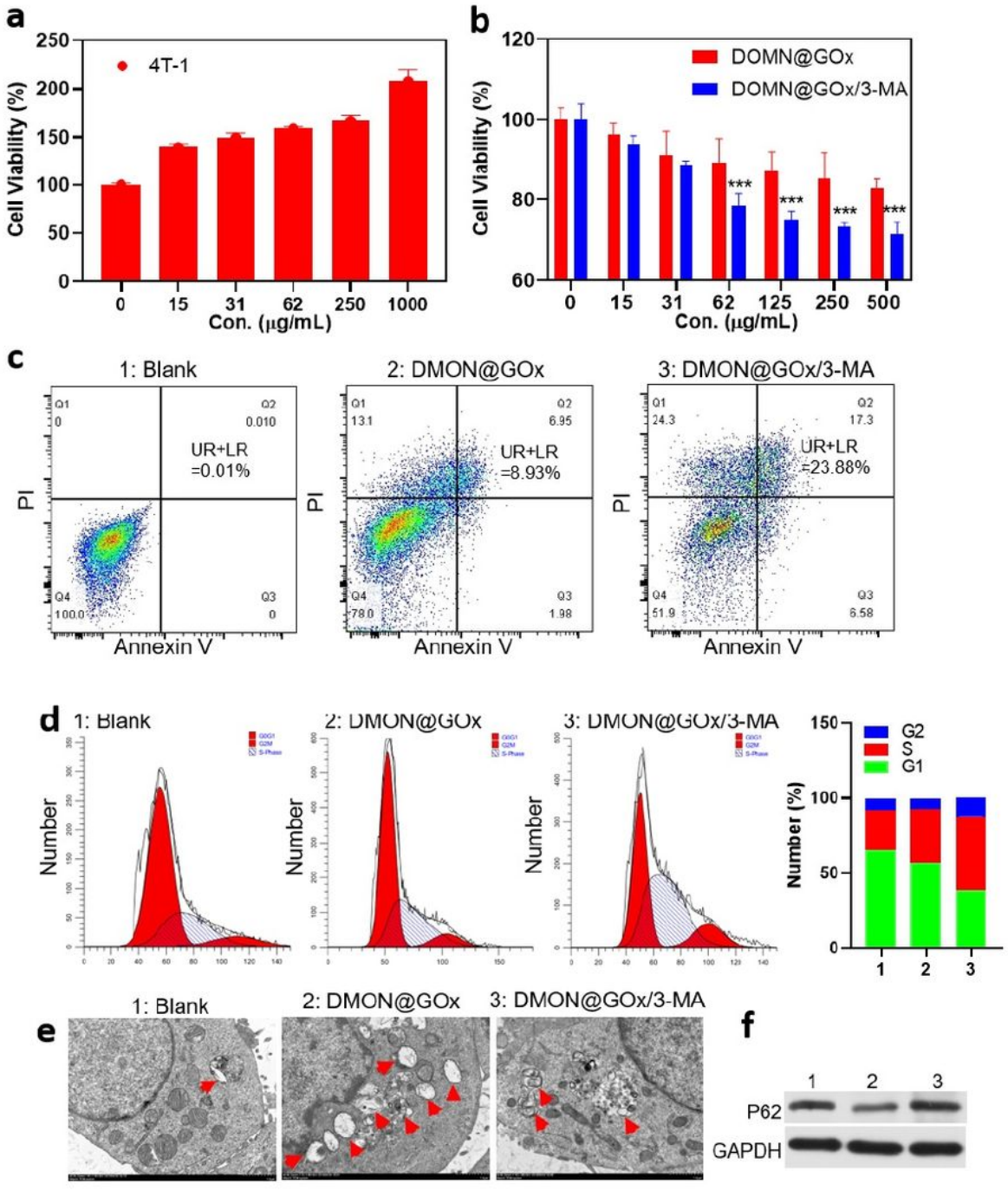

Figure 2

In vitro bioacvivity of DMON@GOx/3-MA a) Cell viability of 4T1 cells treated with different concentrations of glucose for 24h. (b) Cell viability of 4T1 cells treated with different concentrations of DMON@GOx and DMON@GOx/3-MA. (c) Cell apoptosis analysis detected by PI and AnnexinV in 4T1 cells treated with 125μg/mL DMON@GOx and DMON@GOx/3-MA for 24h. (d) Cell cycle analysis of 4T1 cells treated as (c), and the percentage of cells in G1, S and G2 phase is displayed. (ee)) Bio-TEM images of 4T1 cells ,

red arrows indicate autophagosome and autolysosome. (f) Western blot of P62 in 4T1 cells treated as in (c). *** P<0.001, P value was analysed by two-way ANOVA. Data are the means ± sd

