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新型標靶納米載體於腫瘤治療之應用

Development of a novel targeted nanodelivery system for tumor therapy

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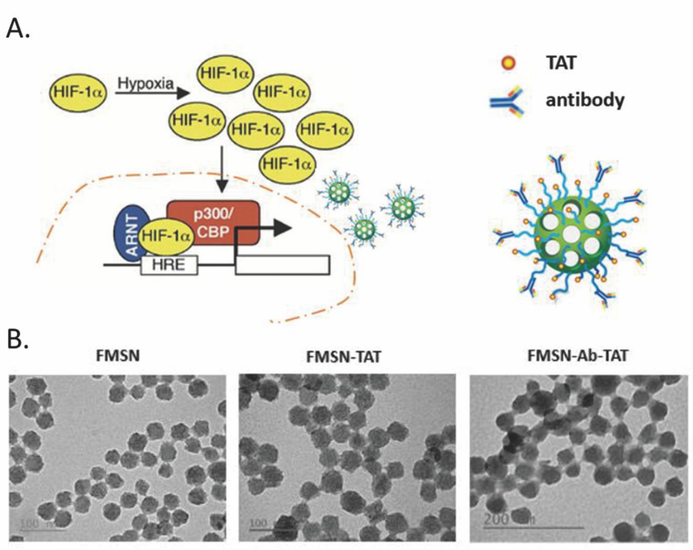
研究重點

The application of nanotechnology in the field of drug delivery has attracted much attention in recent decades. Mesoporous silica nanoparticles (MSNs), whose attributes include uniform mesopores, easy functionalization and significant biocompatibility, are believed to be a promising material for biomedical applications. Here, we utilize MSNs as targeted drug delivery cargo in tumor therapy, by combination with different surface modifications. Two major targets were set in this research: solid tumor under hypoxia condition and the breast cancer, especially the triple-negative breast cancer (TNBC) targeted drug delivery. Meanwhile, to optimized the in vivo circulation of nanoparticles, erythrocyte encapsulated MSNs was included in our research.

研究成果



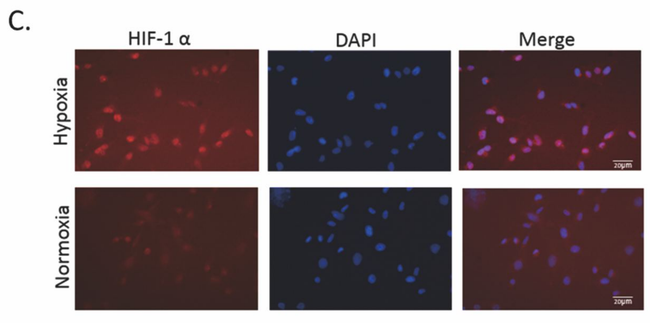


Fig 1. (A) Schematic representation of a smart nanoparticle consisting of mesoporous silica nanoparticle (MSNs) with surface functionalization of HIF-1 α antibody and TAT transducing peptide; (B) Transmission electron microscopy (TEM) images of MSNs; (C) Immunofluorescence assay of the hypoxia induced HIF-1 α translocation. MDA-MB-231 cell lines were cultured on hypoxia (1% oxygen, 5% carbon dioxide, 37℃) or normoxia (20% oxygen, 5% carbon dioxide, 37℃) condition for 6 hour, respecitvely, before the fixation.

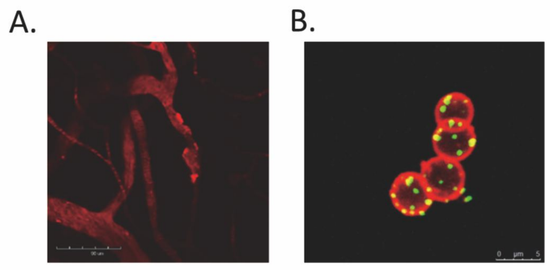


Fig 2. (A) Image of the RITC-MSN-TA (200 nm) nanoparitcles flowing in the blood vessel in the ear of the ICR mouse. Image was taken five minutes after the tail vein injection by two-photon *in vivo* microscopy. The dosage applied is 200 mg/kg; (B) Confocal images of RITC-MSN-TA (200 nm) nanoparticles encapsulated in erythrocytes by hypo-osmotic. Confocal Spectral microscopy images demonstrated the colocalization of the red blood cells membranes (visualized with red DiD dyes) and RITC-MSN-TA (200 nm) nanoparticles (visualized with yellow Rhodamine-B-Isothiocyanate dyes).

In most solid tumors, the microenvironment is quite different from the normal tissues. As a tumor grows, it rapidly outgrows its blood supply, resulting in portion of tumor cells living in region with significant lower oxygen concentration. This deprived of adequate oxygen condition is termed as hypoxia. Hypoxia tumor cells are generally resistant to cancer therapy. Thus, hypoxia targeted anticancer therapy draws a lot of attentions. The hypoxia-inducible fator-1 (HIF-1), which is a heterodimer composed of an alpha and a beta subunit, acts as a key role in the adaption of hypoxia and activates the transcription of genes that are involved in crucial aspects of cancer biology. The HIF-1 β subunit is a constitutively-expressed aryl hydrocarbon receptor nuclear translocator (ARNT), while the expression of HIF-1 α is highly regulated. In normoxic conditions, the HIF-1 α is degraded by the ubiquitin system, while under hypoxia, the HIF-1 α subunit would be accumulated and translocate to the nucleus, then further active the hypoxia response elements (HRE) and downstream related genes.

Here, we try to use a HIF-1 α antibody-conjugated, TAT peptide assisted MSN to specific block the translocation of HIF-1 heterodimer, thereby inhibiting the activation of the HRE and downstream hypoxia-responsive genes (Fig.1 A). By controlling the particle size of the HIF-1 α antibody-conjugated MSN (~50 nm) (Fig.1 B), the particles could capture the cytoplasmic HIF-1 α protein and the whole MSN complex would be too big to enter the nuclear pores. Through size hindrance, one thus intercepts and blocks the translocation of the HIF-1 α. We have revealed a marked HIF-1 α translocation on MDA-MB-231 cell line after cultured for 6 h under hypoxia condition by western blot (data not shown) and immunofluorescence assay (Fig. 1 C). We will further test the HIF-1 α blocking effect of nanoparticle in the near future.

Although our MSNs particle itself could circulated well *in vivo* without significant aggregation (Fig.2 A), we still want to go a step further to extend its retention time. To encapsulate the nanoparticles in erythrocytes seems a good choice, since erythrocyte is a nature component of blood. By now we have successfully capture our nanoparticles by erythrocytes of mouse (Fig.2 B) and more detailed *in vivo* tests will be done.

研究生活及心得

研究生活，好像沒有太輕鬆的時候，總是需要意念堅持還有不斷努力，雖然辛苦，但是每次要看結果時又期待又怕受傷害的感覺，倒也還蠻有趣的，像是和實驗在談戀愛。非常感謝中技社的幫助，也感謝我的指導導師一直以來的照顧支持，路才剛開始，希望繼續努力，當研究生活告一段落時，把空白畫斑斕。

財團法人 中技社 CTCI FOUNDATION