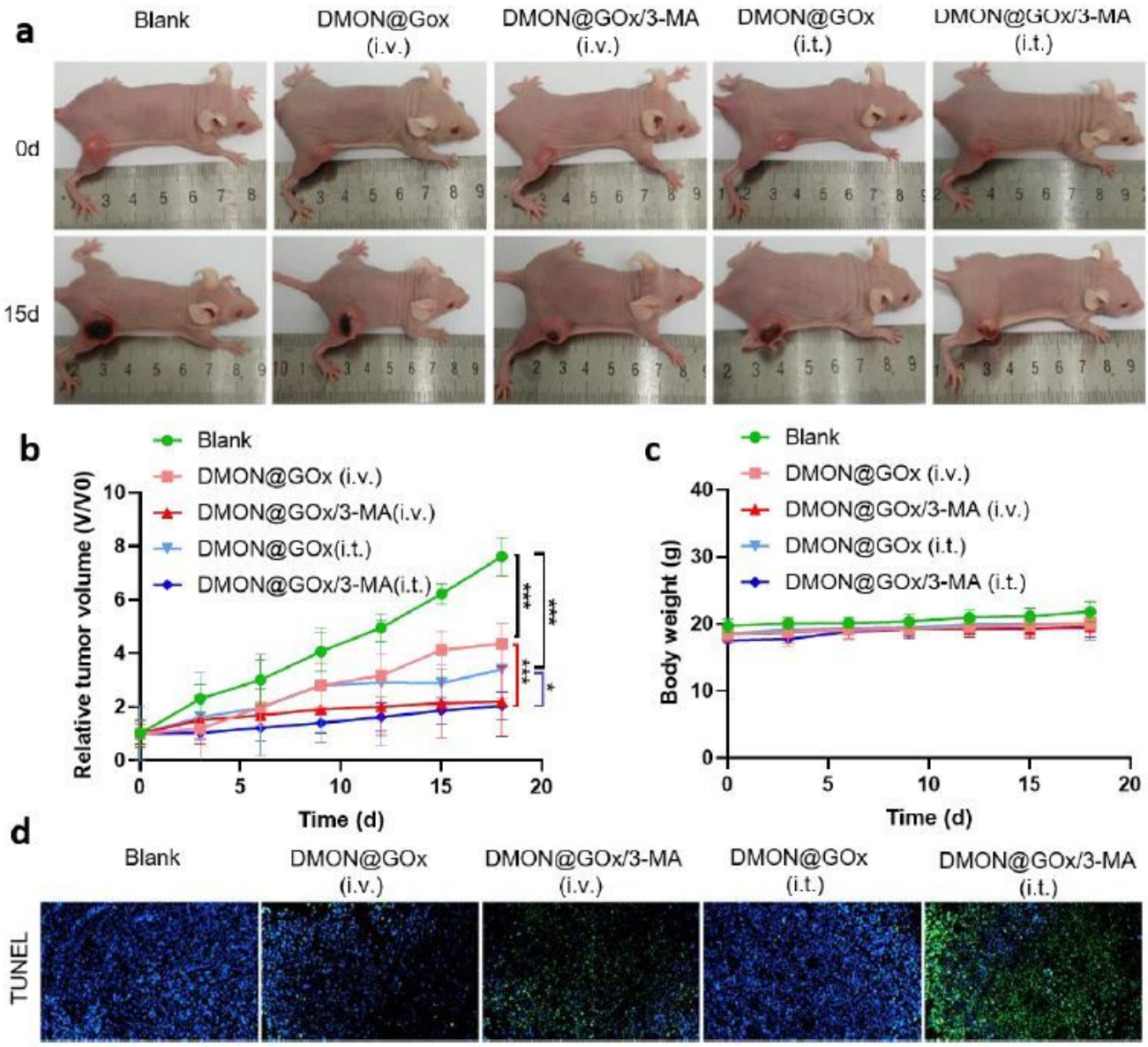

Figure 3

In vivo bioacvivity of DMON@GOx/3-MA (a) Digital pictures of tumors from the 4T1 tumor-bearing nude mice i.v. or i.t. injected with DMON@GOx or DMON@GOx/3-MA. (b) Tumor growth curves of 4T1 tumor-bearing nude mice treated as in (a). (c) Body weight of the mice treated as in (a). (d) TUNEL staining of tumor sections from the 4T1 tumor-bearing mice. *** P<0.001, P value was analysed by two-way ANOVA. Data are the means ± sd

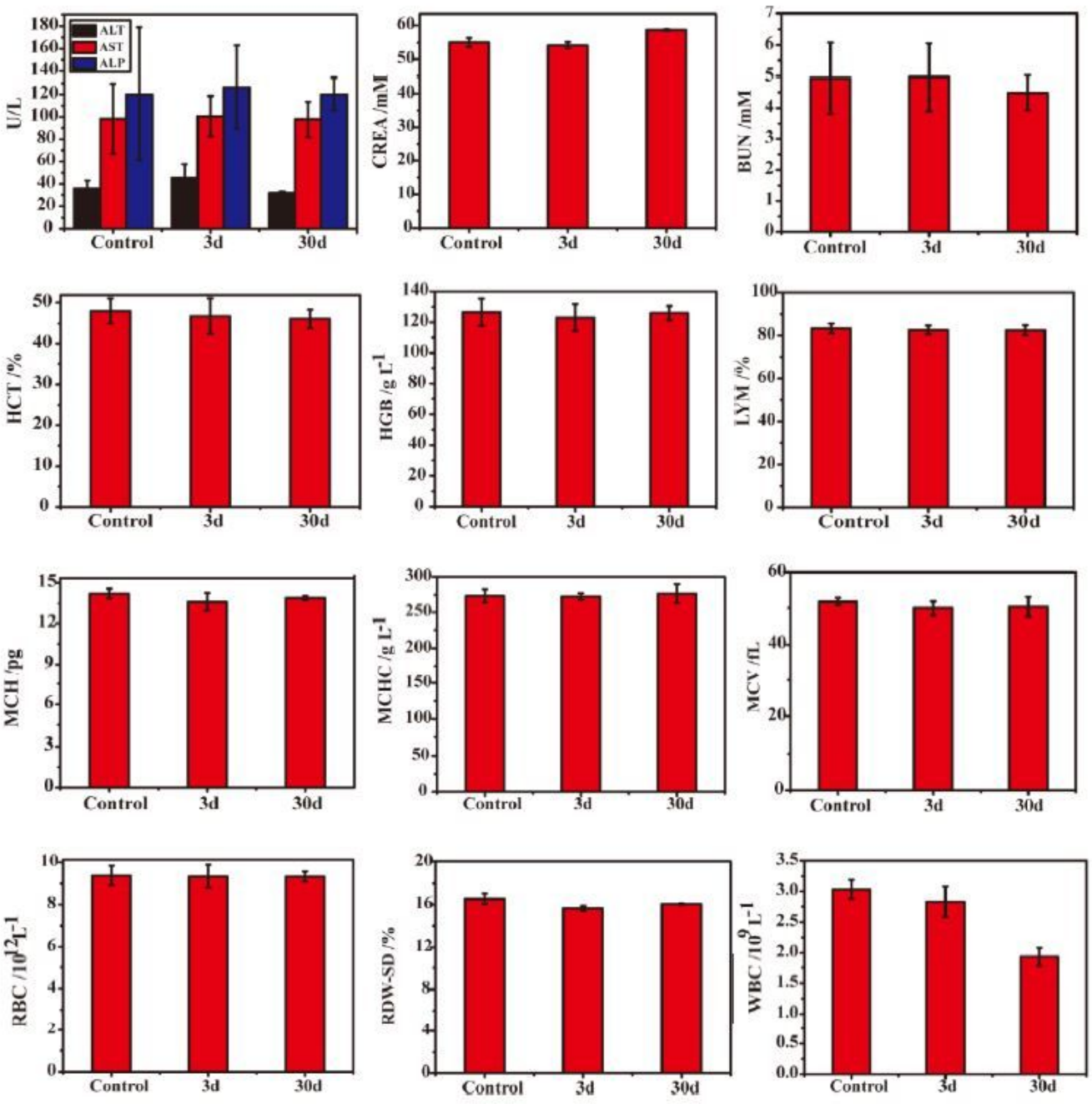

Figure 4

Blood biochemical analysis of Kunming mice after i.v. injection of DMON@GOx/3-MA with a calculated dose of 75 mg/kg at 3 day and 30 day. The liver function related alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and creatinine (CREA), nephric blood urea nitrogen (BUN) and other indices show no significant change after treatment. n = 6, Data are the means ± sd

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